Organizacion y
Digitalizacion CSA Ltda

Industria y Comercio

SUPERINTENDENCIA

Organizacion y
Digitalizacion CSA Ltda

PCT

INVENTIONS 10

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Delegatura de Propiedad Industrial

División de Nuevas Cre

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-117060- -00000-0000
Fecha: 2010-09-22 11:31:40 Dep: 2020 DIR.NULVASCR
Tra: 11 PATENTEIYII Eve: 378 FASLNACIONALI
Act: 411 PRESENTACION Folios: 722

SOLICITUD

PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 10-117060

54. **TÍTULO** DOCOMPUESTOS DE BENZODIAZEPINA Y COMPOSICION FARMACEUTICA

51. **CLASIFICACIÓN INTERNACIONAL**

71. **SOLICITANTE** OTSUKA PHARMACEUTICAL CO., LTD.

DOMICILIO TOKYO, JAPON

74. **APODERADO** LUZ CLEMENCIA DE PAEZ
C.C. 35.456.344 de Usaquén

22. **BOGOTÁ, D.C.,**

(FORMA P-10)

Industria y Comercio
SUPERINTENDENCIA

PETITORIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-117060- -00000-0000
Fecha: 2010-09-22 11:31:40 Dep: 2020 DIR NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 722

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: **OTSUKA PHARMACEUTICAL CO., LTD.**
Sociedad constituida y existente bajo las leyes de Japón.

Dirección: 9, Kanda-Tsukasamachi
2-chome, Chiyoda-ku,
Tokyo 1018535,
Japón

Domicilio: Tokyo,
Japón

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

3 REPRESENTANTE O APODERADO

Nombre: LUZ CLEMENCIA DE PAEZ
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 35.456.344 T.P 23.555

4 INVENTOR (ES) (72)

1. **Kunio OSHIMA**
c/o OTSUKA PHARMACEUTICAL CO., LTD.
1-7-1, Doshomachi
Chuo-ku, Osaka-shi,
Osaka 5410045,
Japón

2. **Takashi OSHIYAMA**
c/o OTSUKA PHARMACEUTICAL CO., LTD.
1-7-1, Doshomachi
Chuo-ku, Osaka-shi,
Osaka 5410045,
Japón

3. **Shinichi TAIRA**
c/o OTSUKA PHARMACEUTICAL CO., LTD.
1-7-1, Doshomachi
Chuo-ku, Osaka-shi,
Osaka 5410045,
Japón

4. **Yasuhiro MENJO**
c/o OTSUKA PHARMACEUTICAL CO., LTD.
1-7-1, Doshomachi
Chuo-ku, Osaka-shi,
Osaka 5410045,
Japón

5. **Hokuto YAMABE**
c/o OTSUKA PHARMACEUTICAL CO., LTD.
1-7-1, Doshomachi
Chuo-ku, Osaka-shi,
Osaka 5410045,
Japón

6. **Shuuji MATSUMURA**
c/o OTSUKA PHARMACEUTICAL CO., LTD.
1-7-1, Doshomachi
Chuo-ku, Osaka-shi,
Osaka 5410045,
Japón

7. **Masataka UEDA**
c/o OTSUKA PHARMACEUTICAL CO., LTD.
1-7-1, Doshomachi
Chuo-ku, Osaka-shi,
Osaka 5410045,
Japón

8. **Yasuo KOGA**
c/o OTSUKA PHARMACEUTICAL CO., LTD.
1-7-1, Doshomachi
Chuo-ku, Osaka-shi,
Osaka 5410045,
Japón

9. **Kuninori TAI**
c/o OTSUKA PHARMACEUTICAL CO., LTD.
1-7-1, Doshomachi
Chuo-ku, Osaka-shi,
Osaka 5410045,
Japón

10. **Sunao NAKAYAMA**
c/o OTSUKA PHARMACEUTICAL CO., LTD.
1-7-1, Doshomachi
Chuo-ku, Osaka-shi,
Osaka 5410045,
Japón

	11. Toshiyuki ONOGAWA c/o OTSUKA PHARMACEUTICAL CO., LTD. 1-7-1, Doshomachi Chuo-ku, Osaka-shi, Osaka 5410045, Japón	**12. Kenji TSUJIMAE** c/o OTSUKA PHARMACEUTICAL CO., LTD. 1-7-1, Doshomachi Chuo-ku, Osaka-shi, Osaka 5410045, Japón

(5) **PCT (86)**

Solicitud Internacional No. PCT/JP2009/053623 Fecha: 20 de febrero de 2009

Publicación Internacional No. WO 2009/104819 A1 Fecha: 27 de agosto de 2009

(6) **Título (54)**

COMPUESTO DE BENZODIAZEPINA Y COMPOSICIÓN FARMACÉUTICA

(folio 325)

(7) **Clasificación Internacional (51)** C07D 243/012 A61P 9/06 A61K 31/551

(8) **Prioridad** SI ☒ NO ☐

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
JP	22 de febrero de 2008	2008-041296
JP	04 de septiembre de 2008	2008-227368

(9)

Comprobante de pago No.: 10-74,150 **Fecha:** 06 de septiembre de 2010

Comprobante de pago No.: 10-75,695 **Fecha:** 13 de septiembre de 2010

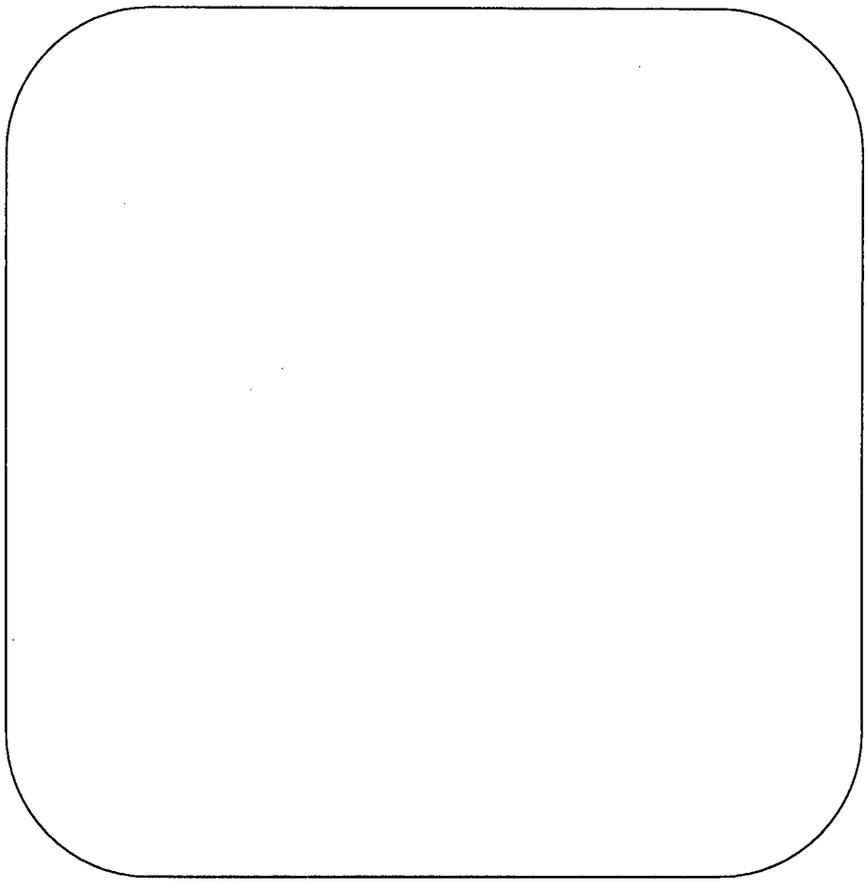
Comprobante de pago No.: 10-75,696 **Fecha:** 13 de septiembre de 2010

Comprobante de pago No.: 10-75,697 **Fecha:** 13 de septiembre de 2010

(10) **Anexos:**

- ☒ Comprobante de pago de la tasa de presentación de la solicitud por $ 554.000.oo.
- ☒ Comprobante de pago por 3 reivindicaciones adicionales después de la décima reivindicación por $78.000.oo.
- ☒ 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**



12 Solicito la concesión de la patente,

NOMBRE: LUZ CLEMENCIA DE PAEZ

FIRMA : Luz Clemencia de Paez

C.C. 35.456.344 de Usaquén T.P. 23.555

SCT

4

DOCUMENTOS ANEXOS

1. ☒ Publicación Internacional WO 2009/104819 A1

   Descripción:

   Páginas 309 en el idioma original

   Páginas 353 en español

   Reivindicaciones: Número (s) 13

   Figuras: Número (s)

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

3. ☒ Listado de Secuencias.

4. ☒ Extracto de publicación.

NO SE REALIZARON MODIFICACIONES EN LA FASE INTERNACIONAL

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.

94

5

REPRESENTACION Y PODER

REPRESENTATION AND POWER- OF- ATTORNEY

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

OTSUKA PHARMACEUTICAL CO., LTD.

domiciliado (s) en/of 9, Kanda-Tsukasamachi 2-chome,

Chiyoda-ku, Tokyo 1018535, Japan

14055
5933

por el presente nombramos a LUZ CLEMENCIA DE PAEZ, tpa. 23555, DANIEL PEÑA, tpa. 65620 y GERMAN MAPHI, tpa. 64239, domiciliados en la Carrera 4ª Nº 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 nombrados 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.

In due compliance with the terms of paragraph 1st. of article 543 of the Commercial Code, do hereby appoint LUZ CLEMENCIA DE PAEZ, tpa. 23555, DANIEL PEÑA, tpa. 65620 and GERMAN MAPHI, tpa. 64239, domiciled at Carrera 4ª Nº 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.

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, cancelación voluntaria; y el registro de licencias de uso de esos derechos;

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 the above rights; b) Actions of unfair competition, protection to the

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6

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.

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 26th of June, 2009

en/in Japan

por/by Yoshio SAMEZAWA, Director of Intellectual Property Department

Firma Signature

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTA D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C. REPUBLICA DE COLOMBIA
21 SEP 2010
NOTARIO ENCARGADO

REPUBLICA DE COLOMBIA
Jaime Vargas Ortiz
NOTARIO ENCARGADO
NOTARIA SEXTA DE BOGOTA

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登簿平成21年第387号

当公証人は次の認証をする。

大塚製薬株式会社

知的財産部部長　鮫澤由夫

上記の者は代理人三枝英二により当公証人の面前でこの証書の署名を自認した。

上記の会社は日本国東京都千代田区神田司町2丁目9番地に所在し日本の法律に基づいて設立された会社であることを東京法務局発行の証明書によって相違ないことが認められるものである。

平成21年6月26日当公証人役場において

大阪市中央区平野町2丁目1番2号(沢の鶴ビル内)

大阪法務局所属

公証人

OSAKA LEGAL AFFAIRS BUREAU
"NOTARY"
1-2, HIRANO-MACHI, 2-CHOME,
CHUO-KU, OSAKA JAPAN

REPÚBLICA DE COLOMBIA
Jaime Vargas
NOTARIO ENCARGADO
NOTARÍA SEXTA DE BOGOTÁ

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTA D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C. REPUBLICA DE COLOMBIA
21 SEP 2010
NOTARIO ENCARGADO

大阪公証人役場

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTA D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C. REPUBLICA DE COLOMBIA
21 SEP 2010
NOTARIO ENCARGADO

REPÚBLICA DE COLOMBIA
Jaime Vargas Ch...
NOTARIO
ENCARGADO
NOTARIA SEXTA DE BOGOTA

Registration No. 387 — 2009

CERTIFICATE

I, the undersigned, hereby certify :

that Eiji SAEGUSA, a proxy for Yoshio SAMEZAWA, Director of Intellectual Property Department of OTSUKA PHARMACEUTICAL CO., LTD., has stated in my presence that Eiji SAEGUSA has acknowledged as true the signature of Yoshio SAMEZAWA on the attached REPRESENTATION AND POWER- OF- ATTORNEY.

that the abovementioned company is a corporation located at 9, Kanda-Tsukasamachi 2-chome, Chiyoda-ku, Tokyo 1018535, Japan; and was established under the laws of Japan ; as verified by the certificate issued by Tokyo District Legal Affairs Bureau.

Dated on this 26th day of June, 2009

Miyotaro TSUJIMOTO
Notary
Osaka Legal Affairs Bureau

OSAKA LEGAL AFFAIRS BUREAU
"NOTARY"
1-2, HIRANO-MACHI, 2-CHOME,
CHUO-KU, OSAKA JAPAN

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTA D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C., REPUBLICA DE COLOMBIA
21 SEP 2010
NOTARIO ENCARGADO
Jaime Vargas
NOTARIO ENCARGADO
NOTARIA SEXTA DE BOGOTA

総第 2833 号

証　　明

大阪法務局所属公証人　**辻本 三代太郎**

平成21年6月26日付

平成21年 登簿 第 387 号

この認証の付与は，在職中の公証人がその権限に基づいてしたものであり，かつ，その押印は，真実のものであることを証明する。

For legalization by the foreign consul in Japan, this is to certify that the Seal affixed hereto is genuine.
Osaka, JUN. 26 2009
Official
Ministry of Foreign Affairs
(Consular Service Division)

平成21年6月26日

大阪法務局長　白石研二

CERTIFICATE

This is to certify that the annexed Notarial Certificate has been executed by Notary,duly authorized and practising in Osaka, Japan, and that the Official Seal appearing on the same is genuine.

Date JUN. 26. 2009

Director of the Osaka Legal Affairs

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTA D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C. REPUBLICA DE COLOMBIA
21 SEP 2010
NOTARIO ENCARGADO
Jaime Vargas
NOTARIA SEXTA DE BOGOTA

NO SE ASUME RESPONSABILIDAD SOBRE EL TEXTO

MINISTERIO DE RELACIONES EXTERIORES

2009 AGO -3 A 10:12

016576

Jose Diaz

UNA FIRMA ILEGIBLE EN EL DOCUMENTO DESMIENTE LAS FUNCIONES INDICADAS

LEGALIZACIONES BOGOTA D.C.

EMBAJADA DE COLOMBIA - SECCION CONSULAR

Tokio, Japón, JUNIO 30, 2009

No. 173

El encargado de las funciones consulares de Colombia
CERTIFICA:

Que el (la) Señor(a) NORIKO KAWAHITO, quien autoriza el presente documento , es la persona legalmente facultada para representar en la fecha señalada al (a la) MINISTERIO DE RELACIONES EXTERIORES,JAPON y que la firma y sello que en el documento aparecen como suyos son las que usa y acostumbra para sus actos oficiales.

El Encargado de Funciones Consulares no asume responsabilidad alguna por el contenido del documento.

Firma del Encargado de Funciones Consulares

JOSE FRANCISCO DIAZ ULLOA
Segundo Secretario
Encargado de Funciones Consulares

Derechos: US$30.oo

COTEJO: NOTARIA SEXTA DEL CIRCULO DE BOGOTA D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA BOGOTA D.C., REPUBLICA DE COLOMBIA

21 SEP 2010

NOTARIO ENCARGADO

REPUBLICA DE COLOMBIA

Jaime Vargas Chacón
NOTARIO
ENCARGADO

NOTARIA SEXTA DE BOGOTA

TRADUCCIÓN OFICIAL No. 08.04/09b realizada por Diego Vargas, Traductor Oficial, Resolución No. 0001 de 1999 del Ministerio de Justicia, registrado ante el Ministerio de Relaciones Exteriores de Colombia.

A continuación se traducen los sellos y legalizaciones de un documento mediante el cual **OTSUKA PHARMACEUTICAL CO., LTD.**, domiciliada en 9, Kanda-Tsukasamachi 2-chome, Chiyoda-ku, Tokio 1018535, Japón, otorga derechos de representación y poder a los Doctores Luz Clemencia de Páez, 23555; Daniel Peña, tpa. 65620 y Germán Marín, tpa. 64239, domiciliados en la Carrera 4 No. 72-35, Bogotá, Colombia.

Dado y firmado el 26 de junio de 2009 en Japón por Yoshio SAMEZAWA, Director del Departamento de Propiedad Intelectual.

Firma *Firma Ilegible*

Registro No. 387 - 2009

CERTIFICADO

Yo, el suscrito, por el presente certifico:

que el señor Eiji SAEGUSA, apoderado de Yoshio SAMEZAWA, Director del Departamento de Propiedad Intelectual de OTSUKA PHARMACEUTICAL CO., LTD., ha declarado en mí presencia que Eiji SEAGUSA ha reconocido como verdadera la firma del señor Yoshio SAMEWAZA en el adjunto documento de Representación y Poder.

que la anterior compañía es una s[illegible] 9, Kanda-Tsukasamachi 2-chome, Chiyoda-ku, T[illegible] 1018535, Japó[illegible] que fue constituida de conformidad con las [illegible] lo constata el certificado expedido por la Oficina de [illegible] de Tokio.

Fechado hoy 26 de junio de 2009

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTA D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C. REPUBLICA DE COLOMBIA
21 SEP 2010
NOTARIO ENCARGADO

REPUBLICA DE COLOMBIA
Jaime Vargas
NOTARIO
ENCARGADO
NOTARIA SEXTA DE BOGOTA

TRADUCCIONES
ESPAÑOL - INGLES - INGLES - ESPAÑOL
RES. 0001 DE ENERO 4 DE 1999
MINISTERIO DE JUSTICIA

Firma ilegible

Miyotaro TSUJIMOTO
Notario
Oficina de Asuntos Legales de Osaka

Sello: Oficina de Asuntos Legales de Osaka
NOTARIO
1-2 HIRANO-MACHI, 2-CHOME,
CHUO-KU, OSAKA, JAPÓN

TEXTO EN JAPONÉS

CERTIFICADO

El presente es para certificar que el Certificado Notarial anexo fue suscrito por un Notario debidamente autorizado y en ejercicio en Osaka, Japón y que el sello oficial que aparece en el mismo es auténtico.

Fecha JUN.-26.2009

Director de la Oficina de Asuntos Legales de Osaka

Se anexa certificación No.173 expedida por la Sección Consular de la Embajada de Colombia en Tokio, Japón con fecha del 30 de junio de 2009 en donde se certifica la firma anterior del señor NORIKO KAWAHITO como funcionario del Ministerio de Relaciones Exteriores, Japón, así como el sello que aparece en el documento anexo. Certificación firmada por José Francisco Díaz Ulloa, Segundo Secretario de las Funciones Consulares. Pagados los Derechos Consulares.

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTA D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C. REPUBLICA DE COLOMBIA
21 SEP 2010
NOTARIO SEXTA DE BOGOTA
Jaime Vargas
NOTARIO ENCARGADO
NOTARIA SEXTA DE BOGOTA

Legalización de la firma anterior por [illegible]nte del Jefe de Legalizaciones en Bogotá D.C. del Mi[illegible]es Exteriores con número **016576** con fecha del 3 de ag[illegible]

Es traducción fiel y completa de la cual se deja copia en esta oficina para su confrontación.
DVZ\DVZ\ID-155360\WPCL002H\COLO 14055-841-003-5

ESTADO [illegible]
REG. CONSULAR [illegible]
MINISTERIO DE JUSTICIA

MINISTERIO DE
RELACIONES EXTERIORES

NO SE ACEPTA
RESPONSABILIDAD
DEL TEXTO

2009 AGO 11 A 9:27

019140

OFICINA DE LEGALIZACIONES
BOGOTA D.C.

DIEGO VARGAS
CURA PARA LA AUTENTICIDAD DE ESTE
DOCUMENTO SE DESEMPEÑA
LAS FUNCIONES INDICADAS.

RECIBO LEGALIZACION 3/3

No. 9853746596.



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

CESION

ASSIGNMENT

Yo, (nosotros) abajo firmado (s)	I (we), the undersigned
	Please see the attached sheet.
domiciliado(s) en	of Please see the attached sheet.
declaro(amos) bajo juramento ser único(s) y verdadero(s) inventor(es) de la invención:	state(s) under oath to be sole and true inventor(s) of the invention: BENZODIAZEPINE COMPOUND AND PHARMACEUTICAL COMPOSITION
declaro(amos) así mismo que cedo(emos) y transfiero(erimos), sin limitación, a favor de la sociedad	state as well, that assign, without reservations or limitations in favour of OTSUKA PHARMACEUTICAL CO., LTD.
constituida y existente de conformidad con las leyes de	a corporation constituted and existing in conformity with the laws of Japan
domiciliada en	domiciled in 9, Kanda-Tsukasamachi 2-chome, Chiyoda-ku, Tokyo 1018535, Japan
todos los derechos inherentes a dicha invención y que la citada Compañía queda facultada para solicitar en su nombre la patente de invención correspondiente en la República de Colombia.	all right inherent to said invention and that the above mentioned company hereby is enabled to apply, in its name, for the corresponding patent invention, in the Republic of Colombia

Dado y firmado hoy/Given and signed this 11th day of August, 2010

en/in Osaka, Japan

por/by Please see the attached sheet.

Firma/Signature Please see the attached sheet.

© CAVELIER ABOGADOS

The undersigned

1) Kunio OSHIMA,
2) Takashi OSHIYAMA,
3) Shinichi TAIRA,
4) Yasuhiro MENJO,
5) Hokuto YAMABE,
6) Shuuji MATSUMURA,
7) Masataka UEDA,
8) Yasuo KOGA,
9) Kuninori TAI,
10) Sunao NAKAYAMA,
11) Toshiyuki ONOGAWA, and
12) Kenji TSUJIMAE

Domiciled in

1)-12)
c/o OTSUKA PHARMACEUTICAL CO., LTD.,
1-7-1, Doshomachi, Chuo-ku,
Osaka-shi, Osaka 5410045, Japan

Singed

Kunio Oshima
Kunio OSHIMA

Takashi Oshiyama
Takashi OSHIYAMA

Shinichi Taira
Shinichi TAIRA

Yasuhiro Menjo
Yasuhiro MENJO

Hokuto Yamabe
Hokuto YAMABE

Shuuji Matsumura
Shuuji MATSUMURA

Masataka Ueda
Masataka UEDA

Yasuo Koga
Yasuo KOGA

Kuninori Tai
Kuninori TAI

Sunao Nakayama
Sunao NAKAYAMA

Toshiyuki ONOGAWA

Kenji Tsujimae
Kenji TSUJIMAE

登簿平成22年第430号

大島邦生、押山　孝、平良伸一、枝條康宏、山邉北斗、松村修二、植田昌孝、古賀康雄、田井国憲、中山　直、小野川利幸および辻前賢司は、代理人三枝　英二により当公証人の面前でこの証書の署名を自認した。

よってこれを認証する。

平成22年8月18日当公証人役場において

大阪市中央区平野町2丁目1番2号(沢の鶴ビル内)

大阪法務局所属

公証人　辻本三枝太郎

OSAKA LEGAL AFFAIRS BUREAU
"NOTARY"
1-2, HIRANO-MACHI, 2-CHOME,
CHUO-KU, OSAKA JAPAN

大阪法務局所属　公証人役場

15

Registration No. 430 −2010

CERTIFICATE

I, the undersigned, hereby certify that Eiji SAEGUSA, a proxy for Kunio OSHIMA, Takashi OSHIYAMA, Shinichi TAIRA, Yasuhiro MENJO, Hokuto YAMABE, Shuuji MATSUMURA, Masataka UEDA, Yasuo KOGA, Kuninori TAI, Sunao NAKAYAMA, Toshiyuki ONOGAWA, and Kenji TSUJIMAE i.e. the inventors and assignors, has stated in my very presence that said Kunio OSHIMA, Takashi OSHIYAMA, Shinichi TAIRA, Yasuhiro MENJO, Hokuto YAMABE, Shuuji MATSUMURA, Masataka UEDA, Yasuo KOGA, Kuninori TAI, Sunao NAKAYAMA, Toshiyuki ONOGAWA, and Kenji TSUJIMAE acknowledged themselves to have signed to the ASSIGNMENT.

Dated on this 18th day of August, 2010

Miyotaro Tsujimoto

Miyotaro TSUJIMOTO
Notary
Osaka Legal Affairs Bureau
1-2, Hirano-Machi, 2-Chome
Chuo-ku, Osaka Japan

OSAKA LEGAL AFFAIRS BUREAU
"NOTARY"
1-2, HIRANO-MACHI, 2-CHOME,
CHUO-KU, OSAKA JAPAN

16

第　3619　号

証　明

この認証の付与は，在職中の公証人がその権限に基づいてしたものであり，かつ，その押印は，真実のものであることを証明する。

For legalization by the foreign consul in Japan, this is to certify that the Seal affixed hereto is genuine.
Osaka, AUG. 19 2010

Official
Ministry of Foreign Affairs
(Consular Service Division)

平成２２年８月１９日
平成　年　月　日

大阪法務局長　石　井　寛　明

Registration No.

CERTIFICATE

This is to certify that the annexed Notarial Certificate has been executed by Notary, duly authorized and practising in Osaka, Japan, and that the Official seal appearing on the same is genuine.

Date AUG. 19. 2010

Director of the Osaka Legal Affairs Bureau

NO SE ASUME RESPONSABILIDAD DEL TEXTO

0324517 José Díaz
LA FIRMA APARECE EN EL DOCUMENTO DESEMPEÑA LAS FUNCIONES INDICADAS

MINISTERIO DE RELACIONES EXTERIORES
2010 SET 19
JEFE DE LEGALIZACIONES BOGOTA D.C.

EMBAJADA DE COLOMBIA - SECCION CONSULAR

Tokio, Japón, AGOSTO 23, 2010

No. 174

El encargado de las funciones consulares de Colombia
CERTIFICA:

Que el (la) Señor(a) NAOMI ASANO, quien autoriza el presente documento , es la persona legalmente facultada para representar en la fecha señalada al (a la) MINISTERIO DE RELACIONES EXTERIORES,JAPON y que la firma y sello que en el documento aparecen como suyos son las que usa y acostumbra para sus actos oficiales.

El Encargado de Funciones Consulares no asume responsabilidad alguna por el contenido del documento.

Firma del Encargado de Funciones Consulares
JOSE FRANCISCO DIAZ ULLOA
Segundo Secretario
Encargado de Funciones Consulares

Derechos: US$30.oo

17

TRADUCCIÓN OFICIAL No. 09.16/10b 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.

CESIÓN

Nosotros, los suscritos, (por favor ver el listado anexo) domiciliados en (por favor ver el listado anexo), declaramos bajo juramento ser únicos y verdaderos inventores de la invención: *COMPUESTO DE BENZODIAZEPINA Y COMPOSICIÓN FARMACÉUTICA* y declaramos así mismo que cedemos y transferimos, sin limitación, a favor de OTSUKA PHARMACEUTICAL CO., LTD. una sociedad constituida y existente de conformidad con las leyes de Japón y domiciliada en 9, Kanda-Tsukasamachi 2-chome, Chiyoda-ku, Tokio 1018535, Japón, todos los derechos inherentes a dicha invención y que la citada compañía queda facultada para solicitar en su nombre la patente de invención correspondiente en la República de Colombia.

Dado y firmado el 11 de agosto de 2010 en Osaka, Japón.

Los suscritos

1) Kunio OSHIMA, 2) Takashi OSHIYAMA, 3) Shinichi TAIRA, 4) Yasuhiro MENJO, 5) Hokuto YAMABE, 6) Shuuji MATSUMURA, 7) Masataka UEDA, 8) Yasuo KOGA, 9) Kuninori TAI, 10) Sunao NAKAYAMA, 11) Toshiyuki ONOGAWA y 12) Kenji TSUJIMAE, domiciliados en 1)-12) c/o OTSUKA PHARMACEUTICAL CO., LTD., 1-7-1, Doshomachi, Chuo-ku, Osaka-shi, Osaka 5410045, Japón.

Firmas ilegibles de todos los inventores nombrados anteriormente.

TEXTO EN JAPONÉS

Diego F. Vargas

MINISTERIO DE JUSTICIA

18

Registro No. 430 - 2010

CERTIFICADO

Yo, el suscrito, por el presente certifico que el Señor Eiji SAEGUSA, apoderado de Kunio OSHIMA, Takashi OSHIYAMA, Shinichi TAIRA, Yasuhiro MENJO, Hokuto YAMABE, Shuuji MATSUMURA, Masataka UEDA, Yasuo KOGA, Kuninori TAI, Sunao NAKAYAMA, Toshiyuki ONOGAWA y Kenji TSUJIMAE, esto es, los inventores y cedentes, ha declarado en mí presencia que los mencionados Kunio OSHIMA, Takashi OSHIYAMA, Shinichi TAIRA, Yasuhiro MENJO, Hokuto YAMABE, Shuuji MATSUMURA, Masataka UEDA, Yasuo KOGA, Kuninori TAI, Sunao NAKAYAMA, Toshiyuki ONOGAWA y Kenji TSUJIMAE reconocen haber firmado ellos mismos la CESIÓN.

Fechado hoy 18 de agosto de 2010

Firma ilegible

Miyotaro TSUJIMOTO
Notario
Oficina de Asuntos Legales de Osaka
1-2 Hirano-Machi, 2-Chome,
Chuo-Ku, Osaka, Japón

Sello: Oficina de Asuntos Legales de Osaka
NOTARIO
1-2 HIRANO-MACHI, 2-CHOME,
CHUO-KU, OSAKA, JAPÓN

Sellos rojos al lado de la firma y parcial en la parte superior del documento.

Documento anterior en idioma japonés

TEXTO EN JAPONÉS

CERTIFICADO

TR... E OFICINA
ESPAÑO... INGLES INGLES ... AÑO...
RES. 0001 DE ENERO 4 DE 1999
MINISTERIO DE JUSTICIA

El presente es para certificar que el Certificado Notarial anexo fue suscrito por un Notario debidamente autorizado y en ejercicio

en Osaka, Japón y que el sello oficial que aparece en el mismo es auténtico.

Fecha AGO.-19.2010

Director de la Oficina de Asuntos Legales de Osaka

Se anexa certificación No.174 expedida por la Sección Consular de la Embajada de Colombia en Tokio, Japón con fecha del 23 de agosto de 2010 en donde se certifica la firma anterior de NAOMI SANO como funcionario del Ministerio de Relaciones Exteriores, Japón, así como el sello que aparece en el documento anexo. Certificación firmada por José Francisco Díaz Ulloa, Segundo Secretario de las Funciones Consulares. Pagados los Derechos Consulares.

Legalización de la firma anterior por parte del Jefe de Legalizaciones en Bogotá D.C. del Ministerio de Relaciones Exteriores con número **032451** con fecha del 16 de septiembre de 2010.

Es traducción fiel y completa de la cual se deja copia en esta oficina para su confrontación.

DVZ\DVZ\ID-178581\WPCL002H\COLO 14055-841-007-6

CP:536 TMIN: 60

TRADUCTOR OFICIAL
ESPAÑOL - INGLES - FRANCES
RES. 0001 DE ENERO 4 DE
MINISTERIO DE JUSTICIA

20

REPUBLICA DE COLOMBIA

MINISTERIO DE JUSTICIA Y DEL DERECHO

RESOLUCION NUMERO 00001 DE 19 14 ENE 1999

Por la cual se expide una licencia para ejercer funciones de Traductor e Intérprete Oficial

EL SECRETARIO GENERAL DEL MINISTERIO DE JUSTICIA Y DEL DERECHO
en ejercicio de la facultad conferida por la Resolución 0404 del 22 de mayo de 1997, y

CONSIDERANDO

Que **DIEGO FELIPE VARGAS ZAMORA.** identificado con la cédula de ciudadanía No. 79.554.011 de Bogotá solicita a este Ministerio le sea expedida licencia para ejercer funciones de Traductor e Intérprete Oficial de conformidad con los Decretos 382 y 2257 de 1951.

Que el peticionario ha acompañado a su solicitud los siguientes documentos:

a. Fotocopia autenticada de la cédula de ciudadanía No. 79.554.011 de Bogotá, en donde se establece la mayoría de edad.

b. Certificación expedida por la Jefe de la Oficina Jurídica del Ministerio de Educación Nacional, en la cual hace constar que el señor **DIEGO FELIPE VARGAS ZAMORA,** reúne las condiciones de idoneidad que lo acredita como Traductor Oficial en los idiomas **INGLES- ESPAÑOL- ESPAÑOL-INGLES,** de conformidad con lo establecido en el Acta No. 694 del 25 de octube de 1998.

c. Tres declaraciones de personas que manifiestan que La solicitante es persona de buena conducta.

d. Fotocopia autenticada del certificado judicial registrado bajo el T.D. No. 79.554.011, expedido por el Departamento Administrativo de Seguridad DAS, en donde consta que **DIEGO FELIPE VARGAS ZAMORA** no tiene asuntos pendientes con las autoridades judiciales y de policía.

Que revisados y analizados los documentos [illegible] el peticionario se encontró que reúne los requisitos legales [illegible] de Traductor e Intérprete Oficial.

NOTARIA SEGUNDA DE BOGOTA D.C. — REPUBLICA DE COLOMBIA

LA FOTOCOPIA COINCIDE EL CIRCULO E BOGOTA
FIEL TENIDO A LA VISTA
13 SEP 2010

MINISTERIO DE JUSTICIA Y DEL DERECHO
OFICINA JURIDICA
ES FIEL COPIA DE SU ORIGINAL

JEFE

21

Hoja 2 de la Resolución "Por la cual se expide una licencia para ejercer funciones de Traductor e Intérprete Oficial a **DIEGO FELIPE VARGAS ZAMORA**

Que mediante Resolución 0404 del 22 de mayo de 1997, la Ministra de Justicia y del Derecho, ha delegado en la Secretaría General el otorgamiento de licencias para Traductores e Intérpretes Oficiales.

Que por lo anteriormente expuesto,

RESUELVE

ARTICULO PRIMERO: Expedir licencia a **DIEGO FELIPE VARGAS ZAMORA** identificado con la cédula de ciudadanía No 79.554.011 de Bogotá, para ejercer las funciones de Traductor e Intérprete Oficial en los idiomas **INGLES-ESPAÑOL, ESPAÑOL-INGLES.**

ARTICULO SEGUNDO: Comunicar el texto de la Resolución a la Subsecretaría de Asuntos Administrativos del Ministerio de Relaciones Exteriores.

ARTICULO TERCERO: El interesado deberá registrar su firma y sello ante la Oficina de Autenticaciones del Ministerio de Relaciones Exteriores, e inscribir su nombre ante el Tribunal Superior del Distrito Judicial correspondiente al territorio donde vaya a desempeñarse.

ARTICULO CUARTO: La presente Resolución rige a partir de la fecha de su expedición, y contra ella procede el recurso de reposición el cual deberá ser interpuesto dentro de los cinco días siguientes a su notificación.

NOTIFÍQUESE, COMUNÍQUESE Y CÚMPLASE
Dada en Santa Fe de Bogotá, D.C. a

13 ENE 1999

ÁLVARO GALÁN VARGAS

REPUBLICA DE COLOMBIA
Mabel Andrea Rodrigue
NOTARIA (E)
NOTARIA SEXTA DE BO

NOTARIO TEXTO (E) DEL CIRCULO DE BOGOTÁ
DICHO HACE CONSTAR QUE LA FOTOCOPIA COINCIDE
CON EL ORIGINAL QUE SE HA TENIDO A LA VISTA
BOGOTÁ COLOMBIA
13 SEP 2010
NOTARIO ENCARGADO

HSA
5-1-99

MINISTERIO DE JUSTICIA Y DEL DERECHO
OFICINA JURIDICA
ES FIEL COPIA DE SU ORIGINAL
JEFE

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(71) Applicant *(for all designated States except US)*: **OTSUKA PHARMACEUTICAL CO., LTD.** [JP/JP]; 9, Kanda-Tsukasamachi 2-chome, Chiyoda-ku, Tokyo, 1018535 (JP).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **OSHIMA, Kunio** [JP/JP]; c/o OTSUKA PHARMACEUTICAL CO., LTD., 1-7-1, Dochomachi, Chuo-ku, Osaka-shi, Osaka, 5410045 (JP). **OSHIYAMA, Takashi** [JP/JP]; c/o OTSUKA PHARMACEUTICAL CO., LTD., 1-7-1, Dochomachi, Chuo-ku, Osaka-shi, Osaka, 5410045 (JP). **TAIRA, Shinichi** [JP/JP]; c/o OTSUKA PHARMACEUTICAL CO., LTD., 1-7-1, Dochomachi, Chuo-ku, Osaka-shi, Osaka, 5410045 (JP). **MENJO, Yasuhiro** [JP/JP]; c/o OTSUKA PHARMACEUTICAL CO., LTD., 1-7-1, Dochomachi, Chuo-ku, Osaka-shi, Osaka, 5410045 (JP). **YAMABE, Hokuto** [JP/JP]; c/o OTSUKA PHARMACEUTICAL CO., LTD., 1-7-1, Doshomachi, Chuo-ku, Osaka-shi, Osaka, 5410045 (JP). **MATSUMURA, Shuuji** [JP/JP]; c/o OTSUKA PHARMACEUTICAL CO., LTD., 1-7-1, Doshomachi, Chuo-ku, Osaka-shi, Osaka, 5410045 (JP). **UEDA, Masataka** [JP/JP]; c/o OTSUKA PHARMACEUTICAL CO., LTD., 1-7-1, Doshomachi, Chuo-ku, Osaka-shi, Osaka, 5410045 (JP). **KOGA, Yasuo** [JP/JP]; c/o OTSUKA PHARMACEUTICAL CO., LTD., 1-7-1, Doshomachi, Chuo-ku, Osaka-shi, Osaka, 5410045 (JP). **TAI, Kuninori** [JP/JP]; c/o OTSUKA PHARMACEUTICAL CO., LTD., 1-7-1, Doshomachi, Chuo-ku, Osaka-shi, Osaka, 5410045 (JP). **NAKAYAMA, Sunao** [JP/JP]; c/o OTSUKA PHARMACEUTICAL CO., LTD., 1-7-1, Dochomachi, Chuo-ku, Osaka-shi, Osaka, 5410045 (JP). **ONOGAWA, Toshiyuki** [JP/JP]; c/o OTSUKA PHARMACEUTICAL CO., LTD., 1-7-1, Dochomachi, Chuo-ku, Osaka-shi, Osaka, 5410045 (JP). **TSUJIMAE, Kenji** [JP/JP]; c/o OTSUKA PHARMACEUTICAL CO., LTD., 1-7-1, Doshomachi, Chuo-ku, Osaka-shi, Osaka, 5410045 (JP).

(74) Agents: **Saegusa & Partners** et al.; Kitahama THK Building, 1-7-1, Dochomachi, Chuo-ku Osaka-shi, Osaka 5410045 (JP).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

— *with sequence listing part of description (Rule 5.2(a))*

WO 2009/104819 A1

(54) Title: BENZODIAZEPINE COMPOUND AND PHARMACEUTICAL COMPOSITION

(57) Abstract: The present invention provides a novel benzodiazepine compound that blocks the I_{Kur} current or the Kv1.5 channel or the IKACH current (the GIRK1/4 channel) potently and more selectively than other K^+ channels. The benzodiazepine compound of the invention is represented by General Formula (1) wherein R^1, R^2, R^3, and R^4 are each independently hydrogen or lower alkyl; R^2 and R^3 may be linked to form lower alkylene; A^1 is lower alkylene optionally substituted with one or more hydroxy; and R^5 is group represented by wherein R^6 and R^7 are each independently hydrogen or organic group; X_A and X_B are each independently bond, lower alkylene, etc.

DESCRIPTION

BENZODIAZEPINE COMPOUND AND PHARMACEUTICAL COMPOSITION

TECHNICAL FIELD

The present invention relates to a benzodiazepine compound and a pharmaceutical composition.

BACKGROUND ART

Atrial fibrillation (hereinafter referred to as "AF") is the most frequently observed type of arrhythmia in clinical examinations. Although not a lethal arrhythmia, AF causes cardiogenic cerebral embolism, and is therefore recognized as an arrhythmia that greatly affects vital prognoses and QOL. It is known that the onset of AF increases with age, and that repeated AF strokes lead to chronic (serious) AF (The Journal of American Medical Association, 285, 2370-2375 (2001) and Circulation, 114, 119-123 (2006)).

To prevent chronic AF, which causes difficulty in restoring sinus rhythm and increases the risk of cardiogenic cerebral embolism, early defibrillation and subsequent prevention of recurrence (maintenance of the sinus rhythm) are required. Antiarrhythmic drugs (classes I and III) are most commonly used as pharmacotherapy, but these drugs achieve insufficient therapeutic effects, while causing serious side effects such as a proarrhythmic effect (Am. J. Cardiol., 72, B44-B49 (1993)).

The onset of AF is triggered by atrial premature contraction with underlining causes such as intra-atrial conduction delay, shortening and heterogeneity of the atrial refractory period (Nature Reviews DRUG DISCOVERY 4, 899-910 (2005)). It is known that the prolongation of refractory period of atrial muscle can terminate AF (defibrillation) or prevent the occurence of AF. The action potential duration of the mammalian cardiac muscle is predominantly determined by voltage-dependent K^+ channels. Inhibition of the K^+ channel prolongs myocardial action potential duration, which results in prolongation of the refractory period (Nature Reviews DRUG DISCOVERY 5, 1034-49 (2006)). The action mechanism of class III antiarrhythmic

drugs (e.g., Dofetilide) is to inhibit rapid delayed rectifier K^+ current (I_{Kr}), K^+ current encoded by HERG. However, since I_{Kr} is present in both the atria and ventricles, such drugs might cause ventricular arrhythmias, such as torsades de pointes (Trends Pharmacol. soc., 22, 240-246 (2001)).

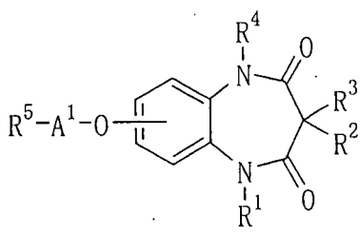
Ultra-rapid delayed rectifier K^+ current (I_{Kur}), K^+ current encoded by Kv1.5, has been identified as K^+ channel that is specifically expressed only in human atria (Cric. Res., 73, 1061-1076 (1993), J. Physiol., 491, 31-50 (1996) and Cric. Res., 80, 572-579 (1997)). Muscarine potassium current (I_{KAch}) encoded by two genes called GIRK1 and GIRK4 is known as a K^+ channel specifically expressed in human atria (Nature 374, 135-141 (1995)). Accordingly, a pharmacologically acceptable substance that selectively blocks the I_{Kur} current (the Kv1.5 channel) or the I_{KAch} current (GIRK1/4 channel) can act selectively on the atrial muscle and is considered effective to exclude the proarrhythmic effect caused by prolonged action potential duration of the ventricular muscle.

DISCLOSURE OF THE INVENTION

The present inventors conducted extensive research to develop a compound that blocks the I_{Kur} current (Kv1.5 channel) and/or the I_{KAch} current (GIRK1/4 channel) potently and more selectively than other K^+ channels. As a result, the inventors found that a novel benzodiazepine compound represented by General Formula (1) below could be the desired compound. The present invention has been accomplished based on the above findings.

The present invention provides benzodiazepine compounds, and pharmaceutical compositions comprising the benzodiazepine compounds as summarized in items 1 to 13 below.

Item 1. A benzodiazepine compound represented by General Formula (1)



(1)

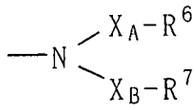
or a salt thereof,

wherein R^1, R^2, R^3, and R^4 are each independently hydrogen or lower alkyl;

R^2 and R^3 may be linked to form lower alkylene;

A^1 is lower alkylene optionally substituted with one or more hydroxy; and

R^5 is group represented by



wherein R^6 and R^7 are each independently hydrogen or organic group;

X_A and X_B are each independently bond, lower alkylene, lower alkenylene, -CO-, $-SO_2-$, $-SO_2$-lower alkylene, -CO-lower alkylene, -CO-lower alkenylene, lower alkylene-N(lower alkyl)-CO-lower alkylene, lower alkylene-N(lower alkyl)-, lower alkylene-N(lower alkyl)-CO- or lower alkylene-O-.

Item 2. A benzodiazepine compound represented by General Formula (1) or a salt thereof according to item 1,

wherein R^6 and R^7 are each independently hydrogen, lower alkyl, cyclo lower alkyl, aryl or heterocyclic group.

Item 3. A benzodiazepine compound represented by General Formula (1) or a salt thereof according to item 2,

wherein R^6 and R^7 are each independently hydrogen, lower alkyl, cyclo lower alkyl, aryl or saturated or unsaturated monocyclic or polycyclic heterocyclic group containing at least one hetero atom selected from among oxygen, sulfur and nitrogen.

Item 4. A benzodiazepine compound represented by General Formula (1) or a salt thereof according to item 3,

wherein R^6 and R^7 are each independently hydrogen, lower alkyl, cyclo lower alkyl, phenyl, naphthyl, furyl, thienyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, pyrrolyl, triazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, imidazo[2,1-b]thiazolyl, thieno[2,3-b]pyrazinyl, 2,3-dihydroimidazo[2,1-b]thiazolyl, benzothiazolyl, indolyl, imidazo[1,2-a]pyridyl, benzothienyl, benzimidazolyl, 2,3-dihydrobenzo[b]furyl, benzofuryl, indazolyl,

furo[2,3-c]pyridyl, furo[3,2-c]pyridyl, thieno[2,3-c]pyridyl, thieno[3,2-c]pyridyl, thieno[2,3-b]pyridyl, benzo[1,3]dioxolyl, benzisoxazolyl, pyrazolo[2,3-a]pyridyl, indolizinyl, 2,3-dihydroindolyl, isoquinolyl, 1,2,3,4-tetrahydro-1H-isoquinolyl, carbostyril, 3,4-dihydrocarbostyril, quinolyl, chromanyl, 5,6,7,8-tetrahydroisoquinolyl, 3,4-dihydro-1H-isoquinolyl, naphthyridinyl, 1,4-benzodioxanyl, cinnolinyl, quinoxalinyl, or 2,3-dihydrobenz-1,4-oxazinyl, each of which is optionally substituted.

Item 5. A benzodiazepine compound represented by General Formula (1) or a salt thereof according to item 4,

wherein R^6 and R^7 are each one of the following (1) to (52):

(1) hydrogen,

(2) lower alkyl,

(3) cyclo lower alkyl,

(4) phenyl optionally substituted with one or more substituents selected from the group consisting of the following (4-1) to (4-25):

(4-1) cyano,

(4-2) hydroxy,

(4-3) halogen,

(4-4) lower alkyl optionally substituted with one or more substituents selected from the group consisting of halogen, imidazolyl and morpholinyl,

(4-5) lower alkoxy optionally substituted with one or more substituents selected from the group consisting of amino and lower alkyl amino,

(4-6) pyridyl,

(4-7) thienyl,

(4-8) piperazinyl optionally substituted with one or more lower alkyl,

(4-9) phenyl,

(4-10) pyrazolyl optionally substituted with one or more lower alkyl,

(4-11) pyrimidinyl optionally substituted with one or more lower alkyl,

(4-12) piperidyl optionally substituted with one or more lower alkyl,

(4-13) furyl,

(4-14) carboxy,

(4-15) lower alkoxycarbonyl,

(4-16) amino optionally substituted with one or more substituents selected from the group consisting of lower alkanoyl and lower alkylsulfonyl,

(4-17) lower alkylthio,

(4-18) triazolyl,

(4-19) imidazolyl,

(4-20) pyrrolidinyl optionally substituted with one or more oxo,

(4-21) lower alkylsulfonyl,

(4-22) lower alkylenedioxy optionally substituted with one or more halogen,

(4-23) nitro,

(4-24) oxazolyl, and

(4-25) thiazolyl optionally substituted with one or more lower alkyl,

(5) naphthyl,

(6) furyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl optionally substituted with halogen, carboxy, sulfo, pyridyloxy, lower alkoxycarbonyl and phenyl,

(7) thienyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower alkylenedioxy, carboxy, halogen, pyridyl, lower alkoxy, lower alkoxycarbonyl, oxazolyl and furyl,

(8) imidazolyl optionally substituted with one or more substituents selected from the group consisting of phenyl, lower alkyl and halogen,

(9) pyrazolyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl optionally substituted with halogen, halogen, phenyl optionally substituted with lower alkoxy, furyl and thienyl,

(10) oxazolyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl and phenyl,

(11) isoxazolyl optionally substituted with one or more substituents selected from the group consisting of phenyl, lower alkyl, thienyl and furyl,

(12) thiazolyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl optionally substituted with lower alkoxy, phenyl and lower alkanoylamino,

(13) pyrrolyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl and lower alkoxycarbonyl,

(14) triazolyl optionally substituted with one or more lower alkyl,

(15) pyridyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl optionally substituted with halogen, oxo, hydroxy, lower alkoxy, halogen, pyrrolidinyl, morpholinyl and thienyl,

(16) pyrimidinyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl and phenyl,

(17) pyridazinyl,

(18) pyrazinyl,

(19) imidazo[2,1-b]thiazolyl optionally substituted with one or more halogen,

(20) thieno[2,3-b]pyrazinyl,

(21) 2,3-dihydroimidazo[2,1-b]thiazolyl optionally substituted with one or more phenyl,

(22) benzothiazolyl optionally substituted with one or more lower alkyl,

(23) indolyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower alkanoyl and halogen,

(24) imidazo[1,2-a]pyridyl optionally substituted with one or more lower alkyl,

(25) benzothienyl optionally substituted with one or more lower alkyl,

(26) benzimidazolyl optionally substituted with one or more lower alkyl,

(27) 2,3-dihydrobenzo[b]furyl,

(28) benzofuryl optionally substituted with one or more halogen,

(29) indazolyl optionally substituted with one or more lower alkyl,

(30) furo[2,3-c]pyridyl optionally substituted with one or more substituents selected from the group consisting of oxo and lower alkyl,

(31) furo[3,2-c]pyridyl optionally substituted with one or more substituents selected from the group consisting of oxo, lower alkyl optionally substituted with halogen, halogen, furyl, pyridyl and phenyl optionally substituted with one or more substituents selected from the group consisting of amino and lower alkoxy,

(32) thieno[2,3-c]pyridyl optionally substituted with one or more substituents selected from the group consisting of oxo group and lower alkyl,

(33) thieno[3,2-c]pyridyl optionally substituted with one or more substituents selected from the group consisting of oxo and lower alkyl,

(34) thieno[2,3-b]pyridyl,

(35) benzo[1,3]dioxolyl optionally substituted with one or more halogen,

(36) benzisoxazolyl,

(37) pyrazolo[2,3-a]pyridyl,

(38) indolizinyl,

(39) 2,3-dihydroindolyl optionally substituted with one or more substituents selected from the group consisting of oxo, lower alkyl and lower alkanoyl,

(40) isoquinolyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl, halogen and oxo,

(41) 1,2,3,4-tetrahydro-1H-isoquinolyl optionally substituted with one or more oxo,

(42) carbostyril optionally substituted with one or more lower alkoxy,

(43) 3,4-dihydrocarbostyril optionally substituted with one or more lower alkoxy,

(44) quinolyl optionally substituted with one or more substituents selected from the group consisting of amino optionally substituted with one or two lower alkyl, lower alkoxy, lower alkyl and oxo,

(45) chromanyl optionally substituted with one or more lower alkyl,

(46) 5,6,7,8-tetrahydroisoquinolyl optionally substituted with one or more oxo,

(47) 3,4-dihydro-1H-isoquinolyl optionally substituted with one or more oxo,

(48) naphthyridinyl,

(49) 1,4-benzodioxanyl,

(50) cinnolinyl,

(51) quinoxalinyl, or

(52) 2,3-dihydrobenz-1,4-oxazinyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl and oxo.

Item 6. A benzodiazepine compound represented by General Formula (1) or a salt thereof according to item 5,

wherein R^6 and R^7 are each one of the following (4a), (6a), (7a), (15a), (30a), (31a), (32a), (33a), (40a) and (44a):

(4a) phenyl optionally substituted with one or more substituents selected from the group consisting of the following (4a-1), (4a-4) and (4a-6):

(4a-1) cyano,

(4a-4) lower alkyl optionally substituted with one or more halogen, and

(4a-6) pyridyl,

(6a) furyl,

(7a) thienyl,

(15a) pyridyl optionally substituted with one or more lower alkyl,

(30a) furo[2,3-c]pyridyl optionally substituted with one or more oxo,

(31a) furo[3,2-c]pyridyl optionally substituted with one or more substituents selected from the group consisting of oxo and lower alkyl,

(32a) thieno[2,3-c]pyridyl optionally substituted with one or more oxo,

(33a) thieno[3,2-c]pyridyl optionally substituted with one or more oxo,

(40a) isoquinolyl optionally substituted with one or more oxo, and

(44a) quinolyl optionally substituted with one or more oxo.

Item 7. A benzodiazepine compound represented by General Formula (1) or a salt thereof according to item 6, which is selected from the group consisting of the following compounds:

1-ethyl-3,3,5-trimethyl-7-{3-[(2-pyridin-3-ylethyl)pyridin-4-yl methylamino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione trihydrochloride,

3,3,5-trimethyl-1-propyl-7-{3-[(2-pyridin-3-ylethyl)pyridin-4-yl methylamino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione trihydrochloride,

1,5-diethyl-3,3-dimethyl-7-{3-[(2-pyridin-3-ylethyl)pyridin-4-yl methylamino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione trihydrochloride,

1,3,3,5-tetramethyl-7-{3-[(2-pyridin-3-ylethyl)pyridin-4-ylmethyl amino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione trihydrochloride,

1-ethyl-3,3,5-trimethyl-7-(3-{[2-(1-oxo-1H-isoquinolin-2-yl)ethyl]pyridin-4-ylmethylamino}propoxy)-1,5-dihydrobenzo[b][1,4] diazepine-2,4-dione dihydrochloride,

1-ethyl-3,3,5-trimethyl-7-(3-{[2-(7-oxo-7H-furo[2,3-c]pyridin-6-yl)ethyl]pyridin-4-ylmethylamino}propoxy)-1,5-dihydrobenzo[b] [1,4]diazepine-2,4-dione dihydrochloride,

N-methyl-N-(2-{pyridin-4-ylmethyl-[3-(1,3,3,5-tetramethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl] amino}ethyl)benzamide dihydrochloride,

1,3,3,5-tetramethyl-7-{3-[(2-methylbenzyl)-(2-pyridin-3-ylethyl) amino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride,

1,3,3,5-tetramethyl-7-{3-[(2-pyridin-3-ylethyl)-(quinolin-4-yl methyl)amino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione trihydrochloride,

1-ethyl-3,3,5-trimethyl-7-{3-[(3-methylpyridin-4-ylmethyl)-(2-pyridin-3-ylethyl)amino]propoxy}-1,5-dihydrobenzo[b][1,4] diazepine-2,4-dione trihydrochloride,

1-ethyl-3,3,5-trimethyl-7-(3-{[2-(2-oxo-2H-quinolin-1-yl)ethyl] pyridin-4-ylmethylamino}propoxy)-1,5-dihydrobenzo[b][1,4] diazepine-2,4-dione dihydrochloride,

1-ethyl-3,3,5-trimethyl-7-(3-{[2-(7-oxo-7H-thieno[2,3-c]pyridin-6-yl)ethyl]pyridin-4-ylmethylamino}propoxy)-1,5-dihydrobenzo[b] [1,4]diazepine-2,4-dione dihydrochloride,

4-({[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]-[2-(1-oxo-1H-isoquinolin-2-

yl)ethyl]amino}methyl)benzonitrile,
1-ethyl-3,3,5-trimethyl-7-(3-{[2-(1-oxo-1H-isoquinolin-2-yl)ethyl]thiophen-3-ylmethylamino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione,
1-ethyl-7-(3-{furan-2-ylmethyl-[2-(1-oxo-1H-isoquinolin-2-yl)ethyl]amino}propoxy)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione,
7-{3-[benzyl-(2-pyridin-3-ylethyl)amino]propoxy}-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione,
3-{[[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]-(2-pyridin-3-ylethyl)amino]methyl}benzonitrile,
1-ethyl-3,3,5-trimethyl-7-{3-[(2-pyridin-3-ylbenzyl)-(2-pyridin-3-ylethyl)amino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione,
4-({[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]-[2-(7-oxo-7H-furo[2,3-c]pyridin-6-yl)ethyl]amino}methyl)benzonitrile,
1-ethyl-3,3,5-trimethyl-7-{3-[[2-(7-oxo-7H-furo[2,3-c]pyridin-6-yl)ethyl]-(4-trifluoromethylbenzyl)amino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione,
1-ethyl-3,3,5-trimethyl-7-(3-{(2-methylbenzyl)-[2-(7-oxo-7H-furo[2,3-c]pyridin-6-yl)ethyl]amino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione,
1-ethyl-3,3,5-trimethyl-7-(3-{[2-(7-oxo-7H-furo[2,3-c]pyridin-6-yl)ethyl]thiophen-2-ylmethylamino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione,
1-ethyl-3,3,5-trimethyl-7-(3-{[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]pyridin-4-ylmethylamino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride,
1-ethyl-3,3,5-trimethyl-7-(3-{[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]pyridin-3-ylmethylamino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione,
1-ethyl-3,3,5-trimethyl-7-(3-{[2-(4-oxo-4H-thieno[3,2-c]pyridin-5-yl)ethyl]pyridin-3-ylmethylamino}propoxy)-1,5-dihydrobenzo[b]

[1,4]diazepine-2,4-dione,
1-ethyl-3,3,5-trimethyl-7-{3-[[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-(4-methylpyridin-3-ylmethyl)amino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione,
1-ethyl-3,3,5-trimethyl-7-(3-{(2-methylpyridin-3-ylmethyl)-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione,
1-ethyl-3,3,5-trimethyl-7-(3-{(4-methylpyridin-3-ylmethyl)-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione,
1-ethyl-3,3,5-trimethyl-7-(3-{(2-methylpyridin-3-ylmethyl)-[2-(4-oxo-4H-thieno[3,2-c]pyridin-5-yl)ethyl]amino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione,
1-ethyl-3,3,5-trimethyl-7-{3-[[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-(2-propylpyridin-3-ylmethyl)amino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride,
N-[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]-N-(2-pyridin-3-ylethyl)benzenesulfonamide hydrochloride,
7-(3-{(2,6-dimethylpyridin-3-ylmethyl)-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}propoxy)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride,
N-[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]-N-(2-pyridin-3-ylethyl)benzamide hydrochloride, and
N-[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]-N-[2-(1-oxo-1H-isoquinolin-2-yl)ethyl]benzenesulfonamide.

Item 8. A pharmaceutical composition comprising a benzodiazepine compound represented by Formula (1) or a salt thereof according to claim 1, and a pharmacologically acceptable carrier.

Item 9. A pharmaceutical composition according to item 8 for preventing and/or treating arrhythmia.

Item 10. A benzodiazepine compound represented by Formula (1) or a salt thereof according to item 1 for use in the pharmaceutical

composition.

Item 11. Use of a benzodiazepine compound represented by Formula (1) or a salt thereof according to item 1 as a pharmaceutical composition.

Item 12. Use of a benzodiazepine compound represented by Formula (1) or a salt thereof according to item 1 for the production of a pharmaceutical composition.

Item 13. A method of preventing and/or treating arrhythmia, comprising administering to a patient a benzodiazepine compound represented by Formula (1) or a salt thereof according to item 1.

The groups represented by R^1, R^2, R^3, R^4, R^5, R^6, R^7, A^1, X_A and X_B, in the specification are described below.

Examples of "organic group" include lower alkyl, cyclo lower alkyl, aryl such as phenyl and naphthyl, heterocyclic group such as the (6) to (52) for R^6 and R^7.

Examples of "heterocyclic group" include saturated or unsaturated monocyclic or polycyclic heterocyclic group containing at least one hetero atom selected from among oxygen, sulfur and nitrogen. More preferable heterocyclic group may be the group such as :

-unsaturated 3 to 8-membered, preferably 5 or 6- membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, and its N-oxide, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.), tetrazolyl (e.g., 1H-tetrazolyl, 2H-tetrazolyl, etc.), dihydrotriazinyl (e.g., 4,5-dihydro-1,2,4-triazinyl, 2,5-dihydro-1,2,4-triazinyl, etc.), etc.;

-saturated 3 to 8-membered, preferably 5 or 6- membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, azetidinyl, pyrrolidinyl, imidazolidinyl, piperidinyl, pyrazolidinyl, piperazinyl, etc.;

-unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 5 nitrogen atom(s), for example, indolyl, dihydroindolyl (e.g., 2,3- dihydroindolyl, etc.), isoindolyl, indolizinyl, benzimidazolyl, uinolyl, isoquinolyl, dihydroisoquinolyl (e.g., 3,4-dihydro-1H-isoquinolyl, etc.), tetrahydroisoquinolyl (e.g., 1,2,3,4-tetrahydro-1H-isoquinolyl, 5,6,7,8-tetrahydroisoquinolyl, etc.), carbostyril, dihydrocarbostyril (e.g., 3,4-dihydrocarbostyril, etc.), indazolyl, benzotriazolyl, tetrazolopyridyl, tetrazolopyridazinyl (e.g., tetrazolo[1,5-b]pyridazinyl, etc.), dihydrotriazolopyridazinyl, imidazopyridyl (e.g., imidazo[1,2-a]pyridyl, etc.,), naphthyridinyl, cinnolinyl, quinoxalinyl, pyrazolopyridyl (e.g., pyrazolo[2,3-a]pyridyl, etc.) etc.;

-unsaturated 3 to 8-membered, preferably 5 or 6- membered heteromonocyclic group containing 1 to 2 oxygen atom(s), for example, furyl, etc.;

-unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 3 oxygen atom(s), for example, benzofuryl, dihydrobenzofuryl (e.g. 2,3-dihydrobenzo[b]furyl, etc.), chromanyl, benzodioxanyl (e.g., 1,4-benzodioxanyl, etc.), dihydrobenzoxazinyl (e.g., 2,3-dihydrobenz-1,4-oxazinyl, etc.), benzodioxolyl (benzo[1,3]dioxolyl, etc.), etc.;

-unsaturated 3 to 8-membered, preferably 5 or 6- membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4- oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.), etc.;

-saturated 3 to 8-membered, preferably 5 or 6- membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, morpholinyl, etc. ;

-unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, benzoxazolyl, benzoxadiazolyl, benzisoxazolyl, furopyridyl (e.g., furo[2,3-b]pyridyl, furo[3,2-c]pyridyl, etc.), etc.;

-unsaturated 3 to 8-membered, preferably 5 or 6- membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolyl, 1,2-thiazolyl, thiazolinyl, thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,2,3-thiadiazolyl, etc.) , etc.;

-saturated 3 to 8-membered, preferably 5 or 6- membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolidinyl, etc.;

-unsaturated 3 to 8-membered, preferably 5 or 6- membered heteromonocyclic group containing a sulfur atom, for example, thienyl, etc.;

-unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 3 sulfur atom(s), for example, benzothienyl (e.g. benzo[b]thienyl, etc.),

-unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, benzothiazolyl, benzothiadiazolyl, thienopyridyl (e.g., thieno[2,3-b]pyridyl, thieno[2,3-c]pyridyl, thieno[3,2-c]pyridyl, etc.), imidazothiazolyl (e.g., imidazo[2,1-b]thiazolyl, etc.), dihydroimidazothiazolyl (e.g., 2,3-dihydroimidazo[2,1-b]thiazolyl, etc.), thienopyrazinyl (e.g., thieno[2,3-b]pyrazinyl, etc.), etc. and the like; wherein said heterocyclic group may be substituted by one or more suitable substituent(s).

Examples of "lower alkyl" include linear or branched alkyl groups having 1 to 6 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, sec-butyl, n-pentyl,

neopentyl, n-hexyl, isohexyl, and 3-methylpentyl.

Examples of "lower alkylene" include linear or branched alkylene groups having 1 to 6 carbon atoms, such as methylene, ethylene, trimethylene, 2-methyltrimethylene, 2,2-dimethyltrimethylene, 1-methyltrimethylene, methylmethylene, ethylmethylene, tetramethylene, pentamethylene, and hexamethylene.

Examples of "cyclo lower alkyl" include linear or branched cyclo alkyl having 3 to 6 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

Examples of "lower alkoxy" include linear or branched alkoxy groups having 1 to 6 carbon atoms, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, tert-butoxy, sec-butoxy, n-pentyloxy, neopentyloxy, n-hexyloxy, isohexyloxy, and 3-methylpentyloxy.

Examples of "halogen" include fluorine, chlorine, bromine, and iodine.

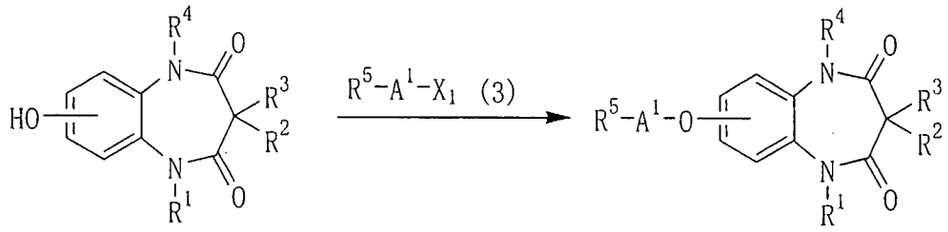
Examples of "lower alkylenedioxy" include linear or branched alkylene groups having 1 to 4 carbon atoms, such as methylenedioxy, ethylenedioxy, trimethylenedioxy, and tetramethylenedioxy.

Examples of "lower alkanoyl" include linear or branched alkanoyl groups having 1 to 6 carbon atoms, such as formyl, acetyl, propionyl, butyryl, isobutyryl, pentanoyl, tert-butylcarbonyl, and hexanoyl.

The term "one or more" may be preferably 1 to 6, more preferably 1 to 3.

The benzodiazepine compound of the present invention represented by Formula (1) or its salt can be produced by, for example, the processes shown in the following reaction formulas.

Reaction Formula 1



(2) (1)

wherein R^1, R^2, R^3, R^4, R^5, and A^1 are the same as above, and X_1 is halogen or hydroxyl.

The reaction of the compound of Formula (2) with the compound of Formula (3) wherein X_1 is halogen can be performed in a usual inert solvent or without using any solvents in the presence or absence of a basic compound.

Examples of inert solvents include water; ethers such as dioxane, tetrahydrofuran, diethyl ether, diethylene glycol dimethyl ether, and ethylene glycol dimethyl ether; aromatic hydrocarbons such as benzene, toluene, and xylene; halogenated hydrocarbons such as dichloromethane, dichloroethane, chloroform, and carbon tetrachloride; lower alcohols such as methanol, ethanol, and isopropanol; ketones such as acetone and methyl ethyl ketone; polar solvents such as dimethylformamide (DMF), dimethyl sulfoxide (DMSO), hexamethylphosphoric triamide, and acetonitrile; and mixed solvents of such solvents.

The basic compound may be selected from various known compounds. Examples of such compounds include inorganic bases, for example, alkali metal hydroxides such as sodium hydroxide, potassium hydroxide, cesium hydroxide, and lithium hydroxide; alkali metal carbonates such as sodium carbonate, potassium carbonate, cesium carbonate, lithium carbonate, lithium hydrogencarbonate, sodium hydrogencarbonate, and potassium hydrogencarbonate; alkali metals such as sodium and potassium; sodium amide; sodium hydride; and potassium hydride; and organic bases, for example, alkali metal alcoholates such as sodium methoxide, sodium ethoxide, potassium methoxide, and potassium ethoxide; triethylamine; tripropylamine; pyridine; quinoline; 1,5-diazabicyclo[4.3.0]nonene-5 (DBN);

1,8-diazabicyclo[5.4.0]undecene-7 (DBU); and 1,4-diazabicyclo[2.2.2]octane (DABCO). These basic compounds can be used singly or in a combination of two or more.

The above reaction may be performed by adding an alkali metal iodide such as potassium iodide or sodium iodide to the reaction system, as required.

The compound of Formula (3) is usually used in an amount of at least 0.5 moles, and preferably 0.5 to 10 moles, per mole of the compound of Formula (2).

The basic compound is usually used in an amount of 0.5 to 10 moles, and preferably 0.5 to 6 moles, per mole of the compound of Formula (2).

The reaction is usually performed at a temperature of 0°C to 250°C, and preferably 0°C to 200°C, and is usually completed in about 1 to about 80 hours.

The reaction of the compound of Formula (2) with the compound of Formula (3) wherein X_1 is hydroxyl is performed in an appropriate solvent in the presence of a condensing agent.

Examples of solvents usable herein include water; halogenated hydrocarbons such as chloroform, dichloromethane, dichloroethane, and carbon tetrachloride; aromatic hydrocarbons such as benzene, toluene, and xylene; ethers such as diethyl ether, diisopropyl ether, tetrahydrofuran, and dimethoxyethane; esters such as methyl acetate, ethyl acetate, and isopropyl acetate; alcohols such as methanol, ethanol, isopropanol, propanol, butanol, 3-methoxy-1-butanol, ethyl cellosolve, and methyl cellosolve; aprotic polar solvents such as acetonitrile, pyridine, acetone, N,N-dimethyl formamide, dimethyl sulfoxide, and hexamethylphosphoric triamide; and mixtures of such solvents.

Examples of condensing agents include azocarboxylates such as di-tert-butyl azodicarboxylate, N,N,N',N'-tetramethyl azodicarboxamide, 1,1'-(Azodicarbonyl)dipiperidine, diethyl azodicarboxylate; and phosphorus compounds such as triphenylphosphine and tri-n-butylphosphine.

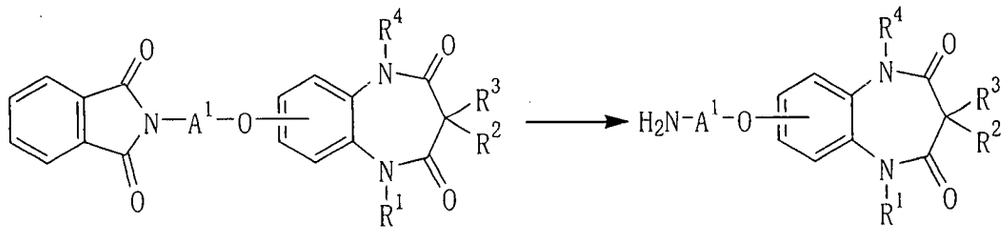
In this reaction, the compound (3) is usually used in an

amount of at least 1 mole, and preferably 1 to 2 moles, per mole of the compound (2).

The condensing agent is usually used in an amount of at least 1 mole, and preferably 1 to 2 moles, per mole of the compound (2).

The reaction proceeds usually at 0 to 200°C, and preferably at about 0 to about 150°C, and is completed in about 1 to about 10 hours.

Reaction Formula 2



(1a) (1b)

wherein R^1, R^2, R^3, R^4 and A^1 are the same as above.

The reaction converting the compound of Formula (1a) to the compound of Formula (1b) can be carried out by either reacting the compound (1a) with hydrazine in a suitable solvent, or by hydrolysis. Here, hydrazine hydrate may be used as the hydrazine.

Examples of solvents used for reaction of the hydrazine include water; halogenated hydrocarbons such as chloroform dichloromethane and dichloroethane; aromatic hydrocarbons such as benzene, toluene, and xylene; ethers such as diethyl ether, diisopropyl ether, tetrahydrofuran, and dimethoxyethane; esters such as methyl acetate and ethyl acetate; and aprotic polar solvents such as N,N-dimethylformamide, dimethylsulfoxide, and hexamethylphosphoric triamide; and mixtures of such solvents. Other examples of solvents used for the reaction include alcohols such as methanol, ethanol, propanol, butanol, 3-methoxy-1-butanol, ethyl cellosolve or methyl cellosolve; acetonitrile, pyridine, acetone, and mixtures of such solvents.

The hydrazine is usually used in an amount of at least about 1 mole, and preferably about 1 to about 5 moles, per mole of the compound (1a).

The reaction proceeds usually at about 0 to about 120°C, and preferably at about 0 to about 100°C, and is usually completed in about 0.5 to about 5 hours.

The hydrolysis of the compound of Formula (1a) is performed in an appropriate solvent or without using any solvents in the presence of an acid or a basic compound.

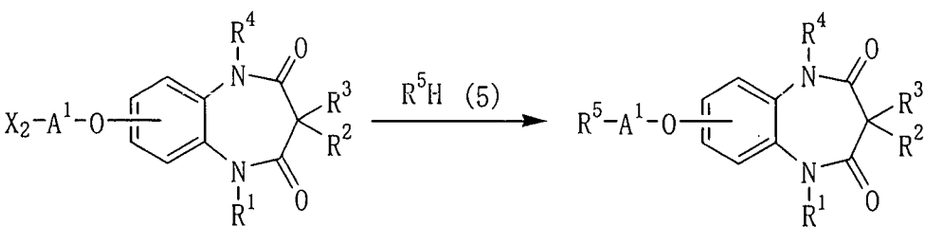
Examples of solvents usable herein include water; lower alcohols such as methanol, ethanol, and isopropanol; ketones such as acetone and methyl ethyl ketone; ethers such as dioxane, tetrahydrofuran and ethylene glycol dimethyl ether; fatty acids such as acetic acid and formic acid; and mixtures of such solvents.

Examples of acids include mineral acids such as hydrochloric acids, sulfuric acid and hydrobromic acid; aliphatic acids such as formic acid, acetic acid; and sulfonic acids such as p-toluenesulfonic acid.

Examples of basic compounds include metal carbonates such as sodium carbonate and potassium carbonate; and metal hydroxides such as sodium hydroxide and potassium hydroxide.

The reaction proceeds usually at room temperature to about 200°C, and preferably at room temperature to about 150°C, and is usually completed in about 10 minutes to 25 hours.

Reaction Formula 3

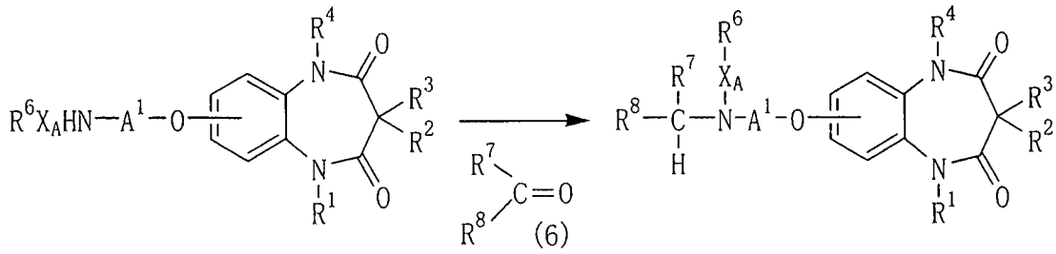


(4) (1)

wherein R^1, R^2, R^3, R^4, R^5, and A^1 are the same as above, and X_2 is halogen, alkanesulfonyloxy, or arylsulfonyloxy.

The reaction of the compound of Formula (4) with the compound of Formula (5) is performed under the same reaction conditions as those for the reaction of the compound of Formula (3), in which X_1 is halogen, with the compound of Formula (2) in Reaction Formula 1.

Reaction Formula 4



(1c) (6) (1d)

wherein R^1, R^2, R^3, R^4, R^6, R^7 and A^1 are the same as above; and R^8 is hydrogen or lower alkyl;

provided that the alkylene moiety of $-CHR^7R^8$ contains no more than 6 carbon atoms, and $-CHR^8$ is the same as X_B in which alkylene is contained.

The reaction of the compound of Formula (1c) and the compound of Formula (6) is carried out, for example, in the presence of a reducing agent in a suitable solvent or without using any solvents.

Examples of solvents usable herein are water; lower alcohols such as methanol, ethanol, isopropanol, butanol, *tert*-butanol and ethylene glycol; acetonitrile; aliphatic acids such as formic acid and acetic acid; ethers such as diethyl ether, tetrahydrofuran, dioxane, monoglyme and diglyme; aromatic hydrocarbons such as benzene, toluene and xylene; halogenated hydrocarbons such as dichloromethane, dichloroethane, chloroform, and carbon tetrachloride; and mixtures of such solvents, etc.

Examples of reducing agents are aliphatic acids such as formic acid and acetic acid; aliphatic acid alkali metal salts such as sodium formate and sodium acetate; hydride reducing agents such as sodium borohydride, sodium cyanoborohydride, sodium triacetoxyborohydride and aluminium lithium hydride; mixtures of such hydride reducing agents; mixtures of aliphatic acids or aliphatic acid alkali metal salts with hydride reducing agents; catalytic hydrogenation reducing agents such as palladium black, palladium carbon, platinum oxide, platinum black, Raney nickel, etc.

When an aliphatic acid such as formic acid, or an aliphatic acid alkali metal salt such as sodium formate or sodium acetate is

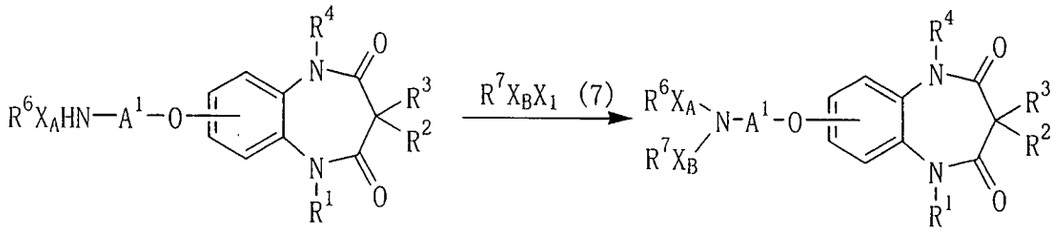
used as a reducing agent, a suitable reaction temperature is usually about room temperature to about 200°C, and preferably about 50 to about 150°C. The reaction is usually completed in about 10 minutes to about 10 hours. Such aliphatic acids and aliphatic acid alkali metal salts are usually used in a large excess relative to the compound of Formula (1c).

When a hydride reducing agent is used, a suitable reaction temperature is usually about -80 to about 100°C, and preferably about -80 to about 70°C. The reaction is usually completed in about 30 minutes to about 60 hours. The hydride reducing agent is usually used in an amount of about 1 to about 20 moles, and preferably about 1 to about 10 moles, per mole of the compound of Formula (1c). In particular, when aluminium lithium hydride is used as a hydride reducing agent, it is preferable to use diethyl ether, tetrahydrofuran, dioxane, monoglyme, diglyme, or like ethers; or benzene, toluene, xylene, or like aromatic hydrocarbons as a solvent. Trimethylamine, triethylamine, *N*-ethyldiisopropylamine, or like amines; or molecular sieves 3A (MS-3A), molecular sieves 4A (MS-4A), or like molecular sieves may be introduced into the reaction system of the reaction.

When a catalytic hydrogenation reducing agent is used, the reaction is usually carried out at about -30 to about 100°C, and preferably about 0 to about 60°C, in a hydrogen atmosphere usually about 1 to about 20 atm, and preferably about 1 to about 10 atm, or in the presence of formic acid, ammonium formate, cyclohexene, hydrazine hydrate, or like hydrogen donor. The reaction is usually completed in about 1 to about 12 hours. The catalytic hydrogenation reducing agent is usually used in an amount of about 0.1 to about 40 wt.%, and preferably about 1 to about 20 wt.%, relative to the compound of Formula (1c).

In the reaction of the compound of Formula (1c) with the compound of Formula (6), the compound of Formula (6) is usually used in an amount at least 1 mole, and preferably 1 to 5 moles, per mole of the compound of Formula (1c).

Reaction Formula 5

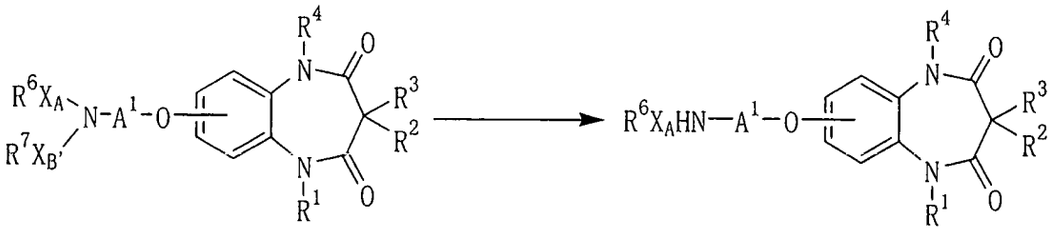


(1c) (1e)

wherein R^1, R^2, R^3, R^4, R^6, R^6, X_A, X_B, A^1 and X_1 are the same as above.

The reaction of the compound of Formula (1c) with the compound of Formula (7) is performed under the same reaction conditions as those for the reaction of the compound of Formula (3) with the compound of Formula (2) in Reaction Formula 1.

Reaction Formula 6



(1f) (1c)

wherein R^1, R^2, R^3, R^4, R^6, R^7, X_A, and A^1 are the same as above, and $X_{B'}$ is $-SO_2-$ or $-CO-$.

The reaction converting the compound of Formula (1f) to the compound of Formula (1c) can be carried out by hydrolysis. The hydrolysis reaction is performed in an appropriate solvent or without using any solvents in the presence of an acid or a basic compound.

Examples of useful solvents include water; lower alcohols such as methanol, ethanol, isopropanol and tert-butanol; ketones such as acetone and methylethyl ketone; ethers such as diethyl ether, dioxane, tetrahydrofuran, monoglyme and diglyme; aliphatic acids such as acetic acid and formic acid; esters such as methyl acetate and ethyl

acetate; halogenated hydrocarbons such as chloroform, dichloromethane, dichloroethane and carbon tetrachloride; dimethyl sulfoxide; N,N-dimethylformamide; and hexamethylphosphoric triamide; and mixtures of such solvents.

Examples of useful acids include mineral acids such as hydrochloric acid, sulfuric acid and hydrobromic acid; and organic acids such as formic acid, acetic acid, thioglycolic acid, trifluoroacetic acid and sulfonic acid (e.g., p-toluenesulfonic acid). Such acids can be used singly or in a combination.

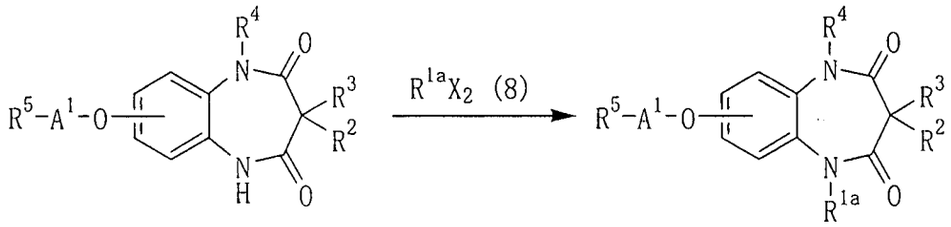
Examples of useful basic compounds include carbonates such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate and potassium hydrogencarbonate; and metal hydroxides such as sodium hydroxide, potassium hydroxide, calcium hydroxide and lithium hydroxide. Such basic compounds can be used singly or in a combination.

An acid or basic compound is usually used in an amount of at least about 1 mole, and preferably about 1 to about 10 moles, per mole of the compound of Formula (1f).

The reaction advantageously proceeds usually at about 0 to about 200°C, and preferably at about 0 to about 150°C, and usually finishes in about 10 minutes to about 80 hours.

In Reaction Formula 6, when $X_{B'}$ in the compound of Formula (1f) is $-SO_2-$, the compound of Formula (1c) can be easily produced from the compound of Formula (1f) when thiol acts on the compound under basic conditions. Any basic compound used in the aforementioned hydrolysis reaction can be used. Examples of thiols include aromatic mercaptans such as thiophenol; lower alkyl thiols such as thioglycolic acid; etc. The reaction is performed under the same reaction conditions as those for the aforementioned hydrolysis reaction, except that thiol is usually used in an amount of at least 0.5 moles, and preferably about 1 to about 3 moles per mole of the compound of Formula (1f).

Reaction Formula 7



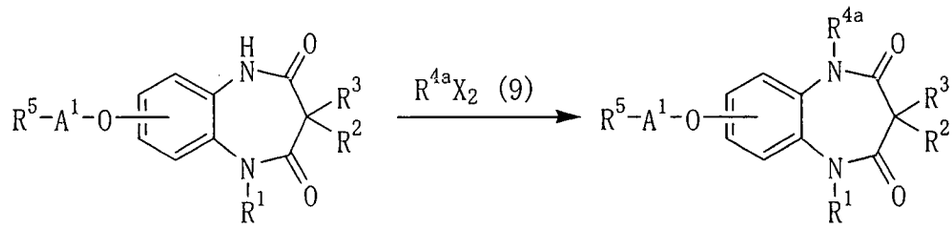
(1g) (1h)

wherein R^2, R^3, R^4, R^5, A^1, and X_2 are the same as above, and R^{1a} is lower alkyl.

The reaction of the compound of Formula (1g) with the compound of Formula (8) is performed under the same reaction conditions as those for the reaction of the compound of Formula (3), in which X_1 is halogen, with the compound of Formula (2) in Reaction Formula 1.

When R^4 in the compound of Formula (1g) is hydrogen in the reaction, a compound in which the first and fifth positions of the benzodiazepine skeleton are simultaneously substituted with R^{1a} may be produced.

Reaction Formula 8



(1i) (1j)

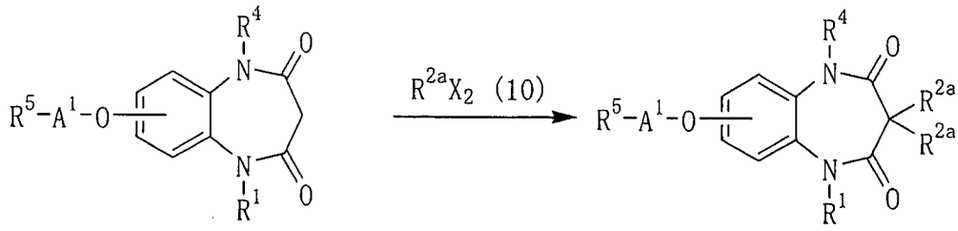
wherein R^1, R^2, R^3, R^5, A^1, and X_2 are the same as above, and R^{4a} is lower alkyl.

The reaction of the compound of Formula (1i) with the compound of Formula (9) is performed under the same reaction conditions as those for the reaction of the compound of Formula (3), in which X_1 is halogen, with the compound of Formula (2) in Reaction Formula

1.

When R^1 in the compound of Formula (1i) is hydrogen in the reaction, a compound in which the first and fifth positions of the benzodiazepine skeleton are simultaneously substituted with R^{4a} may be produced.

Reaction Formula 9



(1k) (11)

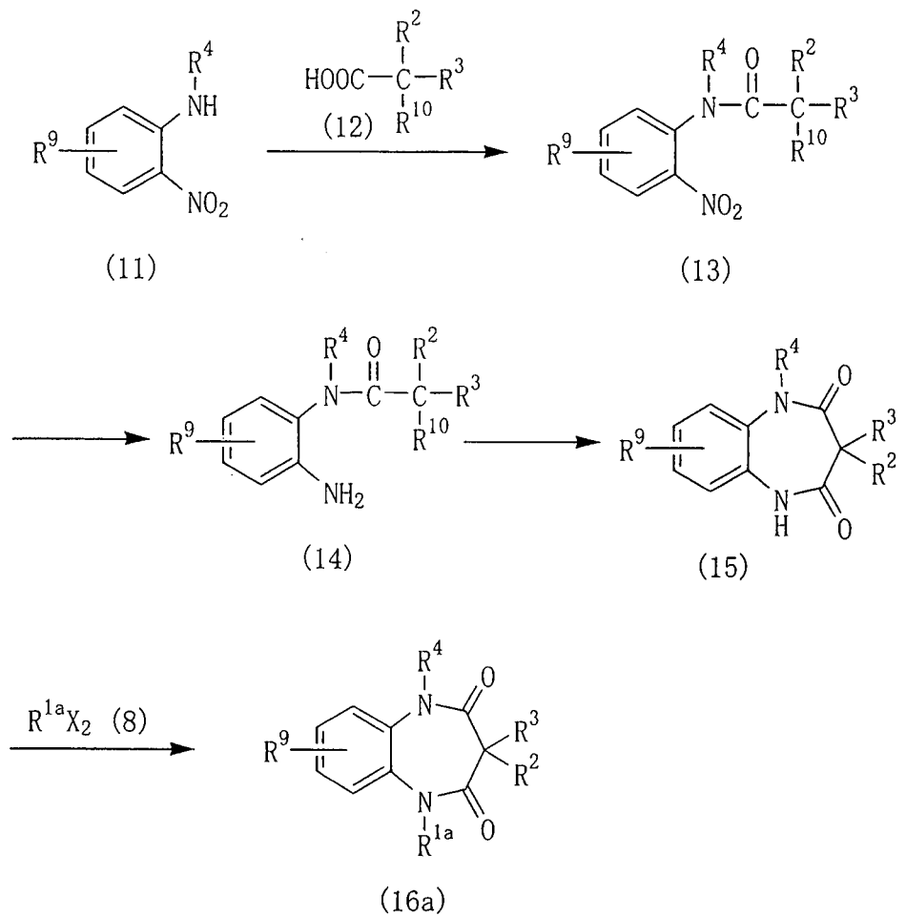
wherein R^1, R^4, R^5, A^1, and X_2 are the same as above, and R^{2a} is lower alkyl.

The reaction of the compound of Formula (1k) with the compound of Formula (10) is performed under the same reaction conditions as those for the reaction of the compound of Formula (3), in which X_1 is halogen, with the compound of Formula (2) in Reaction Formula 1.

When R^1 and/or R^4 is hydrogen in the reaction of the compound of Formula (1k) and the compound of Formula (10), the hydrogen may be replaced with R^{2a}.

The compound of Formula (2), which is used as a starting material in the above-mentioned reaction formula, can be easily produced by the process shown in the following reaction formulae.

Reaction Formula 10



wherein R^2, R^3, R^4, R^{1a}, and X_2 are the same as above. R^9 is lower alkoxy, and R^{10} is lower alkoxycarbonyl.

In the reaction of the compound of Formula (11) and the compound of Formula (12), the compound of Formula (11) is reacted with carboxylic acid of the compound of Formula (12) through a usual amide bond formation reaction. Conditions for known amide bond formation reactions can be easily employed in the above amide formation reaction. For example, the following reaction methods can be employed: (A) a mixed acid anhydride method, in which Carboxylic Acid (12) is reacted with an alkyl halocarboxylate to form a mixed acid anhydride, which is then reacted with Amine (11); (B) an active ester method, in which Carboxylic Acid (12) is converted to an activated ester such as a phenyl ester, p-nitrophenyl ester, N-hydroxysuccinimide ester,

1-hydroxybenzotriazole ester or the like, or an activated amide with benzoxazoline-2-thione, and the activated ester or amide is reacted with Amine (11); (C) a carbodiimide method, in which Carboxylic Acid (12) is subjected to a condensation reaction with Amine (11) in the presence of an activating agent such as dicyclohexylcarbodiimide, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (WSC), carbonyldiimidazole or the like; (D) other methods, for example, a method in which Carboxylic Acid (12) is converted to a carboxylic anhydride using a dehydrating agent such as acetic anhydride, and the carboxylic anhydride is then reacted with Amine (11), a method in which an ester of Carboxylic Acid (12) with a lower alcohol is reacted with Amine (11) at a high pressure and a high temperature, a method in which an acid halide of Carboxylic Acid (12), i.e., a carboxylic acid halide, is reacted with Amine (11), etc.

The mixed acid anhydride used in the mixed acid anhydride method (A) can be obtained by the known Schotten-Baumann reaction, and the obtained mixed acid anhydride is reacted with Amine (11), usually without being isolated, to thereby produce the compound of Formula (13). The Schotten-Baumann reaction is performed in the presence of a basic compound. Usable basic compounds include compounds conventionally used in the Schotten-Baumann reaction, such as triethylamine, trimethylamine, pyridine, dimethylaniline, N-ethyldiisopropylamine, dimethylaminopyridine, N-methylmorpholine, 1,5-diazabicyclo[4.3.0]nonene-5 (DBN), 1,8-diazabicyclo[5.4.0]undecene-7 (DBU), 1,4-diazabicyclo[2.2.2]octane (DABCO) and other organic bases; sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate and other carbonates; sodium hydroxide, potassium hydroxide, calcium hydroxide and other metal hydroxides; potassium hydride, sodium hydride, potassium, sodium, sodium amide, metal alcoholates such as sodium methylate and sodium ethylate, and other inorganic bases; etc. The reaction is usually performed at about -20 to about 150°C, and preferably at about 0 to about 100°C, usually for about 5 minutes to about 10 hours, and preferably for about 5 minutes to about 5 hours. The reaction of the obtained mixed acid anhydride

with Amine (11) is usually carried out at about -20 to about 150°C, and preferably at about 10 to about 50°C, usually for about 5 minutes to about 30 hours, and preferably for about 5 minutes to about 25 hours. Generally, the mixed acid anhydride method is performed in a solvent. Solvents used for conventional mixed acid anhydride methods are usable. Examples of usable solvents include chloroform, dichloromethane, dichloroethane, carbon tetrachloride and other halogenated hydrocarbons; benzene, toluene, xylene and other aromatic hydrocarbons; diethyl ether, diisopropyl ether, tetrahydrofuran, dimethoxyethane and other ethers; methyl acetate, ethyl acetate, isopropyl acetate and other esters; N,N-dimethylformamide, dimethylsulfoxide, hexamethylphosphoric triamide and other aprotic polar solvents; mixtures thereof; etc. Examples of alkyl halocarboxylates usable in the mixed acid anhydride method include methyl chloroformate, methyl bromoformate, ethyl chloroformate, ethyl bromoformate, isobutyl chloroformate, etc. In this method, Carboxylic Acid (12), an alkyl halocarboxylate, and Amine (11) are preferably used in equimolear amounts, but each of the alkyl halocarboxylate and Carboxylic Acid (12) can also be used in an amount of about 1 to about 1.5 moles per mole of Amine (11).

Method (C), in which a condensation reaction is carried out in the presence of an activating agent, can be performed in a suitable solvent in the presence or absence of a basic compound. Solvents and basic compounds usable in this method include those mentioned hereinafter as solvents and basic compounds usable in the method in which a carboxylic acid halide is reacted with Amine (11) mentioned above as one of the other methods (D). A suitable amount of activating agent is at least 1 mole, and preferably 1 to 5 moles per mole of Amine (11). When using WSC as an activating agent, addition of 1-hydroxybenzotriazol to the reaction system enables the reaction to proceed advantageously. The reaction is usually performed at about -20 to about 180°C, and preferably at about 0 to about 150°C, and is usually completed in about 5 minutes to about 90 hours.

When the method in which a carboxylic acid halide is reacted with Amine (11), mentioned above as one of the other methods

(D), is employed, the reaction is performed in the presence of a basic compound in a suitable solvent. Usable basic compounds include a wide variety of known basic compounds, such as those for use in the Schotten-Baumann reaction described above. Usable solvents include, in addition to those usable in the mixed acid anhydride method, methanol, ethanol, isopropanol, propanol, butanol, 3-methoxy-1-butanol, ethylcellosolve, methylcellosolve and other alcohols; acetonitrile; pyridine; acetone; water; etc. The ratio of the carboxylic acid halide to Amine (11) is not limited and can be suitably selected from a wide range. It is usually suitable to use, for example, at least about 1 mole, and preferably about 1 to about 5 moles of the carboxylic acid halide per mole of Amine (11). The reaction is usually performed at about -20 to about 180°C, and preferably at about 0 to about 150°C, and usually completed in about 5 minutes to about 30 hours.

The amide bond formation reaction shown in Reaction Formula 10 can also be performed by reacting Carboxylic Acid (12) with Amine (11) in the presence of a phosphorus compound serving as a condensing agent, such as triphenylphosphine, diphenylphosphinyl chloride, phenyl-N-phenylphosphoramide chloridate, diethyl chlorophosphate, diethyl cyanophosphate, diphenylphosphoric azide, bis(2-oxo-3-oxazolidinyl)phosphinic chloride or the like.

The reaction is carried out in the presence of a solvent and a basic compound usable for the method in which a carboxylic acid halide is reacted with Amine (11), usually at about -20 to about 150°C, and preferably at about 0 to about 100°C, and is usually completed in about 5 minutes to about 30 hours. It is suitable to use each of the condensing agent and Carboxylic Acid (12) in amounts of at least about 1 mole, and preferably about 1 to about 2 moles per mole of Amine (11).

The reaction converting the compound of Formula (13) to the compound of Formula (14) can be carried out by, for example, (1) reducing the compound of Formula (13) in a suitable solvent using a catalytic hydrogenation reducing agent, or (2) reducing the compound of Formula (13) in a suitable inert solvent using as a reducing agent a mixture of an acid with a metal or metal salt, a mixture of a metal or metal salt with an alkali metal hydroxide, sulfide, or ammonium

salt, or the like.

When using Method (1) in which a catalytic hydrogenation reducing agent is used, examples of usable solvents are water; acetic acid; alcohols such as methanol, ethanol and isopropanol; hydrocarbons such as n-hexane and cyclohexane; ethers such as dioxane, tetrahydrofuran, diethyl ether and diethylene glycol dimethyl ether; esters such as ethyl acetate and methyl acetate; aprotic polar solvents such as N,N-dimethylformamide; mixtures of such solvents; etc. Examples of usable catalytic hydrogenation reducing agents include palladium, palladium black, palladium carbon, platinum carbon, platinum, platinum black, platinum oxide, copper chromite, Raney nickel, etc. A reducing agent is usually used in an amount of about 0.02 times to equal to the weight of the compound of Formula (13). The reaction temperature is usually about -20 to about 150°C, and preferably about 0 to about 100°C. The hydrogen pressure is usually about 1 to 10 atm. The reaction is usually completed in about 0.5 to about 100 hours. An acid such as hydrochloric acid may be introduced into the reaction system of the reaction.

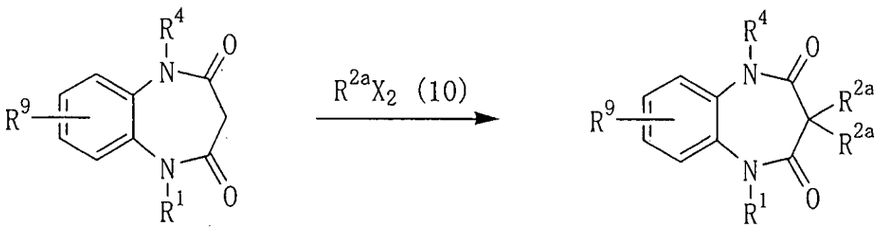
When using Method (2) above, a mixture of iron, zinc, tin, or tin (II) chloride, with a mineral acid such as hydrochloric acid, or sulfuric acid; or a mixture of iron, iron (II) sulfate, zinc, or tin, with an alkali metal hydroxide such as sodium hydroxide, a sulfide such as ammonium sulfide, aqueous ammonia solution, or an ammonium salt such as ammonium chloride, or the like can be used as a reducing agent. Examples of inert solvents are water; acetic acid; alcohols such as methanol and ethanol; ethers such as dioxane; mixtures of such solvents, etc. Conditions for the reduction reaction can be suitably selected according to the reducing agent to be used. For example, when a mixture of tin (II) chloride and hydrochloric acid is used as a reducing agent, it is advantageous to carry out the reaction at about 0 to about 150°C for about 0.5 to about 10 hours. A reducing agent is used in an amount of at least 1 mole, and preferably about 1 to 5 moles, per mole of the compound of Formula (13).

The reaction converting the compound of Formula (14) to the compound of Formula (15) is performed under the same reaction

conditions as those for the reaction of the compound of Formula (11) with the compound of Formula (12).

The reaction of the compound of Formula (15) with the compound of Formula (8) is performed under the same reaction conditions as those for the reaction of the compound of Formula (1g) with the compound of Formula (8) in Reaction Formula 7.

Reaction Formula 11



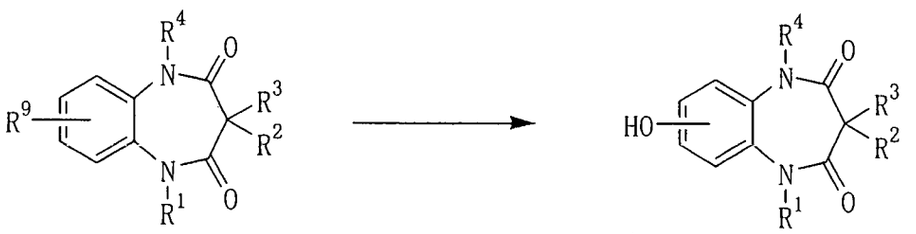
(17) (16b)

wherein R^1, R^{2a}, R^4, R^9, and X_2 are the same as above.

The reaction of the compound of Formula (17) with the compound of Formula (10) is performed under the same reaction conditions as those for the reaction of the compound of Formula (3), in which X_1 is halogen, with the compound of Formula (2) in Reaction Formula 1.

When R^1 and/or R^4 is hydrogen in the reaction of the compound of Formula (17) and the compound of Formula (10), the hydrogen atom may be replaced with R^{2a}.

Reaction Formula 12



(16) (2)

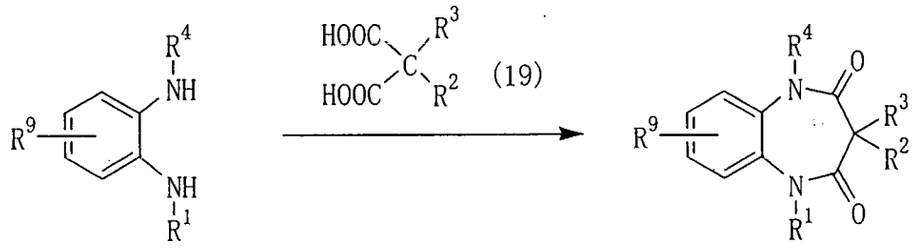
wherein R^1, R^2 R^3, R^4, and R^9 are the same as above.

The reaction converting the compound of Formula (16) to

the compound of Formula (2) can be carried out in a suitable solvent in the presence of an acid. Examples of solvents include water; lower alcohols such as methanol, ethanol, and isopropanol; ethers such as dioxane, tetrahydrofuran, and diethyl ether; halogenated hydrocarbons such as dichloromethane, chloroform, and carbon tetrachloride; polar solvents such as acetonitrile; and mixtures of such solvents. Examples of acids include mineral acids such as hydrochloric acid, sulfuric acid, and hydrobromic acid; aliphatic acids such as formic acid, and acetic acid; sulfonic acids such as p-toluenesulfonic acid; Lewis acids such as boron fluoride, aluminium chloride, and boron tribromide; iodides such as sodium iodide, and potassium iodide; mixtures of such iodides and Lewis acids. The reaction is usually performed at about 0 to about 200°C, and preferably at about 0 to about 150°C, and is usually completed in about 0.5 to about 25 hours. An acid is usually used in an amount of 1 to 10 moles, and preferably about 1 mole to about 2 moles per mole of the compound of Formula (16).

The compound of Formula (16) can be prepared using the processes shown in Reaction Formulae 13 and 14 below.

Reaction Formula 13

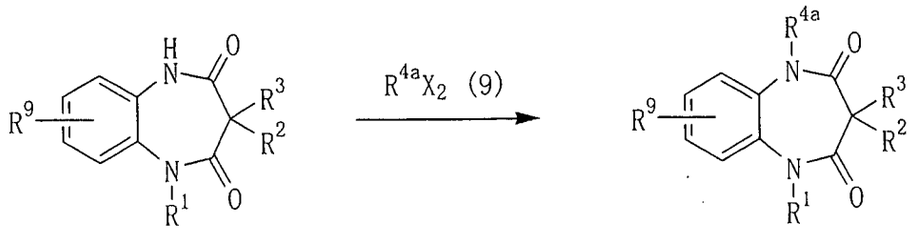


(18) (19) (16)

wherein R^1, R^2, R^3, R^4, and R^9 are the same as above.

The reaction of the compound of Formula (18) with the compound of Formula (19) is performed under the same reaction conditions as those for the reaction of the compound of Formula (11) with the compound of Formula (12) in Reaction Formula 10.

Reaction Formula 14



(20) (16c)

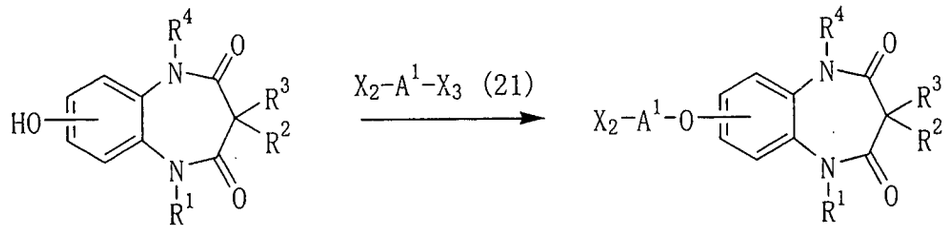
wherein R^1, R^2, R^3, R^{4a}, and R^9 are the same as above.

The reaction of the compound of Formula (20) with the compound of Formula (9) is performed under the same reaction conditions as those for the reaction of the compound of Formula (1i) with the compound of Formula (9) in Reaction Formula 8.

When R^1 in the compound of Formula (20) is hydrogen in the reaction, a compound in which the first and fifth positions of the benzodiazepine skeleton are simultaneously substituted with R^{4a} may be produced.

The compound of Formula 4, which is used as a starting material in the above-mentioned reaction formula, can be easily prepared by the process shown in the following reaction formula.

Reaction Formula 15



(2) (4)

wherein R^1, R^2, R^3, R^4, A^1, and X_2 are the same as above, and X_3 is halogen.

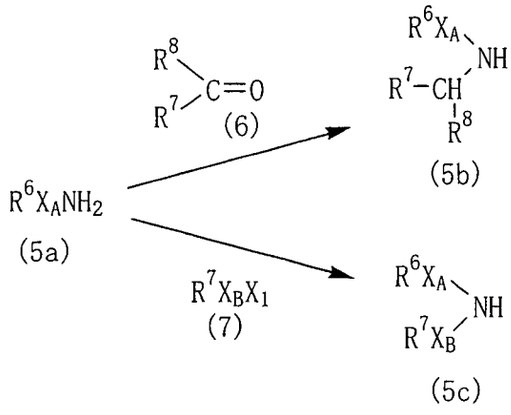
The reaction of the compound of Formula (2) with the compound of Formula (21) is performed under the same reaction conditions as those for the reaction of the compound of Formula (3), in which X_1 is halogen, with the compound of Formula (2) in Reaction

Formula 1.

X_2 in the compound of Formula (4) can be replaced with another halogen atom by adding it to an appropriate solvent with an alkali metal halide, and heating under reflux. Examples of alkali metal halides include sodium iodide, sodium bromide, sodium fluoride, sodium chloride, potassium iodide, potassium bromide, potassium fluoride, potassium chloride, etc. Examples of solvents for halogen exchange include ketones such as acetone, 2-butanone; ethers such as dioxane, tetrahydrofuran, diethyl ether, diethylene glycol dimethyl ether, and ethylene glycol dimethyl ether; and esters such as methyl acetate and ethyl acetate. Such solvents can be used singly or in a combination of two or more. An alkali metal halide is usually used in an amount at least 1 mole, and preferably about 1 mole to about 10 moles, per mole of the compound of Formula (4). Heat-reflux is continued until the reaction finishes. For example, heat-reflux is preferably continued for about 1 to about 15 hours. The heat-reflux temperature varies according to the solvent to be used, and is usually about 0 to about 150°C, and preferably about 0 to about 100°C.

The compound of Formula (5), which is used as a starting material, can be easily prepared by the process shown in the following reaction formula.

Reaction Formula 16



wherein R^6, R^7, X_A, X_B, X_1, and R^8 are the same as above.

The reaction of the compound of Formula (5a) with the

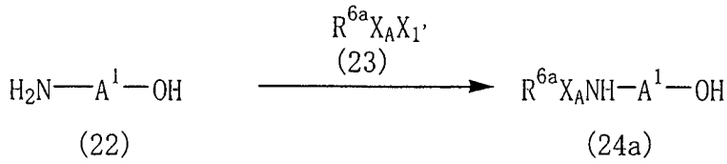
compound of Formula (6) is performed under the same reaction conditions as those for the reaction of the compound of Formula (1c) with the compound of Formula (6) in Reaction Formula 4.

The reaction of the compound of Formula (5a) with the compound of Formula (7) is performed under the same reaction conditions as those for the reaction of the compound of Formula (1c) with the compound of Formula (7) in Reaction Formula 5.

The compound of Formula (3), which is used as a starting material, can be easily prepared by the process shown in the following reaction formula.

Starting material (24) used in the following Reaction Formula 18 can be easily prepared by the process shown in Reaction Formula 17.

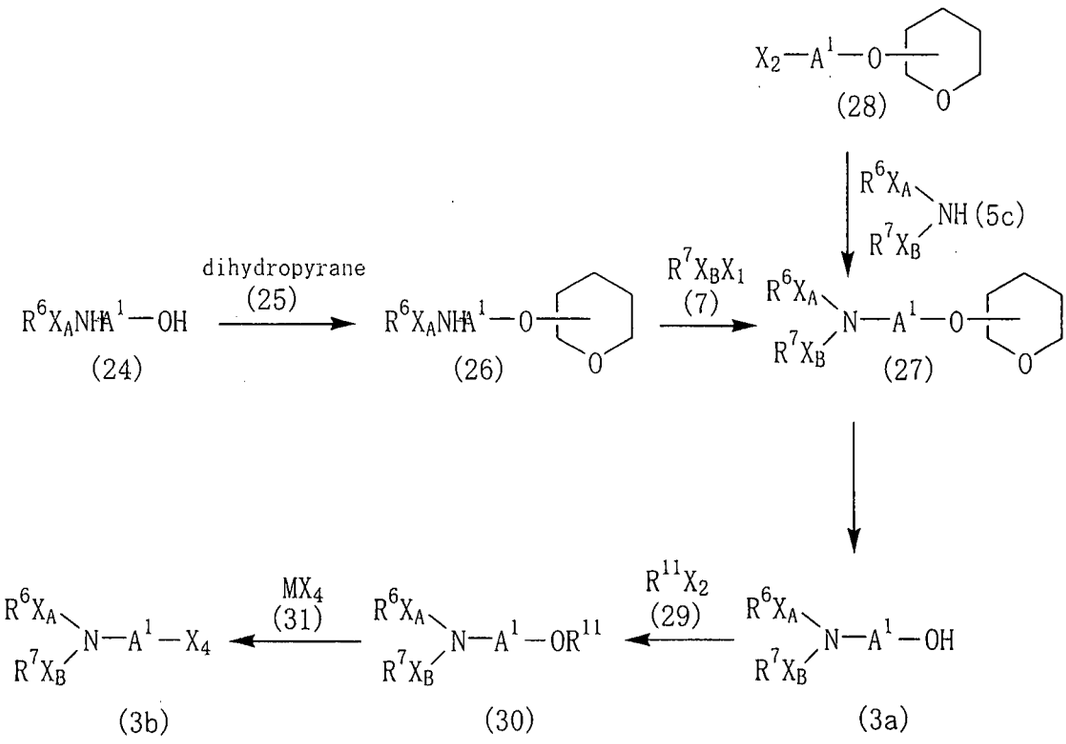
Reaction Formula 17



wherein A^1 and X_A are the same as above, X_1' is halogen , and R^{6a} is the same as R^6 as defined above, excluding the hydrogen atom.

The reaction of the compound of Formula (22) with the compound of Formula (23) is performed under the same reaction conditions as those for the reaction of the compound of Formula (2) with the compound of Formula (3) in Reaction Formula 1.

Reaction Formula 18



wherein R^6, R^7, X_A, X_B, A^1, X_1 and X_2 are the same as above, and R^{11} is lower alkylsulfonyl. X_4 is halogen, and M is alkali metal such as sodium, potassium, etc.

Examples of the lower alkylsulfonyl groups represented by R^{11} include linear or branched C_{1-6} alkylsulfonyl groups, such as methylsulfonyl, ethylsulfonyl, n-propylsulfonyl, isopropylsulfonyl, n-butylsulfonyl, isobutylsulfonyl, tert-butylsulfonyl, sec-butylsulfonyl, n-pentylsulfonyl, isopentylsulfonyl, neopentylsulfonyl, n-hexylsulfonyl, isohexylsulfonyl, and 3-methylpentylsulfonyl.

The reaction of the compound of Formula (24) and the compound of Formula (25) is performed in a suitable solvent or without using any solvents in the presence of an acid. Examples of solvents include the solvents used in the reaction of the compound of Formula (2) and the compound of Formula (3) in Reaction Formula 1. Examples of usable acids include mineral acids such as hydrochloric acid, sulfuric acid, and hydrobromic acid; and organic acids such as formic

acid, acetic acid, thioglycolic acid, trifluoroacetic acid, and sulfonic acid (e.g., p-toluenesulfonic acid). Such acids can be used singly or in a combination. Conditions other than those described above may be the same as those of the reaction between the compound of Formula (2) and the compound of Formula (3) in Reaction Formula 1.

The reaction of the compound of Formula (26) with the compound of Formula (7) is performed under the same reaction conditions as those for the reaction of the compound of Formula (2) with the compound of Formula (3) in Reaction Formula 1.

The reaction of the compound of Formula (5c) with the compound of Formula (28) is performed under the same reaction conditions as those for the reaction of the compound of Formula (3), in which X_1 is halogen, with the compound of Formula (2) in Reaction Formula 1.

The reaction converting the compound of Formula (27) to the compound of Formula (3a) can be carried out in an appropriate solvent or without using any solvents in the presence of an acid or a basic compound.

Examples of useful solvents include water; lower alcohols such as methanol, ethanol, isopropanol, and tert-butanol; ketones such as acetone, and methyl ethyl ketone; ethers such as diethyl ether, dioxane, tetrahydrofuran, monoglyme and diglyme; aliphatic acids such as acetic acid and formic acid; esters such as methyl acetate and ethyl acetate; halogenated hydrocarbons such as chloroform, dichloromethane, dichloroethane, and carbon tetrachloride; dimethyl sulfoxide; N,N-dimethylformamide; and hexamethylphosphoric triamide; and mixtures of such solvents.

Examples of acids include mineral acids such as hydrochloric acid, sulfuric acid, and hydrobromic acid; and organic acids such as formic acid, acetic acid, trifluoroacetic acid, and sulfonic acid (e.g., p-toluenesulfonic acid and pyridinium p-toluenesulfonate); Lewis acids such as boron tribromide and boron trichloride. Such acids can be used singly or in a combination.

Examples of useful basic compounds include carbonates such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate,

and potassium hydrogencarbonate; and metal hydroxides such as sodium hydroxide, potassium hydroxide, calcium hydroxide, and lithium hydroxide. Such basic compounds can be used singly or in a combination.

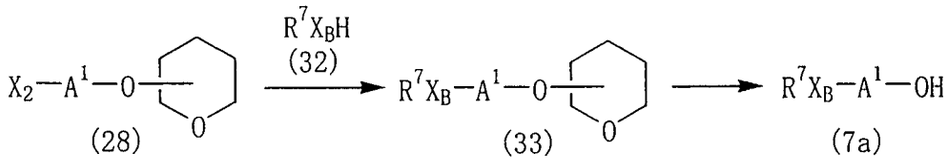
The reaction advantageously proceeds usually at about 0 to about 200°C, and preferably at about 0 to about 150°C, and is usually completed in about 10 minutes to about 50 hours.

The reaction of the compound of Formula (3a) with the compound of Formula (29) is performed under the same reaction conditions as those for the reaction of the compound of Formula (5c) with the compound of Formula (28).

The reaction converting the compound of Formula (30) to the compound of Formula (3b) is performed under the same reaction conditions as those for the reaction of the compound of Formula (3), in which X_1 is halogen, with the compound of Formula (2) in Reaction Formula 1.

The compound of Formula (7), which is used as a starting material, can be easily prepared by the process shown in the following reaction formula.

Reaction Formula 19



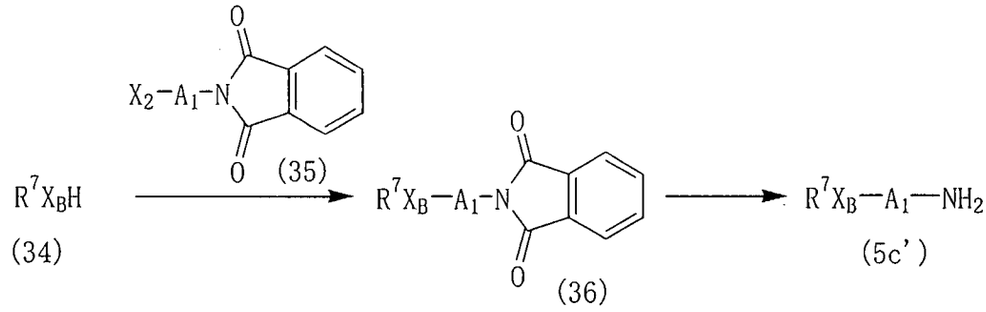
wherein R_7, X_B, X^2 and A^1 are the same as above.

The reaction of the compound of Formula (32) with the compound of Formula (28) is performed under the same reaction conditions as those for the reaction of the compound of Formula (5c) with the compound of Formula (28) in Reaction Formula 18.

The reaction converting the compound of Formula (33) to the compound of Formula (7a) can be carried out under the same reaction conditions as those for the reaction converting the compound of Formula (27) to the compound of Formula (3a) in Reaction Formula 18.

The compound of Formula (5), which is used as a starting material, can be easily prepared by the process shown in the following reaction formula.

Reaction Formula 20

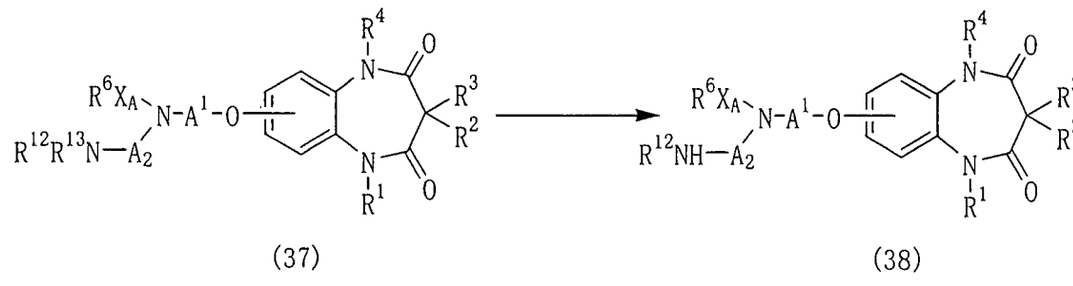


wherein A^1, R^7, X_B, and X_2 are the same as above.

The reaction of the compound of Formula (34) with the compound of Formula (35) is performed under the same reaction conditions as those for the reaction of the compound of Formula (3), in which X_1 is halogen, with the compound of Formula (2) in Reaction Formula 1.

The reaction converting the compound of Formula (36) to the compound of Formula (5c) can be carried out under the same reaction conditions as those for the reaction converting the compound of Formula (1a) to the compound of Formula (1b) in Reaction Formula 2.

Reaction Formula 21



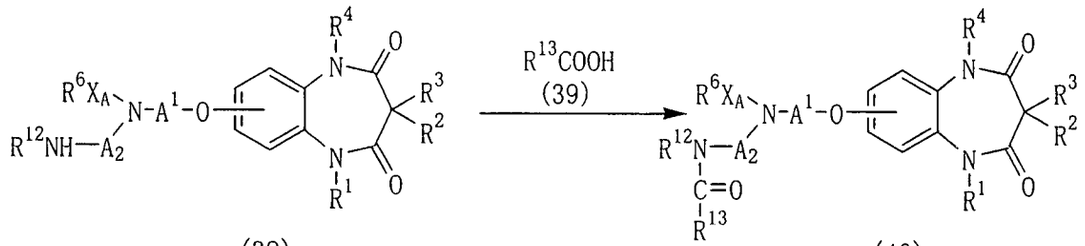
wherein R^1, R^2, R^3, R^4, R^6, X_A and A^1 are the same as above.

R^{12} is hydrogen, lower alkyl, lower alkoxycarbonyl, 2,3-dihydrobenzo[b]furylcarbonyl, or benzoyl. R^{13} is lower

alkoxycarbonyl, 2,3-dihydrobenzo[b]furyl carbonyl, or benzoyl, and A^2 is lower alkylene.

The reaction converting the compound of Formula (37) to the compound of Formula (38) can be carried out under the same reaction conditions as those for the reaction converting the compound of Formula (1f) to the compound of Formula (1c) in Reaction Formula 6.

Reaction Formula 22



(38) (40)

wherein R^1, R^2, R^3, R^4, R^6, X_A, R^{12}, A^1, and A^2 are the same as above. R^{13} is 2,3-dihydrobenzo[b]furyl or phenyl.

The reaction of the compound of Formula (38) with the compound of Formula (39) is performed under the same reaction conditions as those for the reaction of the compound of Formula (11) with the compound of Formula (12) in Reaction Formula 10.

In addition, compounds in the form in which a solvate (for example, a hydrate, ethanolate, etc.) was added to the starting material compounds and object compounds shown in each of the reaction formulae are included in each of the formulae.

The compound of Formula (1) according to the present invention includes stereoisomers and optical isomers.

The starting material compounds and object compounds represented by each of the reaction formulae can be used in an appropriate salt form.

Each of the object compounds obtained according to the above reaction formulae can be isolated and purified from the reaction mixture by, for example, after cooling the reaction mixture, performing an isolation procedure such as filtration, concentration, extraction, etc., to separate a crude reaction product, and then

subjecting the crude reaction product to a usual purification procedure such as column chromatography, recrystallization, etc.

Among the compounds of the present invention, those having a basic group or groups can easily form salts with common pharmaceutically acceptable acids. Examples of such acids include hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and other inorganic acids, methansulfonic acid, p-toluenesulfonic acid, acetic acid, citric acid, tartaric acid, maleic acid, fumaric acid, malic acid, lactic acid and other organic acids, etc.

Among the compounds of the present invention, those having an acidic group or groups can easily form salts by reacting with pharmaceutically acceptable basic compounds. Examples of such basic compounds include sodium hydroxide, potassium hydroxide, calcium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, etc.

The following is an explanation of pharmaceutical preparations comprising the compound of the present invention as an active ingredient.

Such pharmaceutical preparations are obtained by formulating the compound of the present invention into usual pharmaceutical preparations, using usually employed diluents or excipients such as fillers, extenders, binders, wetting agents, disintegrants, surfactants, lubricants, etc.

The form of such pharmaceutical preparations can be selected from various forms according to the purpose of therapy. Typical examples include tablets, pills, powders, solutions, suspensions, emulsions, granules, capsules, suppositories, injections (solutions, suspensions, etc.) and the like.

To form tablets, any of various known carriers can be used, including, for example, lactose, white sugar, sodium chloride, glucose, urea, starch, calcium carbonate, kaolin, crystalline cellulose and other excipients; water, ethanol, propanol, simple syrup, glucose solutions, starch solutions, gelatin solutions, carboxymethylcellulose, shellac, methylcellulose, potassium

phosphate, polyvinylpyrrolidone and other binders; dry starch, sodium alginate, agar powder, laminaran powder, sodium hydrogencarbonate, calcium carbonate, fatty acid esters of polyoxyethylenesorbitan, sodium laurylsulfate, stearic acid monoglyceride, starch, lactose and other disintegrants; white sugar, stearin, cacao butter, hydrogenated oils and other disintegration inhibitors; quaternary ammonium base, sodium lauryl sulfate and other absorption promoters; glycerin, starch and other wetting agents; starch, lactose, kaolin, bentonite, colloidal silicic acid and other adsorbents; purified talc, stearates, boric acid powder, polyethylene glycol and other lubricants; etc.

Such tablets may be coated with usual coating materials as required, to prepare, for example, sugar-coated tablets, gelatin-coated tablets, enteric-coated tablets, film-coated tablets, double- or multi-layered tablets, etc.

To form pills, any of various known carriers can be used, including, for example, glucose, lactose, starch, cacao butter, hydrogenated vegetable oils, kaolin, talc and other excipients; gum arabic powder, tragacanth powder, gelatin, ethanol and other binders; laminaran, agar and other disintegrants; etc.

To form suppositories, any of various known carriers can be used, including, for example, polyethylene glycol, cacao butter, higher alcohols, esters of higher alcohols, gelatin, semisynthetic glycerides, etc.

To form an injection, a solution, emulsion or suspension is sterilized and preferably made isotonic with blood. Any of various known widely used diluents can be employed to prepare the solution, emulsion or suspension. Examples of such diluents include water, ethanol, propylene glycol, ethoxylated isostearyl alcohol, polyoxylated isostearyl alcohol, fatty acid esters of polyoxyethylene sorbitan, etc. In this case, the pharmaceutical preparation may contain sodium chloride, glucose or glycerin in an amount sufficient to prepare an isotonic solution, and may contain usual solubilizers, buffers, analgesic agents, etc., and further, if necessary, coloring agents, preservatives, flavors, sweetening agents, etc., and/or other medicines.

The proportion of the compound of the present invention in the pharmaceutical preparation is not limited and can be suitably selected from a wide range. It is usually preferable that the pharmaceutical preparation contain the compound of the present invention in a proportion of 1 to 70 wt.%.

The route of administration of the pharmaceutical preparation according to the present invention is not limited, and the preparation can be administered by a route suitable for the form of the preparation, the patient's age and sex, the conditions of the disease, and other conditions.

For example, tablets, pills, solutions, suspensions, emulsions, granules and capsules are administered orally.

Injections are intravenously administered singly or as mixed with usual injection transfusions such as glucose solutions, amino acid solutions or the like, or singly administered intramuscularly, intracutaneously, subcutaneously or intraperitoneally, as required.

Suppositories are administered intrarectally.

The dosage of the pharmaceutical preparation is suitably selected according to the method of use, the patient's age and sex, the severity of the disease, and other conditions, and is usually about 0.001 to about 100 mg/kg body weight/day, and preferably 0.001 to 50 mg/kg body weight/day, in single or divided doses.

Since the dosage varies depending on various conditions, a dosage smaller than the above range may be sufficient, or a dosage larger than the above range may be required.

When administered to the human body as a pharmaceutical, the compound of the present invention may be used concurrently with, or before or after, antithrombotics such as blood clotting inhibitors and antiplatelet agents (e.g., warfarin, aspirin, etc.). Further, the present compound may be used concurrently with, or before or after, drugs for treating chronic diseases, such as antihypertensive drugs (ACE inhibitors, beta blockers, angiotensin II receptor antagonists), heart failure drugs (cardiotonic agents, diuretics), and diabetes treatment agents.

The compound of the present invention has potent blocking

effects on human Kv1.5 and/or GIRK1/4 channels, and weak blocking effects on HERG channels. Thus, the compound of the invention has characteristics as an atrial-selective K^+ channel-blocking agent.

Therefore, the compound of the invention can be used as a pharmacologically active substance that is safer and provides a more potent effect on the prolongation of the atrial refractory period than conventional antiarrhythmic agents. The compound of the invention is preferably used as a therapeutic agent for arrhythmia such as atrial fibrillation, atrial flutter, and atrial tachycardia (elimination of arrhythmia and/or prevention of the occurrence of arrhythmia). The compound of the invention is particularly preferably used as a therapeutic agent for atrial fibrillation (defibrillation and maintenance of sinus rhythm). The compound of the invention can also be used as a prophylactic agent for thromboembolism such as cerebral infarction and as a therapeutic agent for heart failure.

The compound having potent blocking effects on both human Kv1.5 and human GIRK1/4 channels has more potent atrial refractory period prolongation effects and is highly safe, compared to compounds inhibiting either one of the channels. Furthermore, this compound has greater therapeutic effects on atrial fibrillation (defibrillation and maintenance of sinus rhythm) than compounds inhibiting either one of the channels. Therefore, the compound having potent blocking effects on both the human Kv1.5 and human GIRK1/4 channels is particularly useful as a therapeutic agent for arrhythmia such as atrial fibrillation, atrial flutter, and atrial tachycardia (termination of arrhythmia and/or prevention of the occurrence of arrhythmia). This compound is particularly useful as a therapeutic agent for atrial fibrillation (defibrillation and maintenance of sinus rhythm).

BEST MODE FOR CARRYING OUT THE INVENTION

The following Examples are intended to illustrate the present invention in future detail.

Reference Example 1

Synthesis of ethyl N-(5-methoxy-2-nitrophenyl)-N-methyl malonamate

Sodium hydride (60% in oil, 96 mg, 2.4 mmol) was suspended in 10 ml of dimethylformamide (DMF).

N-Methyl-5-methoxy-2-nitroaniline (364 mg, 2 mmol) was added thereto at 0°C, and stirring was conducted for 30 minutes at room temperature. Ethyl malonyl chloride (0.38 ml, 3 mmol) was added at 0°C to the stirred mixture, and the reaction mixture was stirred at room temperature overnight. Water was added thereto, and extraction with ethyl acetate was performed. The organic layer was dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate=2:1-1:2). The purified product was concentrated under reduced pressure to thereby obtain 554 mg (yield: 90%) of ethyl N-(5-methoxy-2-nitrophenyl)-N-methyl malonamate as a yellow oil.

^{1}H-NMR ($CDCl_3$) δppm:

1.24 (3H, t, J = 7.1 Hz), 3.15 - 3.17 (2H, m), 3.25 (3H, s), 3.92 (3H, s), 4.13 (2H, q, J = 7.1 Hz), 6.93 (1H, d, J = 2.8 Hz), 7.02 (1H, dd, J = 2.8 and 9.2 Hz), 8.15 (1H, d, J = 9.2 Hz).

Reference Example 2

Synthesis of ethyl N-ethyl-N-(5-methoxy-2-nitrophenyl) malonamate

Using an appropriate starting material and following the procedure of Reference Example 1, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

1.11 (3H, t, J = 7.2 Hz), 1.24 (3H, t, J = 7.1 Hz), 3.11-3.25 (2H, m), 3.39-3.46 (1H, m), 3.92 (3H, s), 3.98-4.17 (3H, m), 6.89 (1H, d, J = 2.8 Hz), 7.03 (1H, dd, J = 9.2 and 2.8 Hz), 8.13 (1H, d, J = 9.2 Hz).

Reference Example 3

Synthesis of ethyl N-(2-amino-5-methoxyphenyl)-N-methyl malonamate

Palladium carbon (10%, 0.5 g) was added to an ethanol solution (150 ml) of ethyl N-(5-methoxy-2-nitrophenyl)-N-methyl malonamate (3.0 g, 10 mmol), and catalytic reduction was conducted at room temperature and normal pressure. The reaction mixture was filtered through Celite to remove the catalyst. The filtrate was concentrated under reduced pressure to thereby obtain 2.68 g (yield: quantitative) of ethyl N-(2-amino-5-methoxyphenyl)-N-methyl malonamate as a yellow

oil.

^{1}H-NMR ($CDCl_3$) δppm:

1.22 (3H, t, J = 7.1 Hz), 3.19 - 3.27 (5H, m), 3.52-3.68 (2H, br), 3.74 (3H, s), 4.11 (2H, q, J = 7.1 Hz), 6.62 (1H, d, J = 2.7 Hz), 6.73 (1H, d, J = 8.7 Hz), 6.79 (1H, dd, J = 2.7 and 8.7 Hz).

Reference Example 4

Synthesis of 8-methoxy-1-methyl-1,5-dihydrobenzo[b][1,4] diazepine-2,4-dione

Sodium ethoxide (204 mg, 3.0 mmol) was added to an ethanol solution (15 ml) of ethyl N-(2-amino-5-methoxyphenyl)-N-methyl malonamate (266 mg, 1.0 mmol), and stirred at 65°C for 2.5 hours. The reaction mixture was cooled to room temperature, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane:methanol=1:0→10:1). The purified product was concentrated to dryness under reduced pressure to thereby obtain 176.3 mg (yield: 80%) of 8-methoxy-1-methyl-1,5-dihydrobenzo [b][1,4]diazepine-2,4-dione as a white powder.

^{1}H-NMR ($CDCl_3$) δppm:

3.36 (2H, s), 3.43 (3H, s), 3.84 (3H, s), 6.79-6.83 (1H, m), 7.06-7.09 (1H, m), 8.72 (1H, br-s).

Reference Example 5

Synthesis of

1-ethyl-8-methoxy-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Palladium carbon (10%, 1.1 g) was added to an ethanol solution (250 ml) of ethyl N-ethyl-N-(5-methoxy-2-nitrophenyl) malonamate (21.05 g, 67.8 mmol), and cooled in an ice water bath. Catalytic reduction was conducted at about room temperature. Celite filtration was conducted to remove the catalyst, and the filtrate was concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (THF) (200 ml). Sodium ethoxide (6.9 g, 102 mmol) was added thereto, and then heating was conducted under reflux for 15 minutes. The reaction mixture was cooled to room temperature, and the precipitated insoluble matter was collected by filtration. The filtrate was concentrated under reduced pressure. Water was added to the residue and the collected insoluble matter, and the mixture was neutralized

with hydrochloric acid. Extraction with ethyl acetate was then performed. The organic layer was washed with a saturated sodium chloride aqueous solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was recrystallized from ethanol to thereby obtain 7.9 g (yield: 50%) of 1-ethyl-8-methoxy-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione as a white powder. The mother liquor was then concentrated, and the residue was purified using a silica gel flash column (n-hexane:ethyl acetate= 1:1→0:1) to thereby obtain 2.9 g of object compound.

^{1}H-NMR ($CDCl_3$) δppm:

1.19 (3H, t, J = 7.1 Hz), 3.33 (2H, s), 3.78-3.84 (1H, m), 3.84 (3H, s), 4.13 - 4.25 (1H, m), 6.82 (1H, dd, J = 8.8 and 2.7 Hz), 6.87 (1H, d, J = 2.7 Hz), 7.09 (1H, d, J = 8.8 Hz), 8.82 (1H, br-s).

Reference Example 6

Synthesis of 1-ethyl-7-methoxy-5-methyl-1,5-dihydrobenzo[b][1,4] diazepine-2,4-dione

Sodium hydride (60% in oil, 44 mg, 1.1 mmol) was suspended in dimethylformamide (DMF) (8 ml), and cooled in an ice water bath to 0°C. 8-Methoxy-1-methyl-1,5-dihydrobenzo[b][1,4] diazepine-2,4-dione (220 mg, 1.0 mmol) was added to the suspension at the same temperature, and stirred at 0°C for 1 hour. Ethyl iodide (187 mg, 1.2 mmol) was added to the mixture and stirred at room temperature overnight. Water was added to the reaction mixture, and extraction with ethyl acetate was performed. The organic layer was dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate=4:1→1:1). The purified product was concentrated to dryness under reduced pressure to thereby obtain 190.2 mg (yield: 77%) of 1-ethyl-7-methoxy-5-methyl-1,5-dihydrobenzo [b][1,4]diazepine-2,4-dione as a yellow solid.

^{1}H-NMR ($CDCl_3$) δppm:

1.11 (3H, t, J = 7.1 Hz), 3.31 - 3.32 (2H, m), 3.40 (3H, s), 3.59-3.68 (1H, m), 3.85 (3H, s), 4.18-4.30 (1H, m), 6.78 (1H, d, J = 2.8 Hz), 6.84 (1H, dd, J = 9.0 and 2.8 Hz), 7.26 (1H, d, J = 9.0 Hz).

Reference Example 7

Synthesis of 1,5-diethyl-7-methoxy-1,5-dihydrobenzo[b][1,4] diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Reference Example 6, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

1.04-1.14 (6H, m), 3.28 (2H, s), 3.50-3.64 (2H, m), 3.85 (3H, s), 4.35-4.47 (2H, m), 6.83-6.88 (2H, m), 7.25-7.27 (1H, m).

Reference Example 8

Synthesis of 7-methoxy-5-methyl-1-propyl-1,5-dihydrobenzo[b][1,4] diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Reference Example 6, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.76 (3H, t, J = 7.3 Hz), 1.35-1.62 (2H, m), 3.32 (2H, s), 3.40 (3H, s), 3.33-3.51 (1H, m), 3.49 (3H, s), 4.21-4.38 (1H, m), 6.78 (1H, d, J = 2.8 Hz), 6.84 (1H, dd, J = 9.0 and 2.8 Hz), 7.25 (1H, d, J = 9.0 Hz).

Reference Example 9

Synthesis of 1-isobutyl-7-methoxy-5-methyl-1,5-dihydrobenzo [b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Reference Example 6, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.69 (3H, d, J = 6.7 Hz), 0.77 (3H, d, J = 6.7 Hz), 1.56-1.90 (1H, m), 3.24 (1H, dd, J = 13.6 and 5.9 Hz), 3.33 (2H, s), 3.40 (3H, s), 3.85 (3H, s), 4.32 (1H, dd, J = 13.6 and 9.0 Hz), 6.78 (1H, d, J = 2.8 Hz), 6.84 (1H, dd, J = 9.0 and 2.9 Hz), 7.24 (1H, d, J = 9.0 Hz).

Reference Example 10

Synthesis of 7-methoxy-5-methyl-1-(3-methylbutyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Reference Example 6, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.80 (3H, d, J = 6.3 Hz), 0.86(3H, d, J = 6.3 Hz), 1.22-1.53 (3H, m),

3.32 (2H, s), 3.39 (3H, s), 3.36-3.62 (1H, m), 3.85 (3H, s), 4.31-4.48 (1H, m), 6.78 (1H, d, J = 2.8 Hz), 6.85 (1H, dd, J = 8.8 and 2.8 Hz), 7.25 (1H, d, J = 8.8 Hz).

Reference Example 11

Synthesis of

7-methoxy-5-methyl-1-(3-methylbut-2-enyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Reference Example 6, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

1.63 (6H, s), 3.32 - 3.34 (2H, m), 3.38 (3H, s), 3.84 (3H, s), 4.33 (1H, dd, J = 13.6 and 6.2 Hz), 4.51 (1H, dd, J = 13.6 and 6.9 Hz), 5.14 - 5.19 (1H, m), 6.76 (1H, d, J = 2.8 Hz), 6.81 (1H, dd, J = 9.0 and 2.8 Hz), 7.27 (1H, d, J = 9.0 Hz).

Reference Example 12

Synthesis of

1-ethyl-7-methoxy-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Sodium hydride (60% in oil, 76 mg, 1.9 mmol) was suspended in DMF (8 ml).

1-Ethyl-7-methoxy-5-methyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione (190 mg, 0.76 mmol) was added thereto at 0°C, and stirring was conducted at the same temperature for 1 hour. Methyl iodide (0.19 ml, 3.1 mmol) was added to the mixture, and stirred at room temperature for 3 days. Water was added to the reaction mixture, and extraction with ethyl acetate was performed. The organic layer was dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate). The purified product was concentrated to dryness under reduced pressure to thereby obtain 169 mg (yield: 80%) of

1-ethyl-7-methoxy-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione as a yellow powder.

^{1}H-NMR ($CDCl_3$) δppm:

0.86 (3H, s), 1.15 (3H, t, J = 7.1 Hz), 1.53 (3H, s), 3.40 (3H, s), 3.65-3.76 (1H, m), 3.85 (3H, s), 4.12-4.24 (1H, m), 6.73 (1H, d, J

= 2.8 Hz), 6.83 (1H, dd, J = 9.0 and 2.8 Hz), 7.22 (1H, d, J = 9.0 Hz).

Reference Example 13

Synthesis of 7-methoxy-3,3,5-trimethyl-1-propyl-1,5-dihydro benzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Reference Example 12, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.76 (3H, t, J = 7.3 Hz), 0.85 (3H, s), 1.52 (3H, s), 1.38-1.68 (2H, m), 3.41 (3H, s), 3.42-3.58 (1H, m), 3.85 (3H, s), 4.19-4.31 (1H, m), 6.72 (1H, d, J = 2.8 Hz), 6.81 (1H, dd, J = 9.0 and 2.8 Hz), 7.20 (1H, d, J = 9.0 Hz).

Reference Example 14

Synthesis of 7-methoxy-3,3,5-trimethyl-1-(3-methylbutyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Reference Example 12, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.82 (3H, d, J = 6.2 Hz), 0.85 (3H, s), 0.86 (3H, d, J = 6.2 Hz), 1.30-1.49 (3H, m), 1.52 (3H, s), 3.40 (3H, s), 3.49-3.62 (1H, m), 3.85 (3H, s), 4.21-4.36 (1H, m), 6.71 (1H, d, J = 2.8 Hz), 6.80 (1H, dd, J = 9.0 and 2.8 Hz), 7.20 (1H, d, J = 9.0 Hz).

Reference Example 15

Synthesis of 1,5-diethyl-7-methoxy-3,3-dimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Reference Example 12, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.84 (3H, s), 1.06-1.18 (6H, m), 1.51 (3H, s), 3.56-3.83 (2H, m), 3.85 (3H, s), 4.29-4.42 (2H, m), 6.79-6.86 (2H, m), 7.21 (1H, d, J = 8.9

Hz).

Reference Example 16

Synthesis of 1,3-diethyl-7-methoxy-5-methyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Reference Example 12, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.86 (3H, t, J = 7.3 Hz), 1.06 (3H, t, J = 7.0 Hz), 1.94-2.05 (2H, m), 2.97 (1H, t, J = 6.9 Hz), 3.40 (3H, s), 3.55-3.66 (1H, m), 3.86 (3H, s), 4.20-4.33 (1H, m), 6.79 (1H, d, J = 2.8 Hz), 6.84-6.88 (1H, m), 7.26-7.29 (1H, m).

Reference Example 17

Synthesis of 3,3-diethyl-7-methoxy-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Diethylmalonyl dichloride (0.95 ml, 5.5 mmol) was added to a dichloromethane solution (20 ml) of 4-methoxy-o-phenylenediamine (691 mg, 5 mmol) and triethylamine (1.7 ml, 12.5 mmol) at 0°C, and stirred at room temperature overnight. Water was added to the reaction mixture, and extraction with dichloromethane was performed. The organic layer was washed with a saturated sodium chloride aqueous solution, dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate=9:1→1:1). The purified product was concentrated to dryness under reduced pressure to thereby obtain 452.3 mg (yield: 34%) of 3,3-diethyl-7-methoxy-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione as a yellow oil.

^{1}H-NMR ($CDCl_3$) δppm:

1.10 (6H, t, J = 7.5 Hz), 1.86 (4H, q, J = 7.5 Hz), 3.76 (3H, s), 4.18 (2H, br), 6.30 (1H, d, J = 2.7 Hz), 6.35 (1H, dd, J = 8.7 and 2.7 Hz), 7.23 (1H, d, J = 8.7 Hz).

Reference Example 18

Synthesis of 3,3-diethyl-7-methoxy-1,5-dimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Sodium hydride (60% in oil, 170 mg, 4.3 mmol) was suspended

in DMF (15 ml).

3,3-Diethyl-7-methoxy-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione (452 mg, 1.7 mmol) was added thereto at 0°C, and stirring was conducted at the same temperature for 1 hour. Methyl iodide (0.42 ml, 6.8 mmol) was added to the mixture, and stirred at room temperature for 3 days. Water was added to the reaction mixture and extraction with ethyl acetate was performed. The organic layer was dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate=2:1→1:1). The purified product was concentrated to dryness under reduced pressure to thereby obtain 373 mg (yield: 76%) of 3,3-diethyl-7-methoxy-1,5-dimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione as a white powder.

^{1}H-NMR ($CDCl_3$) δppm:

0.56 (3H, t, J = 7.4 Hz), 1.02 (3H, t, J = 7.3 Hz), 1.20-1.31 (2H, m), 2.15 (2H, q, J = 7.3 Hz), 3.38 (3H, s), 3.41 (3H, s), 3.85 (3H, s), 6.71 (1H, d, J = 2.8 Hz), 6.81 (1H, dd, J = 9.0 and 2.8 Hz), 7.14 (1H, d, J = 9.0 Hz).

Reference Example 19

Synthesis of 7-methoxy-1,3,3,5-tetramethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Sodium hydride (60% in oil, 128 mg, 3.2 mmol) was suspended in DMF (10 ml).

8-Methoxy-1-methyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione (176 mg, 0.8 mmol) was added thereto at 0°C, and stirring was conducted at the same temperature for 1 hour. Methyl iodide (0.25 ml, 4.0 mmol) was added to the mixture, and stirred at room temperature overnight. Water was added to the reaction mixture, and extraction with ethyl acetate was performed. The organic layer was washed with water, dried over sodium sulfate, and concentrated under reduced pressure. The residue was recrystallized from n-hexane to thereby obtain 161.6 mg (yield: 77%) of 7-methoxy-1,3,3,5-tetramethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione as a white powder.

^{1}H-NMR ($CDCl_3$) δppm:

0.87 (3H, s), 1.54 (3H, s), 3.40 (3H, s), 3.42 (3H, s), 3.84 (3H, s),

6.73 (1H, s), 6.84 (1H, d, J = 8.9 Hz), 7.14 (1H, d, J = 8.9 Hz).

Reference Example 20

Synthesis of 5-ethyl-7-methoxy-1,3,3-trimethyl-1,5-dihydrobenzo [b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Reference Example 19, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.86 (3H, s), 1.19 (3H, t, J = 7.1 Hz), 1.53 (3H, s), 3.38 (3H, s), 3.75-3.82 (1H, m), 3.84 (3H, s), 4.12-4.19 (1H, m), 6.80-6.85 (2H, m), 7.16 (1H, dd, J = 8.6 and 0.5 Hz).

Reference Example 21

Synthesis of 1,3,3,5-tetraethyl-7-methoxy-1,5-dihydrobenzo [b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Reference Example 19, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.56 (3H, t, J = 7.4 Hz), 0.98 (3H, t, J = 7.4 Hz), 1.07-1.26 (6H, m), 2.10-2.17 (2H, m), 3.59-3.74 (2H, m), 3.85 (3H, s), 4.24-4.32 (2H, m), 6.78-6.85 (2H, m), 7.20 (1H, d, J = 8.9 Hz).

Reference Example 22

Synthesis of 1,3,3-triethyl-7-methoxy-5-methyl-1,5-dihydrobenzo [b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Reference Example 19, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.57 (3H, t, J = 7.4 Hz), 1.00 (3H, t, J = 7.3 Hz), 1.16 (3H, t, J = 7.2 Hz), 1.21-1.29 (2H, m), 2.10-2.19 (2H, m), 3.40 (3H, s), 3.72-3.83 (1H, m), 3.85 (3H, s), 4.06-4.14 (1H, m), 6.71 (1H, d, J = 2.8 Hz), 6.82 (1H, dd, J = 9.0 and 2.8 Hz), 7.21 (1H, d, J = 9.0 Hz).

Reference Example 23

Synthesis of 1,3,5-triethyl-7-methoxy-1,5-dihydrobenzo[b][1,4] diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Reference Example 19, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.85 (3H, t, J = 7.5 Hz), 0.88-1.11 (6H, m), 2.92 - 2.97 (1H, m), 3.50-3.65 (2H, m), 3.86 (3H, s), 4.12 (2H, q, J = 7.2 Hz), 4.38-4.45 (2H, m), 6.84-6.89 (2H, m), 7.25-7.28 (1H, m).

Reference Example 24

Synthesis of 1-ethyl-7-hydroxy-3,3,5-trimethyl-1,5-dihydrobenzo [b][1,4]diazepine-2,4-dione

A 1.0 M boron tribromide/dichloromethane solution (1.22 ml) was added to a dichloromethane solution (3 ml) of 1-ethyl-7-methoxy-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione (169 mg, 1.0 mmol) at 0°C, and stirred at room temperature overnight. Water and methanol were added to the reaction mixture and extraction with the mixture solvent (dichloromethane:methanol =10:1) was performed. The organic layer was dried over anhydrous sodium sulfate, and concentrated to dryness under reduced pressure to thereby obtain 156.4 mg (yield: 98%) of 1-ethyl-7-hydroxy-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione as a white powder.

^{1}H-NMR ($CDCl_3$) δppm:

0.90 (3H, s), 1.16 (3H, t, J = 7.0 Hz), 1.55 (3H, s), 3.41 (3H, s), 3.66-3.78 (1H, m), 4.12-4.23 (1H, m), 6.79 (1H, d, J = 2.7 Hz), 6.84 (1H, dd, J = 8.8 and 2.7 Hz), 6.88 (1H, d, J = 2.7 Hz), 7.18 (1H, d, J = 8.8 Hz).

Reference Example 25

Synthesis of 3,3-diethyl-7-hydroxy-1,5-dimethyl-1,5-dihydrobenzo [b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Reference Example 24, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.55 (3H, t, J = 7.3 Hz), 1.00 (3H, t, J = 7.3 Hz), 1.15-1.29 (2H, m), 2.12 (2H, q, J = 7.3 Hz), 3.37 (3H, s), 3.38 (3H, s), 6.69 (1H,

d, J = 2.7 Hz), 6.76 (1H, dd, J = 8.8 and 2.7 Hz), 7.06 (1H, d, J = 8.8 Hz).

Reference Example 26

Synthesis of 1,3,3-triethyl-7-hydroxy-5-methyl-1,5-dihydrobenzo [b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Reference Example 24, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.59 (3H, t, J = 7.3 Hz), 1.01 (3H, t, J = 7.3 Hz), 1.18 (3H, t, J = 7.1 Hz), 1.21-1.34 (2H, m), 2.13-2.24 (2H, m), 3.40 (3H, s), 3.71-3.82 (1H, m), 4.05-4.16 (1H, m), 6.78 (1H, d, J = 2.7 Hz), 6.84 (1H, dd, J = 8.8 and 2.7 Hz), 7.04 (1H, br-s), 7.17 (1H, d, J = 8.8 Hz).

Reference Example 27

Synthesis of 1,3-diethyl-7-hydroxy-5-methyl-1,5-dihydrobenzo[b] [1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Reference Example 24, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.87 (3H, t, J = 7.4 Hz), 1.07 (3H, t, J = 7.1 Hz), 1.95-2.05 (2H, m), 3.00 (1H, t, J = 6.9 Hz), 3.39 (3H, s), 3.58-3.64 (1H, m), 4.22-4.29 (1H, m), 5.87 (1H, br-s), 6.80-6.84 (2H, m), 7.21-7.24 (1H, m).

Reference Example 28

Synthesis of 1,3-diethyl-7-hydroxy-3,5-dimethyl-1,5-dihydrobenzo [b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Reference Example 24, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.64 (3H, t, J = 7.3 Hz), 1.11 - 1.26 (5H, m), 1.54 (3H, s), 3.40 (3H, s), 3.70-3.82 (1H, m), 4.06-4.17 (1H, m), 6.39 (1H, br-s), 6.75-6.83 (2H, m), 7.17-7.24 (1H, d, J = 8.8 Hz).

Reference Example 29

Synthesis of 5-ethyl-7-hydroxy-1,3,3-trimethyl-1,5-dihydrobenzo

[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Reference Example 24, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.88 (3H, s), 1.20 (3H, t, J = 7.1 Hz), 1.53 (3H, s), 3.38 (3H, s), 3.73-3.84 (1H, m), 4.07-4.19 (1H, m), 6.76-6.81 (2H, m), 7.11 (1H, d, J = 8.7 Hz).

Reference Example 30

Synthesis of 7-hydroxy-3,3,5-trimethyl-1-propyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Reference Example 24, the object compound was synthesized.

^{1}H-NMR (CD_3OD) δppm:

0.74 (3H, t, J = 7.4 Hz), 0.85 (3H, s), 1.43 (3H, s), 1.38-1.61 (2H, m), 3.36 (3H, s), 3.53-3.61 (1H, m), 4.21-4.29 (1H, m), 6.76-6.82 (2H, m), 7.26 (1H, d, J = 8.5 Hz).

Reference Example 31

Synthesis of 7-hydroxy-3,3,5-trimethyl-1-(3-methylbutyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Reference Example 24, the object compound was synthesized.

^{1}H-NMR (CD_3OD) δppm:

0.79 (3H, d, J = 6.1 Hz), 0.85 (3H, s), 0.85 (3H, d, J = 6.1 Hz), 1.26-1.40 (3H, m), 1.42 (3H, s), 3.35 (3H, s), 3.56-3.63 (1H, m), 4.34-4.41 (1H, m), 6.76-6.82 (2H, m), 7.28 (1H, d, J = 8.7 Hz).

Reference Example 32

Synthesis of 1,3,3,5-tetraethyl-7-hydroxy-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Reference Example 24, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.58 (3H, t, J = 7.4 Hz), 0.98 (3H, t, J = 7.3 Hz), 1.08-1.29 (8H, m), 2.12-2.19 (2H, m), 3.57-3.76 (2H, m), 4.20-4.34 (2H, m), 6.09 (1H, br-s), 6.78-6.82 (2H, m), 7.14-7.17 (1H, m).

Reference Example 33

Synthesis of 1,5-diethyl-7-hydroxy-3,3-dimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Reference Example 24, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.87 (3H, s), 1.08-1.17 (6H, m), 1.54 (3H, s), 3.57-3.73 (2H, m), 4.27-4.39 (2H, m), 6.85-6.87 (2H, m), 7.15-7.18 (1H, m).

Reference Example 34

Synthesis of 1,3,5-triethyl-7-hydroxy-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Reference Example 24, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.84 (3H, t, J = 7.4 Hz), 1.02-1.12 (6H, m), 1.95-2.19 (2H, m), 3.03 (1H, t, J = 6.9 Hz), 3.51-3.70 (2H, m), 4.33-4.46 (2H, m), 6.89-6.93 (2H, m), 7.23 (1H, d, J = 8.5 Hz), 7.57 (1H, s).

Reference Example 35

Synthesis of 7-hydroxy-1,3,3,5-tetramethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Reference Example 24, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.90 (3H, s), 1.49 (3H, s), 3.39 (3H, s), 3.40 (3H, s), 6.73 (1H, d, J = 2.7 Hz), 6.80 (1H, dd, J = 8.9 and 2.7 Hz), 7.13 (1H, d, J = 8.9 Hz).

Reference Example 36

Synthesis of

7-hydroxy-1-isobutyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Reference Example 24, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.69 (3H, d, J = 6.7 Hz), 0.75 (3H, d, J = 6.7 Hz), 0.87 (3H, s), 1.53 (3H, s), 1.72-1.91 (1H, m), 3.24 (1H, dd, J = 6.3 and 13.5 Hz), 3.40 (3H, s), 4.35 (1H, dd, J = 8.6 and 13.5 Hz), 6.72-6.79 (2H, m), 7.13 (1H, d, J = 8.6 Hz).

Reference Example 37

Synthesis of

7-(3-chloropropoxy)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

1-Ethyl-7-hydroxy-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione (1.85 g, 7.1 mmol) and potassium carbonate (1.2 g, 8.5 mmol) were added to 50% water-containing acetonitrile (40 ml), and dissolved by heating to 70°C. 1-Bromo-3-chloropropane (2.1 ml, 21 mmol) was added thereto, and heating was conducted under reflux for 6 hours. The reaction mixture was cooled to room temperature. Water was added, and extraction with ethyl acetate was performed. The organic layer was dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate=2:1→1:1). The purified product was concentrated to dryness under reduced pressure to thereby obtain 2.18 g (yield: 91%) of 7-(3-chloropropoxy)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione as a colorless oil.

^{1}H-NMR ($CDCl_3$) δppm:

0.86 (3H, s), 1.15 (3H, t, J = 7.1 Hz), 1.53 (3H, s), 2.21-2.38 (2H, m), 3.40 (3H, s), 3.63-3.89 (4H, m), 4.10-4.26 (2H, m), 6.74 (1H, d, J = 2.8 Hz), 6.83 (1H, dd, J = 2.8 and 9.0 Hz), 7.21 (1H, d, J = 9.0 Hz).

Reference Example 38

Synthesis of

7-(3-chloropropoxy)-1,3,3,5-tetramethyl-1,5-dihydrobenzo[b][1,4]

diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Reference Example 37, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.88 (3H, s), 1.53 (3H, s), 2.20-2.32 (2H, m), 3.40 (3H, s), 3.42 (3H, s), 3.77 (2H, t, J = 6.1 Hz), 4.15 (2H, t, J = 5.8 Hz), 6.74 (1H, d, J = 2.7 Hz), 6.83 (1H, dd, J = 2.7 and 9.0 Hz), 7.15 (1H, d, J = 9.0 Hz).

Reference Example 39

Synthesis of

1-ethyl-7-(3-iodopropoxy)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

7-(3-Chloropropoxy)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione (2.18 g, 6.4 mmol) and sodium iodide (4.8 g, 32 mmol) were added to acetone (50 ml), and heated under reflux for 8.5 hours. The reaction mixture was cooled to room temperature, water was added, and extraction with ethyl acetate was performed. The organic layer was dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate=1:1). The purified product was concentrated under reduced pressure to thereby obtain 2.76 g (yield: 100%) of 1-ethyl-7-(3-iodopropoxy)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione as a colorless oil.

^{1}H-NMR ($CDCl_3$) δppm:

0.87 (3H, s), 1.15 (3H, t, J = 7.1 Hz), 1.53 (3H, s), 2.26 - 2.34 (2H, m), 3.39 (2H, t, J = 6.6 Hz), 3.65-3.76 (1H, m), 3.41 (3H, s), 4.07 (2H, t, J = 5.8 Hz), 4.12-4.24 (1H, m), 6.74 (1H, d, J = 2.8 Hz), 6.83 (1H, dd, J = 9.0 and 2.8 Hz), 7.22 (1H, d, J = 9.0 Hz).

Reference Example 40

Synthesis of

7-(3-iodopropoxy)-1,3,3,5-tetramethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Reference Example 39, the object compound was

synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.88 (3H, s), 1.54 (3H, s), 2.22-2.34 (2H, m), 3.39 (2H, t, J = 6.6 Hz), 3.40 (3H, s), 3.42 (3H, s), 4.07 (2H, t, J = 5.8 Hz), 6.74 (1H, d, J = 2.8 Hz), 6.83 (1H, dd, J = 2.8 and 9.0 Hz), 7.15 (1H, d, J = 9.0 Hz).

Reference Example 41

Synthesis of (2-pyridin-3-ylethyl)pyridin-4-ylmethylamine

4-Pyridinecarbaldehyde (5.36 g, 50 mmol) and 3-(2-aminoethyl)pyridine (6.5 ml, 50 mmol) were added to methanol (100 ml), and stirred at room temperature for 7 hours. The resulting mixture was cooled to 0°C. Sodium borohydride (2.8 g, 74 mmol) was added to the mixture, and stirred at 0°C for 1 hour. Water was then added to the reaction mixture to distill the methanol off under reduced pressure. The residue was extracted with dichloromethane. The organic layer was washed with a saturated sodium chloride aqueous solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography (ethyl acetate:methanol=95:5→85:5). The purified product was concentrated under reduced pressure to thereby obtain 10.03 g (yield: 94%) of (2-pyridin-3-ylethyl)pyridin-4-ylmethylamine as a colorless oil.

^{1}H-NMR ($CDCl_3$) δppm:

2.79-2.98 (4H, m), 3.82 (2H, s), 7.21 - 7.25 (3H, m), 7.51 - 7.55 (1H, m), 8.47 - 8.50 (2H, m), 8.52 - 8.54 (2H, m)

Reference Example 42

Synthesis of (2-pyridin-3-ylethyl)pyridin-4-ylmethyl-[3-(tetrahydropyran-2-yloxy)propyl]amine

Sodium iodide (1.5 g, 10 mmol) was added to a DMF solution (20 ml) of 2-(3-bromopropoxy)tetrahydropyran (0.85 ml, 5 mmol), and stirred at 70°C for 7 hours. The reaction mixture was cooled to room temperature. (2-Pyridin-3-ylethyl)pyridin-4-ylmethylamine (1.28 g, 6 mmol) and N-ethyl diisopropylamine (1.3 ml, 7.5 mmol) were then added to the reaction mixture and stirred at room temperature overnight.

Water was added to the reaction mixture, and extraction with ethyl acetate was performed. The organic layer was washed with water, and a saturated sodium chloride aqueous solution, in this order. The organic layer was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:methanol=20:1→4:1). The purified product was concentrated under reduced pressure to thereby obtain 236 mg (yield: 13%) of (2-pyridin-3-ylethyl)pyridin-4-ylmethyl-[3-(tetrahydropyran-2-yloxy)propyl]amine as a colorless oil.

^{1}H-NMR ($CDCl_3$) δppm:

1.40-1.92 (8H, m), 2.52-2.83 (6H, m), 3.30-3.56 (2H, m), 3.62 (2H, s), 3.66-3.90 (2H, m), 4.51 - 4.53 (1H, m), 7.16 (2H, d, J = 6.0 Hz), 7.19 (1H, d, J = 4.8 Hz), 7.42 (1H, d, J = 6.6 Hz), 8.41-8.49 (4H, m)

Reference Example 43

Synthesis of 3-[(2-pyridin-3-ylethyl)pyridin-4-ylmethylamino] propan-1-ol

A 2N-hydrogen chloride methanol solution (1.2 ml) was added to a methanol solution (4 ml) of (2-pyridin-3-ylethyl)pyridin-4-ylmethyl-[3-(tetrahydropyran-2-yloxy)propyl]amine (236 mg, 0.66 mmol), and stirred at room temperature overnight. A 2N-hydrogen chloride methanol solution (0.5 ml) was added to the mixture, and stirred at 50°C for 3 hours. Triethylamine (0.64 ml) was then added to the reaction mixture, and concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography (dichloromethane). The purified product was concentrated under reduced pressure to thereby obtain 186.3 mg (yield: quantitative) of 3-[(2-pyridin-3-ylethyl)pyridin-4-ylmethylamino]propan-1-ol as an orange oil.

^{1}H-NMR ($CDCl_3$) δppm:

1.70-1.86 (2H, m), 2.67-2.78 (4H, m), 2.81 (2H, t, J = 6.0 Hz), 3.65 (2H, s), 3.72 (2H, t, J = 5.5 Hz), 7.18 (2H, d, J = 5.9 Hz), 7.21 (1H, d, J = 4.9 Hz), 7.42 (1H, dt, J = 1.8 and 7.8 Hz), 8.42-8.54 (2H, m), 8.54 (2H, d, J = 5.9 Hz).

Reference Example 44

Synthesis of 6-[2-(tetrahydropyran-2-yloxy)ethyl]-6H-furo[2,3-c]pyridin-7-one

Sodium hydride (60% in oil, 138 mg, 3.5 mmol) was suspended in DMF (10 ml). A DMF solution (5 ml) of 6H-furo[2,3-c]pyridin-7-one (310 mg, 2.3 mmol) was added thereto at 0°C, and stirring was conducted at the same temperature for 1 hour. A DMF solution (5 ml) of 2-(2-iodoethoxy)tetrahydropyran (1175 mg, 4.6 mmol) was added thereto, and stirring was conducted at room temperature overnight. Water was added to the reaction mixture and extraction with ethyl acetate was performed. The organic layer was washed with water, dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate=2:1→1:1). The purified product was concentrated under reduced pressure to thereby obtain 450 mg (yield: 74%) of 6-[2-(tetrahydropyran-2-yloxy)ethyl]-6H-furo[2,3-c]pyridin-7-one as a yellow oil.

^{1}H-NMR ($CDCl_3$) δppm:

1.46-1.81 (6H, m), 3.40-3.47 (1H, m), 3.63-3.79 (2H, m), 4.00-4.07 (1H, m), 4.16-4.24 (1H, m), 4.34-4.41 (1H, m), 4.54 (1H, t, J = 3.1 Hz), 6.43 (1H, d, J = 7.0 Hz), 6.65 (1H, d, J = 1.9 Hz), 7.26 (1H, d, J = 7.0 Hz), 7.73 (1H, d, J = 1.9 Hz).

Reference Example 45

Synthesis of 7-methyl-2-[2-(tetrahydropyran-2-yloxy)ethyl]-2H-isoquinolin-1-one

Using an appropriate starting material and following the procedure of Reference Example 44, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

1.39-1.88 (6H, m), 2.49 (3H, s), 3.33-3.48 (1H, m), 3.61-3.81 (2H, m), 4.00-4.21 (2H, m), 4.28-4.39 (1H, m), 4.53 - 4.56 (1H, m), 6.43 (1H, d, J = 7.4 Hz), 7.15 (1H, d, J = 7.4 Hz), 7.41 (1H, d, J = 8.1 Hz), 7.45 (1H, dd, J = 1.7 and 8.1 Hz), 8.23 (1H, s).

Reference Example 46

Synthesis of 6-(2-hydroxyethyl)-6H-furo[2,3-c]pyridin-7-one

Pyridinium p-toluenesulfonate (0.21 g, 0.85 mmol) was added to a methanol solution (20 ml) of 6-[2-(tetrahydropyran-2-yloxy) ethyl]-6H-furo[2,3-c]pyridin-7-one (0.45 g, 1.7 mmol), and stirred at room temperature for 2 days. An aqueous sodium hydrogen carbonate solution was added to the reaction mixture, and extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Diethyl ether was added to the residue to precipitate crystals. The crystals were collected by filtration and dried to thereby obtain 223 mg (yield: 73%) of 6-(2-hydroxyethyl)-6H-furo[2,3-c]pyridin-7-one as a white powder.

^{1}H-NMR ($CDCl_3$) δppm:

3.15 (1H, t, J = 5.3 Hz), 3.96-4.01 (2H, m), 4.25 (2H, t, J = 5.3 Hz), 6.49 (1H, d, J = 7.0 Hz), 6.66 (1H, d, J = 2.0 Hz), 7.18 (1H, d, J = 7.0 Hz), 7.75 (1H, d, J = 2.0 Hz).

Reference Example 47

Synthesis of 2-(2-hydroxyethyl)-7-methyl-2H-isoquinolin-1-one

Using an appropriate starting material and following the procedure of Reference Example 46, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

2.48 (3H, s), 3.29 (1H, t, J = 5.2 Hz), 3.96 - 4.01 (2H, m), 4.16 - 4.19 (2H, m), 6.49 (1H, d, J = 7.3 Hz), 7.05 (1H, d, J = 7.3 Hz), 7.41 (1H, d, J = 8.1 Hz), 7.46 (1H, dd, J = 1.7 and 8.1 Hz), 8.20 (1H, d, J = 1.7 Hz).

Reference Example 48

Synthesis of 2-nitro-N-[3-(tetrahydropyran-2-yloxy) propyl]benzenesulfonamide

2-Nitrobenzenesulfonyl chloride (22.1 g, 0.10 mol) was added to a dichloromethane solution (400 ml) of 3-aminopropanol (8.2 g, 0.11 mol) and triethylamine (21 ml, 0.15 mol) at 0°C, and stirred at room temperature overnight. Water was added to the reaction mixture and extraction with dichloromethane was performed. The organic layer was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was dissolved in dichloromethane (400 ml), and

3,4-dihydro-2H-pyrane (9.3 g, 0.11 mol) and p-toluenesulfonic acid (1.9 g, 0.01 mol) were added thereto. Stirring was conducted at room temperature overnight. A 1N-sodium hydroxide aqueous solution was added to the reaction mixture, and extraction with dichloromethane was performed. The organic layer was washed with water, dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate=2:1→1:2). The purified product was concentrated under reduced pressure to thereby obtain 27.56 g (yield: 80%) of 2-nitro-N-[3-(tetrahydropyran-2-yloxy)propyl]benzenesulfonamide as a pale brown oil.

^{1}H-NMR ($CDCl_3$) δppm:

1.40-1.93 (6H, m), 3.12-3.38 (2H, m), 3.38-3.58 (2H, m), 3.75-3.92 (2H, m), 4.11 - 4.17 (1H, m), 4.51 - 4.54 (1H, m), 5.85 - 5.93 (1H, m), 7.63-7.79 (2H, m), 7.79-7.92 (1H, m), 8.07-8.20 (1H, m).

Reference Example 49

Synthesis of 2-nitro-N-[2-(7-oxo-7H-furo[2,3-c]pyridin-6-yl)ethyl]-N-[3-(tetrahydropyran-2-yloxy)propyl]benzenesulfon amide

Triphenylphosphine (393 mg, 1.5 mmol) and azodicarboxylic acid di-tert-butyl ester(345 mg, 1.5 mmol) were added to a tetrahydrofuran (THF) solution (10 ml) of 6-(2-hydroxyethyl)-6H-furo[2,3-c]pyridin-7-one (179 mg, 1.0 mmol) and 2-nitro-N-[3-(tetrahydropyran-2-yloxy)propyl]benzenesulfonamide (413 mg, 1.2 mmol), and stirred overnight. The resulting reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate=1:1→0:1). The purified product was concentrated to dryness under reduced pressure to thereby obtain 286 mg (yield: 57%) of 2-nitro-N-[2-(7-oxo-7H-furo[2,3-c]pyridin-6-yl)ethyl]-N-[3-(tetrahydropyran-2-yloxy)propyl]benzenesulfonamide as a white amorphous solid.

^{1}H-NMR ($CDCl_3$) δppm:

1.37-1.91 (8H, m), 3.25-3.59 (4H, m), 3.61-3.88 (4H, m), 4.27 (2H, t, J = 6.5 Hz), 4.45-4.49 (1H, m), 6.43 (1H, d, J = 7.0 Hz), 6.64 (1H,

s), 7.19 (1H, d, J = 7.0 Hz), 7.49-7.69 (3H, m), 7.72 (1H, s), 7.92-8.02 (1H, m).

Reference Example 50

Synthesis of 2-nitro-N-[2-(1-oxo-1H-isoquinolin-2-yl)ethyl]-N-[3-(tetrahydropyran-2-yloxy)propyl]benzenesulfonamide

Using an appropriate starting material and following the procedure of Reference Example 49, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

1.40-1.91 (8H, m), 3.21-3.61 (4H, m), 3.61-3.86 (4H, m), 4.21 (2H, t, J = 6.6 Hz), 4.45 - 4.48 (1H, m), 6.45 (1H, d, J = 7.3 Hz), 7.14 (1H, d, J = 7.3 Hz), 7.38-7.79 (6H, m), 7.91-8.01 (1H, m), 8.34 (1H, d, J = 7.5 Hz).

Reference Example 51

Synthesis of 2-nitro-N-[2-(1-oxo-3,4-dihydro-1H-isoquinolin-2-yl)ethyl]-N-[3-(tetrahydropyran-2-yloxy)propyl]benzenesulfonamide

Using an appropriate starting material and following the procedure of Reference Example 49, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

1.44-1.98 (8H, m), 3.01 (2H, t, J = 6.6 Hz), 3.28-3.82 (12H, m), 4.46 - 4.49 (1H, m), 7.18 (1H, d, J = 7.6 Hz), 7.29-7.72 (5H, m), 7.98-8.07 (2H, m).

Reference Example 52

Synthesis of N-(3-hydroxypropyl)-2-nitro-N-[2-(7-oxo-7H-furo[2,3-c]pyridin-6-yl)ethyl]benzenesulfonamide

Using an appropriate starting material and following the procedure of Reference Example 46, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

1.73-1.87 (2H, m), 3.51 (2H, t, J = 6.9 Hz), 3.63 (2H, t, J = 5.7 Hz), 3.71 (2H, t, J = 6.8 Hz), 4.27 (2H, t, J = 6.8 Hz), 6.46 (1H, d, J = 7.0 Hz), 6.65 (1H, d, J = 1.9 Hz), 7.20 (1H, d, J = 7.0 Hz), 7.50-7.69 (3H, m), 7.73 (1H, d, J = 1.9 Hz), 7.92-8.01 (1H, m).

Reference Example 53

Synthesis of N-(3-hydroxypropyl)-2-nitro-N-[2-(1-oxo-1H-isoquinolin-2-yl)ethyl]benzenesulfonamide

Using an appropriate starting material and following the procedure of Reference Example 46, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

1.72-1.89 (2H, m), 3.54 (2H, t, J = 6.7 Hz), 3.65 (2H, t, J = 5.5 Hz), 3.72 (2H, t, J = 6.7 Hz), 4.23 (2H, t, J = 6.8 Hz), 6.49 (1H, d, J = 7.3 Hz), 7.15 (1H, d, J = 7.3 Hz), 7.42-7.70 (6H, m), 7.90-8.00 (1H, m), 8.34 (1H, d, J = 7.9 Hz).

Reference Example 54

Synthesis of N-(3-hydroxypropyl)-2-nitro-N-[2-(1-oxo-3,4-dihydro-1H-isoquinolin-2-yl)ethyl]benzenesulfonamide

Using an appropriate starting material and following the procedure of Reference Example 46, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

1.75-2.05 (2H, m), 3.01 (2H, t, J = 6.2 Hz), 3.46-3.88 (10H, m), 7.18 (1H, d, J = 7.6 Hz), 7.34 (1H, d, J = 7.7 Hz), 7.39-7.42 (1H, m), 7.57-7.70 (3H, m), 7.97-8.06 (2H, m).

Reference Example 55

Synthesis of 3-{(2-nitrobenzenesulfonyl)-[2-(7-oxo-7H-furo[2,3-c]pyridin-6-yl)ethyl]amino}propyl methanesulfonate

Methanesulfonyl chloride (0.14 ml, 1.8 mmol) was added to a THF solution (30 ml) of N-(3-hydroxypropyl)-2-nitro-N-[2-(7-oxo-7H-furo[2,3-c]pyridin-6-yl)ethyl]benzenesulfonamide (644 mg, 1.5 mmol) and triethylamine (0.34 ml, 2.3 mmol), and stirred at room temperature overnight. Water was added to the reaction mixture, and extraction with dichloromethane was performed. The organic layer was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:methanol=1:0→10:1). The purified product was concentrated to dryness under reduced pressure to thereby obtain 480 mg (yield: 64%) of 3-{(2-nitrobenzenesulfonyl)-[2-(7-oxo-7H-furo

[2,3-c]pyridin-6-yl)ethyl]amino}propyl methanesulfonate as a white amorphous solid.

^{1}H-NMR ($CDCl_3$) δppm:

1.95-2.05 (2H, m), 3.04 (3H, s), 3.50 (2H, t, J = 7.1 Hz), 3.70 (2H, t, J = 6.7 Hz), 4.18 (2H, t, J = 5.8 Hz), 4.26 (2H, t, J = 6.7 Hz), 6.47 (1H, d, J = 7.0 Hz), 6.66 (1H, d, J = 1.9 Hz), 7.19 (1H, d, J = 7.0 Hz), 7.50 - 7.74 (4H, m), 7.94-8.02 (1H, m).

Reference Example 56

Synthesis of 3-{(2-nitrobenzenesulfonyl)-[2-(1-oxo-1H-isoquinolin-2-yl)ethyl]amino}propyl methanesulfonate

Using an appropriate starting material and following the procedure of Reference Example 55, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

1.98-2.09 (2H, m), 3.01 (3H, s), 3.52 (2H, t, J = 6.9 Hz), 3.71 (2H, t, J = 6.6 Hz), 4.17 (2H, t, J = 5.8 Hz), 4.21 (2H, t, J = 6.9 Hz), 6.47 (1H, d, J = 7.4 Hz), 7.13 (1H, d, J = 7.4 Hz), 7.45-7.70 (6H, m), 7.90-8.00 (1H, m), 8.33 (1H, d, J = 7.7 Hz).

Reference Example 57

Synthesis of 3-{(2-nitrobenzenesulfonyl)-[2-(1-oxo-3,4-dihydro-1H-isoquinolin-2-yl)ethyl]amino}propyl methanesulfonate

Using an appropriate starting material and following the procedure of Reference Example 55, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

2.04-2.19 (2H, m), 3.01 (2H, t, J = 6.7 Hz), 3.02 (3H, s), 3.39-3.48 (6H, m), 3.75 (2H, t, J = 7.2 Hz), 4.26 (2H, t, J = 5.9 Hz), 7.17 (1H, d, J = 7.4 Hz), 7.28-7.45 (2H, m), 7.60-7.74 (3H, m), 7.96-8.04 (2H, m).

Reference Example 58

Synthesis of N-(3-iodopropyl)-2-nitro-N-[2-(7-oxo-7H-furo[2,3-c]pyridin-6-yl)ethyl]benzenesulfonamide

3-{(2-Nitrobenzenesulfonyl)-[2-(7-oxo-7H-furo[2,3-c]pyridin-6-yl)ethyl]amino}propyl methanesulfonate (480 mg, 0.96 mmol) and sodium iodide (720 mg, 4.8 mmol) were added to acetone (20 ml),

and heated under reflux for 5 hours. The reaction mixture was cooled to room temperature, water was added, and extraction with dichloromethane was performed. The organic layer was dried over sodium sulfate, and concentrated under reduced pressure to thereby obtain 474 mg (yield: 93%) of N-(3-iodopropyl)-2-nitro-N-[2-(7-oxo-7H-furo [2,3-c]pyridin-6-yl)ethyl]benzenesulfonamide as a yellow amorphous solid.

^{1}H-NMR (DMSO-D_6) δppm:

1.89-2.02 (2H, m), 3.12 (2H, t, J = 6.9 Hz), 3.42 (2H, t, J = 7.3 Hz), 3.66 (2H, t, J = 5.8 Hz), 4.15 (2H, t, J = 5.9 Hz), 6.49 (1H, d, J = 7.0 Hz), 6.84 (1H, d, J = 1.9 Hz), 7.37 (1H, d, J = 7.0 Hz), 7.69-7.81 (2H, m), 7.87-7.99 (2H, m), 8.09 (1H, d, J = 1.9 Hz).

Reference Example 59

Synthesis of N-(3-iodopropyl)-2-nitro-N-[2-(1-oxo-1H-isoquinolin-2-yl)ethyl]benzenesulfonamide

Using an appropriate starting material and following the procedure of Reference Example 58, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

2.02-2.18 (2H, m), 3.06 (2H, t, J = 7.0 Hz), 3.44 (2H, t, J = 7.2 Hz), 3.72 (2H, t, J = 6.5 Hz), 4.21 (2H, t, J = 6.5 Hz), 6.46 (1H, d, J = 7.3 Hz), 7.13 (1H, d, J = 7.3 Hz), 7.41-7.70 (6H, m), 7.95-8.06 (1H, m), 8.34 (1H, d, J = 7.9 Hz).

Reference Example 60

Synthesis of N-(3-iodopropyl)-2-nitro-N-[2-(1-oxo-3,4-dihydro-1H-isoquinolin-2-yl)ethyl]benzenesulfonamide

Using an appropriate starting material and following the procedure of Reference Example 58, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

2.03-2.20 (2H, m), 3.02 (2H, t, J = 6.6 Hz), 3.12 (2H, t, J = 6.6 Hz), 3.50 (2H, t, J = 7.1 Hz), 3.56-3.70 (4H, m), 3.76 (2H, t, J = 7.0 Hz), 7.17 (1H, d, J = 7.5 Hz), 7.28-7.45 (2H, m), 7.60-7.70 (3H, m), 8.00-8.11 (2H, m).

Reference Example 61

Synthesis of tert-butyl methyl-[2-(2-nitrobenzenesulfonylamino) ethyl]carbamate

2-Nitrobenzenesulfonyl chloride (4.9 g, 22 mmol) was added to a dichloromethane solution (100 ml) of tert-butyl (2-aminoethyl)methyl carbamate (3.5 g, 20 mmol) and triethylamine (3.3 ml, 24 mmol) at 0°C, and stirred at room temperature overnight. Water was added to the reaction mixture, and extraction with dichloromethane was performed. The organic layer was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate=3:2→2:3). The purified product was concentrated under reduced pressure to thereby obtain 5.06 g (yield: 70%) of tert-butyl methyl-[2-(2-nitrobenzenesulfonylamino)ethyl]carbamate as a yellow oil.

^{1}H-NMR ($CDCl_3$) δppm:

1.45 (9H, s), 2.84 (3H, s), 3.26 - 3.41 (4H, m), 7.68-7.79 (2H, m), 7.79-7.90 (1H, m), 8.09-8.19 (1H, m).

Reference Example 62

Synthesis of 2-nitro-N-(2-pyridin-3-ylethyl)benzenesulfonamide

Using an appropriate starting material and following the procedure of Reference Example 61, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

2.88 (2H, t, J = 7.1 Hz), 3.41 (2H, q, J = 7.1 Hz), 5.44 (1H, t, J = 5.4 Hz), 7.18-7.22 (1H, m), 7.50 (1H, dt, J = 7.8 and 1.8 Hz), 7.71-7.77 (2H, m), 7.82-7.88 (1H, m), 8.07-8.12 (1H, m), 8.35 (1H, d, J = 1.8 Hz), 8.45 (1H, dd, J = 4.8 and 1.8 Hz).

Example 1

Synthesis of 7-(3-(1,3-dioxo-1,3-dihydroisoindol-2-yl)propoxy)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Potassium carbonate (2.99 g, 21.6 mmol) and N-(3-bromopropyl)phthalimide (2.32 g, 8.65 mmol) were added to a DMF solution (50 ml) of 1-ethyl-7-hydroxy-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione (1.89 g, 7.2 mmol), and

stirred at room temperature overnight. Water was added to the reaction mixture, and extraction with ethyl acetate was performed. The organic layer was washed with water and a saturated sodium chloride aqueous solution, in this order. The organic layer was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate=2:1→3:7). The purified product was concentrated to dryness under reduced pressure to thereby obtain 2.70 g (yield: 83%) of 7-(3-(1,3-dioxo-1,3-dihydroisoindol-2-yl) propoxy)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4] diazepine-2,4-dione as a white powder.

^{1}H-NMR ($CDCl_3$) δppm:

0.84 (3H, s), 1.13 (3H, t, J = 7.1 Hz), 1.52 (3H, s), 2.18-2.24 (2H, m), 3.33 (3H, s), 3.63-3.75 (1H, m), 3.93 (2H, t, J = 6.8 Hz), 4.06 (2H, t, J = 5.9 Hz), 4.10-4.10 (1H, m), 6.59 (1H, d, J = 2.8 Hz), 6.73 (1H, dd, J = 9.0 and 2.8 Hz), 7.16 (1H, d, J = 9.0 Hz), 7.72-7.76 (2H, m), 7.82-7.88 (2H, m).

Example 2

Synthesis of 7-(3-aminopropoxy)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Hydrazine hydrate (1.17 ml, 24 mmol) was added to a methanol solution (60 ml) of 7-[3-(1,3-dioxo-1,3-dihydroisoindol-2-yl) propoxy]-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4] diazepine-2,4-dione (2.70 g, 6.0 mmol), and stirred while heating under reflux for 2 hours. The reaction mixture was concentrated under reduced pressure. A 1N-sodium hydroxide aqueous solution was added to the residue, and stirred for 30 minutes, and extraction with dichloromethane was performed. The organic layer was washed with water and a saturated sodium chloride aqueous solution, in this order. The organic layer was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to thereby obtain 1.48 g (yield: 77%) of 7-(3-aminopropoxy)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione as a colorless oil.

^{1}H-NMR ($CDCl_3$) δppm:

0.86 (3H, s), 1.14 (3H, t, J = 7.1 Hz), 1.52 (3H, s), 1.90-2.00 (2H,

m), 2.94 (2H, t, J = 6.8 Hz), 3.40 (3H, s), 3.66-3.76 (1H, m), 4.08 (2H, t, J = 6.2 Hz), 4.11-4.21 (1H, m), 6.73 (1H, d, J = 2.8 Hz), 6.82 (1H, dd, J = 9.0 and 2.8 Hz), 7.20 (1H, d, J = 9.0 Hz).

Example 3

Synthesis of 7-(3-aminopropoxy)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione hydrochloride

A 4N-hydrogen chloride ethyl acetate solution (0.42 ml) was added to an ethyl acetate solution (3 ml) of 7-(3-aminopropoxy)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione (264 mg), and stirred at room temperature for 30 minutes. The reaction mixture was concentrated to dryness under reduced pressure to thereby obtain 0.22 g of 7-(3-aminopropoxy)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione hydrochloride as a white amorphous solid.

^{1}H-NMR (DMSO-D_6) δppm:

0.77 (3H, s), 1.01 (3H, t, J = 6.6 Hz), 1.33 (3H, s), 1.92-2.38 (4H, m), 3.33 (3H, s), 3.67-4.20 (6H, m), 6.95-7.00 (2H, m), 7.42 (1H, d, J = 8.8 Hz), 8.28 (1H, br-s).

Example 4

Synthesis of N-(3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl)-2-nitrobenzenesulfonamide

Triethylamine (0.8 ml, 5.7 mmol) was added to a dichloromethane solution (50 ml) of 7-(3-aminopropoxy)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione (1.22 g, 3.8 mmol) and ice-cooled. o-Nitrobenzenesulfonyl chloride (1.03 g, 4.2 mmol) was added to the resulting mixture, and stirred at room temperature for 2 hours. Water was added to the reaction mixture, and extraction with dichloromethane was performed. The organic layer was washed with water and a saturated sodium chloride aqueous solution, in this order, then dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate=1:1→0:1). The purified product was concentrated to dryness under reduced pressure to thereby obtain 1.86 g (yield: 97%) of

N-(3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl)-2-nitrobenzenesulfonamide as a white amorphous solid.

^{1}H-NMR ($CDCl_3$) δppm:

0.86 (3H, s), 1.15 (3H, t, J = 7.1 Hz), 1.52 (3H, s), 2.05-2.13 (2H, m), 3.34-3.40 (2H, m), 3.40 (3H, s), 3.65-3.77 (1H, m), 4.07-4.21 (3H, m), 5.76 (1H, t, J = 5.9 Hz), 6.77 (1H, d, J = 2.7 Hz), 6.82 (1H, dd, J = 8.9 and 2.8 Hz), 7.21 (1H, d, J = 9.0 Hz), 7.73-7.79 (2H, m), 7.85-7.89 (1H, m), 8.14-8.18 (1H, m).

Example 5

Synthesis of 1-ethyl-3,3,5-trimethyl-7-[3-(2-pyridin-3-ylethyl amino)propoxy]-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

1-Ethyl-7-(3-iodopropoxy)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione (5.3 mmol) was added to a methanol solution (100 ml) of 3-(2-aminoethyl)pyridine (3.3 g, 26.7 mmol), and stirred at 50°C for 9 hours. The reaction mixture was cooled to room temperature, and concentrated under reduced pressure. Water was added to the residue, and extraction with dichloromethane was performed. The organic layer was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane:methanol=20:1 →10:1). The purified product was concentrated under reduced pressure, and the residue was purified by basic silica gel column chromatography (ethyl acetate:methanol=1:0→10:1) again. The purified product was concentrated under reduced pressure to thereby obtain 1.57 g (yield: 70%) of 1-ethyl-3,3,5-trimethyl-7-[3-(2-pyridin-3-ylethylamino) propoxy]-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione as a yellow oil.

^{1}H-NMR ($CDCl_3$) δppm:

0.86 (3H, s), 1.14 (3H, t, J = 7.1 Hz), 1.52 (3H, s), 1.93-2.00 (2H,m), 2.80-2.96 (6H, m), 3.39 (3H, s), 3.66-3.73 (1H, m), 4.04 (2H, t, J = 6.1 Hz), 4.14-4.21 (1H, m), 6.70 (1H, d, J = 2.8 Hz), 6.78 (1H, dd, J = 9.0 and 2.0 Hz), 7.17-7.24 (2H, m), 7.54 (1H, dt, J = 7.8 and 1.9 Hz), 8.46 (1H, dd, J = 4.8 and 1.6 Hz), 8.49 (1H, d, J = 2.0 Hz).

Example 6

Synthesis of 1-ethyl-3,3,5-trimethyl-7-[3-(2-pyridin-3-ylethyl amino)propoxy]-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

A 4N-hydrogen chloride ethyl acetate solution (0.37 ml) was added to an ethyl acetate solution (10 ml) of 1-ethyl-3,3,5-trimethyl-7-[3-(2-pyridin-3-ylethylamino)propoxy]-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione (207 mg, 0.49 mmol), and stirred for 30 minutes at room temperature. The precipitated insoluble matter was collected by filtration, washed with ethyl acetate, and dried to thereby obtain 208 mg (yield: 85%) of 1-ethyl-3,3,5-trimethyl-7-[3-(2-pyridin-3-ylethylamino)propoxy]-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride as a pale yellow amorphous solid.

^{1}H-NMR (DMSO-D_6) δppm:

0.76 (3H, s), 1.01 (3H, t, J = 7.0 Hz), 1.32 (3H, s), 2.14-2.20 (2H, m), 3.10 (2H, br-s), 3.25-3.33 (6H, m), 3.61-3.73 (1H, m), 3.99-4.18 (4H, m), 6.92-6.99 (2H, m), 7.42 (1H, d, J = 8.9 Hz), 7.94-7.89 (1H, m), 8.46 (1H, d, J = 8.0 Hz), 8.80 (1H, dd, J = 5.5 and 1.0 Hz), 8.90 (1H, d, J = 1.0 Hz), 9.46 (2H, br-s).

Example 7

Synthesis of 1-ethyl-3,3,5-trimethyl-7-{3-[(2-pyridin-3-ylethyl) pyridin-4-ylmethylamino]propoxy}-1,5-dihydrobenzo[b][1,4] diazepine-2,4-dione

4-Pyridinecarbaldehyde (1.18 ml, 12.5 mmol) and a catalytic amount of acetic acid were added to a 1,2-dichloroethane solution (40 ml) of 1-ethyl-3,3,5-trimethyl-7-[3-(2-pyridin-3-ylethylamino) propoxy]-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione (4.44 g, 10.5 mmol), and stirred for 30 minutes. Sodium triacetoxyhydroborate (3.33 g, 15.7 mmol) was added to the resulting mixture, and stirred at room temperature overnight. The reaction mixture was diluted with dichloromethane, washed with water and a saturated sodium chloride aqueous solution in this order, then dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (ethyl acetate:methanol=1:0→9:1). The purified product was concentrated

under reduced pressure to thereby obtain 4.73 g (yield: 88%) of 1-ethyl-3,3,5-trimethyl-7-{3-[(2-pyridin-3-ylethyl)pyridin-4-ylmethylamino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione as a pale yellow oil.

^{1}H-NMR ($CDCl_3$) δppm:

0.86 (3H, s), 1.15 (3H, t, J = 7.0 Hz), 1.52 (3H, s), 1.87-1.95 (2H, m), 2.67-2.80 (6H, m), 3.40 (3H, s), 3.66-3.77 (3H, m), 3.89 (2H, t, J = 6.0 Hz), 4.09-4.21 (1H, m), 6.63 (1H, d, J = 2.7 Hz), 6.72 (1H, dd, J = 9.0 and 2.7 Hz), 7.12-7.22 (4H, m), 7.42 (1H, dt, J = 7.8 and 1.9 Hz), 8.42-8.46 (4H, m).

Example 8

Synthesis of 1-ethyl-3,3,5-trimethyl-7-{3-[(2-pyridin-3-ylethyl)pyridin-4-ylmethylamino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione trihydrochloride

Triphenylphosphine (186 mg, 0.71 mmol) and di-tert-butyl azodicarboxylate (163 mg, 0.71 mmol) were added to a tetrahydrofuran (THF) solution (5 ml) of 1-ethyl-7-hydroxy-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione (156 mg, 0.59 mmol) and 3-[(2-pyridin-3-ylethyl)pyridin-4-ylmethylamino]propan-1-ol (161 mg, 0.59 mmol), and stirred overnight. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:methanol=1:0→4:1), and the purified product was concentrated under reduced pressure. A 4N-hydrogen chloride ethyl acetate solution (0.29 ml) was added to the residue (ethyl acetate solution), stirred at room temperature for 30 minutes, and concentrated to dryness under reduced pressure to thereby obtain 206 mg (yield: 56%) of 1-ethyl-3,3,5-trimethyl-7-{3-[(2-pyridin-3-ylethyl)pyridin-4-ylmethylamino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione trihydrochloride as a white amorphous solid.

^{1}H-NMR (DMSO-D_6) δppm:

0.75 (3H, s), 1.01 (3H, t, J = 7.0 Hz), 1.32 (3H, s), 2.22-2.41 (2H, m), 3.15-3.53 (6H, m), 3.33 (3H, s), 3.64-3.71 (1H, m), 4.07-4.14 (3H, m), 4.62-4.86 (2H, m), 6.88-6.94 (2H, m), 7.42 (1H, d, J = 8.8 Hz), 8.03 (1H, dd, J = 8.0 and 5.7 Hz), 8.27-8.42 (2H, m), 8.54 (1H, d,

J = 8.0 Hz), 8.84 (1H, d, J = 4.8 Hz), 8.94-9.02 (3H, m).

Example 9

Synthesis of 1-isobutyl-3,3,5-trimethyl-7-{3-[(2-pyridin-3-yl ethyl)pyridin-4-ylmethylamino]propoxy}-1,5-dihydrobenzo[b][1,4] diazepine-2,4-dione trihydrochloride

N,N,N',N'-Tetramethylazodicarboxamide(TMAD)(189 mg, 1.1 mmol) and tri-n-butyl phosphine (0.28 ml, 1.1 mmol) were added to a THF solution (5 ml) of 7-hydroxy-1-isobutyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione (213 mg, 0.73 mmol) and 3-[(2-pyridin-3-ylethyl)pyridin-4-ylmethylamino]propan-1-ol (199 mg, 0.73 mmol), and stirred at room temperature overnight. Water was added to the reaction mixture, and extraction with dichloromethane was performed. The organic layer was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:methanol=20:1→10:1). The purified product was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (dichloromethane:methanol=40:1→10:1) again. The purified product was concentrated under reduced pressure. A 4N-hydrogen chloride ethyl acetate solution (0.57 ml) was added to the residue (ethyl acetate solution), stirred at room temperature for 30 minutes, and concentrated to dryness under reduced pressure to thereby obtain 480 mg (yield: quantitative) of 1-isobutyl-3,3,5-trimethyl-7-{3-[(2-pyridin-3-ylethyl)pyridin-4-ylmethylamino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione trihydrochloride as a white amorphous solid.

^{1}H-NMR (DMSO-D_6) δppm:

0.58 (3H, d, J = 6.6 Hz), 0.71 (3H, d, J = 6.6 Hz), 0.75 (3H, s), 1.33 (3H, s), 1.51-1.78 (2H, m), 2.19-2.38 (2H, m), 3.00-3.48 (7H, m), 3.34 (3H, s), 4.02-4.28 (2H, m), 4.38-4.59 (2H, m), 6.86-6.94 (2H, m), 7.45 (1H, d, J = 9.0 Hz), 7.63-7.67 (1H, m), 7.87 (2H, d, J = 5.2 Hz), 8.07 (1H, d, J = 7.9 Hz), 8.62 (1H, d, J = 1.3 Hz), 8.66-8.78 (3H, m).

Example 10

Synthesis of 3,3,5-trimethyl-1-propyl-7-{3-[(2-pyridin-3-ylethyl) pyridin-4-ylmethylamino]propoxy}-1,5-dihydrobenzo[b][1,4]

diazepine-2,4-dione trihydrochloride

Using an appropriate starting material and following the procedure of Example 9, the object compound was synthesized.

^{1}H-NMR (DMSO-D_6) δppm:

0.64 (3H, t, J = 7.4 Hz), 0.75 (3H, s), 1.32 (3H, s), 1.28-1.51 (2H, m), 2.18-2.41 (2H, m), 3.09-3.61 (7H, m), 3.32 (3H, s), 4.02-4.26 (3H, m), 4.47-4.82 (2H, m), 6.82-6.97 (2H, m), 7.42 (1H, d, J = 8.8 Hz), 7.92-8.03 (1H, m), 8.08-8.31 (2H, m), 8.41-8.50 (1H, m), 8.82 (1H, d, J = 5.6 Hz), 8.83-8.98 (3H, m).

Example 11

Synthesis of 3,3,5-trimethyl-1-(3-methylbutyl)-7-{3-[(2-pyridin-3-ylethyl)pyridin-4-ylmethylamino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione trihydrochloride

Using an appropriate starting material and following the procedure of Example 9, the object compound was synthesized.

^{1}H-NMR (DMSO-D_6) δppm:

0.68-1.80 (15H, m), 2.28-2.48 (2H, m), 3.19-3.40 (2H, m), 3.31 (3H, s), 3.40-3.64 (5H, m), 4.03-4.18 (2H, m), 4.18-4.33 (1H, m), 4.70-4.92 (2H, m), 6.87-6.99 (2H, m), 7.44 (1H, d, J = 8.9 Hz), 8.00-8.09 (1H, m), 8.38-8.50 (2H, m), 8.51-8.62 (1H, m), 8.86 (1H, d, J = 5.5 Hz), 8.94-9.08 (3H, m).

Example 12

Synthesis of 5-ethyl-1,3,3-trimethyl-7-{3-[(2-pyridin-3-ylethyl)pyridin-4-ylmethylamino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione trihydrochloride

Using an appropriate starting material and following the procedure of Example 9, the object compound was synthesized.

^{1}H-NMR (DMSO-D_6) δppm:

0.75 (3H, s), 1.03 (3H, t, J = 7.0 Hz), 1.32 (3H, s), 2.21-2.41 (2H, m), 3.15-3.32 (2H, m), 3.28 (3H, s), 3.32-3.58 (4H, m), 3.64-3.82 (1H, m), 4.01-4.18 (3H, m), 4.59-4.82 (2H, m), 6.86-7.00 (2H, m), 7.38 (1H, d, J = 8.9 Hz), 8.02 (1H, dd, J = 5.7 and 8.0 Hz), 8.32 (2H, s), 8.53 (1H, d, J = 8.1 Hz), 8.83 (1H, d, J = 5.2 Hz), 8.90-8.99 (3H, m).

Example 13

Synthesis of 1,3,3,5-tetraethyl-7-{3-[(2-pyridin-3-ylethyl)

pyridin-4-ylmethylamino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione trihydrochloride

Using an appropriate starting material and following the procedure of Example 9, the object compound was synthesized.

^{1}H-NMR (DMSO-D_6) δppm:

0.47 (3H, t, J = 7.1 Hz), 0.76-1.80 (13H, m), 1.80 - 2.00 (2H, m), 2.25-2.44 (2H, m), 3.22-3.40 (2H, m), 3.40-3.58 (2H, m), 3.58-3.79 (2H, m), 4.02-4.30 (4H, m), 4.70-4.92 (2H, m), 6.93 (2H, dd, J = 2.5 and 9.0 Hz), 6.99 (1H, d, J = 2.5 Hz), 7.44 (1H, d, J = 9.0 Hz), 8.06 (1H, dd, J = 5.8 and 7.9 Hz), 8.49 (1H, s), 8.60 (1H, d, J = 8.1 Hz), 8.86 (1H, d, J = 5.5 Hz), 8.96-9.09 (3H, m).

Example 14

Synthesis of 1,5-diethyl-3,3-dimethyl-7-{3-[(2-pyridin-3-ylethyl) pyridin-4-ylmethylamino]propoxy}-1,5-dihydrobenzo[b][1,4] diazepine-2,4-dione trihydrochloride

Using an appropriate starting material and following the procedure of Example 9, the object compound was synthesized.

^{1}H-NMR (DMSO-D_6) δppm:

0.73 (3H, s), 0.79-1.01 (6H, m), 1.31 (3H, s), 2.20-2.45 (2H, m), 3.18-3.38 (2H, m), 3.38-3.52 (2H, m), 3.52-3.79 (2H, m), 4.09-4.16 (2H, m), 4.16-4.35 (2H, m), 4.63-4.89 (2H, m), 6.92 (1H, dd, J = 2.6 and 9.0 Hz), 6.99 (1H, d, J = 2.6 Hz), 7.43 (1H, d, J = 9.0 Hz), 8.02 (1H, dd, J = 5.7 and 8.0 Hz), 8.34 (2H, s), 8.55 (1H, d, J = 8.0Hz), 8.84 (1H, d, J = 5.4 Hz), 8.94-8.97 (3H, m).

Example 15

Synthesis of 1,3,5-triethyl-7-{3-[(2-pyridin-3-ylethyl)pyridin-4-ylmethylamino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione trihydrochloride

Using an appropriate starting material and following the procedure of Example 9, the object compound was synthesized.

^{1}H-NMR (DMSO-D_6) δppm:

0.62-1.80 (11H, m), 2.22-2.41 (2H, m), 2.81-3.00 (1H, m), 3.12-3.37 (2H, m), 3.37-3.55 (4H, m), 3.55-3.85 (2H, m), 4.08-4.19 (2H, m), 4.19-4.38 (2H, m), 4.62-4.88 (2H, m), 6.92 (1H, d, J = 9.1 Hz), 7.05

(1H, s), 7.50 (1H, d, J = 9.1 Hz), 8.03 (1H, dd, J = 5.9 and 7.9 Hz), 8.37 (2H, s), 8.56 (1H, d, J = 8.0Hz), 8.84 (1H, d, J = 5.5 Hz), 8.92-9.02 (3H, m).

Example 16

Synthesis of 2-nitro-N-(2-pyridin-3-ylethyl)-N-[3-(1,3,3,5-tetramethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]benzenesulfonamide

2-Nitro-N-(2-pyridin-3-ylethyl)benzenesulfonamide (1.8 g, 5.8 mmol) and potassium carbonate (1.0 g, 7.2 mmol) were added to a DMF solution (30 ml) of 7-(3-iodopropoxy)-1,3,3,5-tetramethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione (2.0 g, 4.8 mmol) and stirred at room temperature overnight. The reaction mixture was added to ice water, and extraction with ethyl acetate was performed. The organic layer was washed with water, dried over anhydrous sodium sulfate, concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate=1:2→ethyl acetate→ethyl acetate:methanol=20:1). The purified product was concentrated to dryness under reduced pressure to thereby obtain 2.29 g (yield: 80%) of 2-nitro-N-(2-pyridin-3-ylethyl)-N-[3-(1,3,3,5-tetramethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]benzenesulfonamide as a yellow amorphous solid.

^{1}H-NMR ($CDCl_3$) δppm:

0.86 (3H, s), 1.53 (3H, s), 2.02-2.12 (2H, m), 2.91 (2H, t, J = 8.1 Hz), 3.39 (3H, s), 3.41 (3H, s), 3.57 (2H, t, J = 8.4 Hz), 3.60 (2H, t, J = 7.4 Hz), 4.01 (2H, t, J = 5.9 Hz), 6.71 (1H, d, J = 2.7 Hz), 6.77 (1H, d, J = 8.8 Hz), 7.14 (1H, d, J = 8.9 Hz), 7.18-7.24 (1H, m), 7.48-7.64 (4H, m), 8.00 (1H, d, J = 9.2 Hz), 8.41 (1H, d, J = 2.1 Hz), 8.45 (1H, d, J = 4.8 Hz).

Example 17

Synthesis of 2-nitro-N-(2-pyridin-3-ylethyl)-N-[3-(1,3,3,5-tetramethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]benzenesulfonamide hydrochloride

A 4N-hydrogen chloride ethyl acetate solution (0.57 ml) was added to an ethyl acetate solution (1 ml) of 2-nitro-N-(2-pyridin-3-ylethyl)-N-[3-(1,3,3,5-tetramethyl-2,4-

dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl] benzenesulfonamide (236 mg), and stirred at room temperature for 1 minute. The precipitated insoluble matter was collected by filtration, washed with ethyl acetate, and dried to thereby obtain 163 mg (yield: 65%) of 2-nitro-N-(2-pyridin-3-ylethyl)-N-[3-(1,3,3,5-tetramethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy) propyl]benzenesulfonamide hydrochloride as a white powder.

^{1}H-NMR (DMSO-D_6) δppm:

0.76 (3H, s), 1.33 (3H, s), 1.89-2.08 (2H, m), 3.10 (2H, t, J = 7.0 Hz), 3.30 (3H, s), 3.33 (3H, s), 3.55 (2H, t, J = 7.6 Hz), 3.69 (2H, t, J = 6.8 Hz), 4.00 (2H, t, J = 6.0 Hz), 6.82-6.95 (2H, m), 7.34 (1H, d, J = 8.8 Hz), 7.76-7.96 (4H, m), 8.03 (1H, d, J = 7.4 Hz), 8.40 (1H, d, J = 7.8 Hz), 8.75 (1H, d, J = 5.3 Hz), 8.85 (1H, s).

Example 18

Synthesis of 1,3,3,5-tetramethyl-7-[3-(2-pyridin-3-ylethylamino) propoxy]-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Lithium hydroxide (0.36 g, 15 mmol) and thioglycolic acid (0.48 ml, 6.9 mmol) were added to a DMF solution (20 ml) of 2-nitro-N-(2-pyridin-3-ylethyl)-N-[3-(1,3,3,5-tetramethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl] benzenesulfonamide (2.05 g, 3.4 mmol), and stirred at room temperature for 3 days. The reaction mixture was added to ice water, and extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:methanol=20:1→dichloromethane:methanol=10:1→4:1). The purified product was concentrated under reduced pressure to thereby obtain 1.13 g (yield: 81%) of 1,3,3,5-tetramethyl-7-[3-(2-pyridin-3-ylethylamino)propoxy]-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione as a yellow oil.

^{1}H-NMR ($CDCl_3$) δppm:

0.87 (3H, s), 1.53 (3H, s), 1.92-2.02 (2H, m), 2.78-2.90 (4H, m), 2.93 (2H, t, J = 6.5 Hz), 3.39 (3H, s), 3.41 (3H, s), 4.04 (2H, t, J = 6.2 Hz), 6.71 (1H, d, J = 2.7 Hz), 6.78 (1H, dd, J = 2.7 and 8.9 Hz), 7.13 (1H, d, J = 9.0 Hz), 7.16-7.25 (1H, m), 7.54 (1H, d, J = 7.8 Hz), 8.46

(1H, dd, J = 1.6 and 4.8 Hz), 8.49 (1H, d, J = 1.6 Hz).

Example 19

Synthesis of 1,3,3,5-tetramethyl-7-{3-[(2-pyridin-3-ylethyl) pyridin-4-ylmethylamino]propoxy}-1,5-dihydrobenzo[b][1,4] diazepine-2,4-dione trihydrochloride

Using an appropriate starting material and following the procedure of Example 8, the object compound was synthesized.

^{1}H-NMR (DMSO-D_6) δppm:

0.76 (3H, s), 1.33 (3H, s), 2.18-2.40 (2H, m), 3.10-3.64 (6H, m), 3.30 (3H, s), 3.33 (3H, s), 3.97-4.14 (2H, m), 4.40-4.72 (2H, m), 6.81-6.92 (2H, m), 7.36 (1H, d, J = 8.6 Hz), 7.73-8.02 (3H, m), 8.28 (1H, d, J = 6.4 Hz), 8.68-8.82 (4H, m).

Example 20

Synthesis of 3,3-diethyl-1,5-dimethyl-7-{3-[(2-pyridin-3-ylethyl) pyridin-4-ylmethylamino]propoxy}-1,5-dihydrobenzo[b][1,4] diazepine-2,4-dione trihydrochloride

Using an appropriate starting material and following the procedure of Example 8, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.54 (3H, t, J = 7.5 Hz), 1.01 (3H, t, J = 7.5 Hz), 1.12-1.31 (4H, m), 2.09-2.24 (2H, m), 2.99-3.41 (6H, m), 3.38 (3H, s), 3.41 (3H, s), 3.97-4.08 (2H, m), 4.40-4.88 (2H, m), 6.67 (1H, d, J = 2.6 Hz), 6.74 (1H, dd, J = 9.0 and 2.6 Hz), 7.14 (1H, d, J = 9.0 Hz), 7.51-7.62 (1H, m), 7.70 (2H, d, J = 5.3 Hz), 7.96 (1H, d, J = 7.1 Hz), 8.61 (1H, d, J = 4.7 Hz), 8.70 (2H, d, J = 5.3 Hz), 8.89 (1H, s).

Example 21

Synthesis of N-[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]-2-nitro-N-[2-(1-oxo-1H-isoquinolin-2-yl)ethyl]benzenesulfonamide

Potassium carbonate (0.22 g, 1.6 mmol) was added to a DMF solution (10 ml) of N-(3-iodopropyl)-2-nitro-N-[2-(1-oxo-1H-isoquinolin-2-yl)ethyl]benzenesulfonamide (0.57 g, 1.05 mmol) and 1-ethyl-7-hydroxy-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4] diazepine-2,4-dione (0.33 g, 1.26 mmol), and stirred at room temperature overnight. The reaction mixture was added to ice water,

and extraction with ethyl acetate was performed. The organic layer was washed with 1N-sodium hydroxide aqueous solution and water, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate=1:1→0:1). The purified product was concentrated to dryness under reduced pressure to thereby obtain 0.49 g (yield: 69%) of N-[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]-2-nitro-N-[2-(1-oxo-1H-isoquinolin-2-yl)ethyl]benzenesulfonamide as a white amorphous solid.

^{1}H-NMR ($CDCl_3$) δppm:

0.84 (3H, s), 1.14 (3H, t, J = 7.0 Hz), 1.52 (3H, s), 2.08-2.14 (2H, m), 3.39 (3H, s), 3.62 (2H, t, J = 7.4 Hz), 3.66-3.77 (3H, m), 3.94 (2H, t, J = 5.8 Hz), 4.13-4.22 (1H, m), 4.24 (2H, t, J = 6.7 Hz), 6.46 (1H, d, J = 7.3 Hz), 6.67 (1H, d, J = 2.7 Hz), 6.72 (1H, dd, J = 8.9 and 2.7 Hz), 7.12-7.19 (2H, m), 7.47-7.67 (6H, m), 7.95-7.98 (1H, m), 8.35 (1H, d, J = 7.5 Hz).

Example 22

Synthesis of 1-ethyl-3,3,5-trimethyl-7-{3-[2-(1-oxo-1H-isoquinolin-2-yl)ethylamino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 18, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.84 (3H, s), 1.14 (3H, t, J = 7.0 Hz), 1.52 (3H, s), 1.92-2.00 (2H, m), 2.87 (2H, t, J = 6.7 Hz), 3.06 (2H, t, J = 6.2 Hz), 3.38 (3H, s), 3.63-3.74 (1H, m), 4.02 (2H, t, J = 6.1 Hz), 4.09-4.23 (3H, m), 6.46 (1H, d, J = 7.3 Hz), 6.69 (1H, d, J = 2.7 Hz), 6.74 (1H, dd, J = 9.0 and 2.7 Hz), 7.10-7.16 (2H, m), 7.46-7.51 (2H, m), 7.64 (1H, t, J = 8.1 Hz), 8.41 (1H, d, J = 8.2 Hz).

Example 23

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{[2-(1-oxo-1H-isoquinolin-2-yl)ethyl]pyridin-4-ylmethylamino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using appropriate starting materials and following the

procedures of Examples 7 and 6, the object compound was synthesized.

^{1}H-NMR (DMSO-D_6) δppm:

0.74 (3H, s), 1.01 (3H, t, J = 7.0 Hz), 1.32 (3H, s), 2.01-2.39 (2H, m), 2.89-3.51 (2H, m), 3.30 (3H, s), 3.61-3.73 (1H, m), 3.89-4.12 (5H, m), 4.19-4.77 (4H, m), 6.67 (1H, d, J = 7.0 Hz), 6.71-6.90 (2H, m), 7.37 (1H, d, J = 9.0 Hz), 7.50-7.54 (2H, m), 7.66-7.76 (2H, m), 8.20 (1H, d, J = 8.0 Hz), 7.87-8.13 (2H, m), 8.60-8.96 (2H, m).

Example 24

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{[2-(1-oxo-1H-isoquinolin-2-yl)ethyl]pyridin-4-ylmethylamino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

White powder (ethyl acetate)

Melting point 119.8-121.6°C

^{1}H-NMR ($CDCl_3$) δppm:

0.86 (3H, s), 1.16 (3H, t, J = 7.0 Hz), 1.53 (3H, s), 1.87-1.96 (2H, m), 2.70-2.74 (2H, m), 2.83-2.93 (2H, m), 3.36 (3H, s), 3.36-3.74 (3H, m), 3.86 (2H, t, J = 6.0 Hz), 4.10 (2H, t, J = 6.1 Hz), 4.12-4.21 (1H, m), 6.41 (1H, d, J = 7.3 Hz), 6.58-6.62 (2H, m), 6.98 (1H, d, J = 7.3 Hz), 7.08-7.17 (3H, m), 7.47-7.52 (2H, m), 7.66 (1H, td, J = 7.5 and 1.7 Hz), 8.27 (2H, dd, J = 4.4 and 1.6 Hz), 8.59 (1H, dt, J = 8.1 and 0.7 Hz).

Example 25

Synthesis of 2-nitro-N-[2-(7-oxo-7H-furo[2,3-c]pyridin-6-yl)ethyl]-N-[3-(1,3,3,5-tetramethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]benzenesulfonamide

Using an appropriate starting material and following the procedure of Example 21, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.85 (3H, s), 1.53 (3H, s), 2.03-2.15 (2H, m), 3.39 (3H, s), 3.42 (3H, s), 3.59 (2H, t, J = 7.4 Hz), 3.73 (2H, t, J = 6.9 Hz), 3.94 (2H, t, J = 5.8 Hz), 4.29 (2H, t, J = 6.7 Hz), 6.45 (1H, d, J = 7.0 Hz), 6.64 (1H, d, J = 2.0 Hz), 6.69-6.75 (2H, m), 7.12 (1H, d, J = 8.8 Hz), 7.19 (1H, d, J = 7.0 Hz), 7.56-7.66 (3H, m), 7.73 (1H, d, J = 1.9 Hz), 7.98-8.02

(1H, m).

Example 26

Synthesis of 1,3,3,5-tetramethyl-7-{3-[2-(7-oxo-7H-furo[2,3-c]pyridin-6-yl)ethylamino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 18, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.86 (3H, s), 1.53 (3H, s), 1.90-2.02 (2H, m), 2.87 (2H, t, J = 6.7 Hz), 3.07 (2H, t, J = 6.2 Hz), 3.39 (3H, s), 3.41 (3H, s), 4.03 (2H, t, J = 6.1 Hz), 4.20 (2H, t, J = 6.5 Hz), 6.45 (1H, d, J = 7.0 Hz), 6.65 (1H, d, J = 2.0 Hz), 6.72 (1H, d, J = 2.7 Hz), 6.78 (1H, dd, J = 2.7 and 8.9 Hz), 7.12 (1H, d, J = 8.9 Hz), 7.17 (1H, d, J = 7.0 Hz), 7.74 (1H, d, J = 2.0 Hz).

Example 27

Synthesis of 1,3,3,5-tetramethyl-7-(3-{[2-(7-oxo-7H-furo[2,3-c]pyridin-6-yl)ethyl]pyridin-4-ylmethylamino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using appropriate starting materials and following the procedures of Examples 7 and 6, the object compound was synthesized.

^{1}H-NMR (DMSO-D_6) δppm:

0.76 (3H, s), 1.33 (3H, s), 1.89-2.32 (2H, m), 2.89-3.51 (6H, m), 3.30 (3H, s), 3.33 (3H, s), 3.91-4.12 (2H, m), 4.22-4.61 (2H, m), 6.62 (1H, d, J = 6.5 Hz), 6.72-6.98 (3H, m), 7.35 (1H, d, J = 8.9 Hz), 7.56 (1H, d, J = 7.0 Hz), 8.08 (2H, br-s), 8.13 (1H, s), 8.81 (2H, br-s).

Example 28

Synthesis of N-[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]-2-nitro-N-[2-(7-oxo-7H-furo[2,3-c]pyridin-6-yl)ethyl]benzenesulfonamide

Using an appropriate starting material and following the procedure of Example 21, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.84 (3H, s), 1.14 (3H, t, J = 7.1 Hz), 1.52 (3H, s), 2.06-2.13 (2H, m), 3.40 (3H, s), 3.57-3.75 (5H, m), 3.94 (2H, t, J = 5.8 Hz), 4.11-4.20 (1H, m), 4.29 (2H, t, J = 6.9 Hz), 6.45 (1H, d, J = 7.0 Hz), 6.64 (1H,

d, J = 2.0 Hz), 6.70-6.76 (2H, m), 7.18 (1H, d, J = 8.9 Hz), 7.20 (1H, d, J = 7.0 Hz), 7.55-7.66 (3H, m), 7.74 (1H, d, J = 2.0 Hz), 7.99-8.02 (1H, m).

Example 29

Synthesis of 1-ethyl-3,3,5-trimethyl-7-{3-[2-(7-oxo-7H-furo [2,3-c]pyridin-6-yl)ethylamino]propoxy}-1,5-dihydrobenzo[b][1,4] diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 18, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.85 (3H, s), 1.14 (3H, t, J = 7.1 Hz), 1.52 (3H, s), 1.92-2.01 (2H, m), 2.86 (2H, t, J = 6.8 Hz), 3.05 (2H, t, J = 6.2 Hz), 3.39 (3H, s), 3.66-3.75 (1H, m), 4.02 (2H, t, J = 6.1 Hz), 4.12-4.24 (3H, m), 6.43 (1H, d, J = 7.0 Hz), 6.64 (1H, d, J = 2.0 Hz), 6.71 (1H, d, J = 2.8 Hz), 6.78 (1H, dd, J = 9.0 and 2.8 Hz), 7.14 (1H, d, J = 7.0 Hz), 7.18 (1H, d, J = 9.0 Hz), 7.73 (1H, d, J = 2.0 Hz).

Example 30

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{[2-(7-oxo-7H-furo [2,3-c]pyridin-6-yl)ethyl]pyridin-4-ylmethylamino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

White powder (ethyl acetate-n-hexane)

Melting point 80.7-82.8°C

^{1}H-NMR ($CDCl_3$) δppm:

0.86 (3H, s), 1.15 (3H, t, J = 7.1 Hz), 1.52 (3H, s), 1.89-1.97 (2H, m), 2.73 (2H, t, J = 6.8 Hz), 2.87 (2H, t, J = 4.9 Hz), 3.40 (3H, s), 3.66-3.77 (3H, m), 3.91 (2H, t, J = 6.1 Hz), 4.09-4.22 (3H, m), 6.37 (1H, d, J = 7.0 Hz), 6.64-6.72 (3H, m), 6.99 (1H, d, J = 7.0 Hz), 7.09 (2H, d, J = 5.9 Hz), 7.19 (1H, d, J = 8.9 Hz), 7.75 (1H, d, J = 2.0 Hz), 8.33 (2H, dd, J = 4.5 and 1.5 Hz).

Example 31

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{[2-(7-oxo-7H-furo [2,3-c]pyridin-6-yl)ethyl]pyridin-4-ylmethylamino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 3, the object compound was synthesized.

^{1}H-NMR (DMSO-D_6) δppm:

0.75 (3H, s), 1.01 (3H, t, J = 7.0 Hz), 1.32 (3H, s), 1.98-2.20 (2H, m), 2.92-3.40 (4H, m), 3.31 (3H, s), 3.63-3.71 (1H, m), 3.99-4.12 (4H, m), 4.22-4.66 (3H, m), 6.62 (1H, d, J = 6.7 Hz), 6.82-6.90 (3H, m), 7.39 (1H, d, J = 9.0 Hz), 7.55 (1H, d, J = 6.8 Hz), 7.89-8.19 (3H, m), 8.65-8.94 (2H, m).

Example 32

Synthesis of 2-nitro-N-[2-(1-oxo-3,4-dihydro-1H-isoquinolin-2-yl) ethyl]-N-[3-(1,3,3,5-tetramethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]benzenesulfonamide

Using an appropriate starting material and following the procedure of Example 21, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.85 (3H, s), 1.53 (3H, s), 2.10-2.20 (2H, m), 2.95 - 3.07 (2H, m), 3.39 (3H, s), 3.41 (3H, s), 3.55-3.69 (6H, m), 3.79 (2H, t, J = 6.9 Hz), 3.99 (2H, t, J = 5.9 Hz), 6.65-6.77 (2H, m), 7.11 (1H, d, J = 8.8 Hz), 7.18 (1H, d, J = 7.8 Hz), 7.30-7.49 (2H, m), 7.58-7.69 (3H, m), 7.98-8.08 (2H, m).

Example 33

Synthesis of 1,3,3,5-tetramethyl-7-{3-[2-(1-oxo-3,4-dihydro-1H-isoquinolin-2-yl)ethylamino]propoxy}-1,5-dihydrobenzo[b][1,4] diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 18, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.86 (3H, s), 1.53 (3H, s), 1.92-2.02 (2H, m), 2.87-3.02 (6H, m), 3.38 (3H, s), 3.40 (3H, s), 3.62 (2H, t, J = 6.4 Hz), 3.72 (2H, t, J = 6.5 Hz), 4.06 (2H, t, J = 6.1 Hz), 6.72 (1H, d, J = 2.7 Hz), 6.79 (1H, dd, J = 2.7 and 9.0 Hz), 7.10 (1H, d, J = 8.9 Hz), 7.17 (1H, d, J = 7.4 Hz), 7.29-7.43 (2H, m), 8.05 (1H, d, J = 7.6 Hz).

Example 34

Synthesis of 1,3,3,5-tetramethyl-7-(3-{[2-(1-oxo-3,4-dihydro-1H-isoquinolin-2-yl)ethyl]pyridin-4-ylmethylamino}propoxy)-1,5-

dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using appropriate starting materials and following the procedures of Examples 7 and 6, the object compound was synthesized.

^{1}H-NMR (DMSO-D_6) δppm:

0.76 (3H, s), 1.33 (3H, s), 2.20-2.41 (2H, m), 2.98-3.08 (2H, m), 3.16-3.45 (4H, m), 3.29 (3H, s), 3.33 (3H, s), 3.53-3.71 (2H, m), 3.82-4.01 (2H, m), 4.03-4.20 (2H, m), 4.55-4.89 (2H, m), 6.81-6.97 (2H, m), 7.28-7.40 (3H, m), 7.42-7.54 (1H, m), 7.87 (1H, d, J = 7.6 Hz), 8.28 (2H, d, J = 4.9 Hz), 8.94 (2H, d, J = 5.6 Hz).

Example 35

Synthesis of N-[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]-2-nitro-N-[2-(1-oxo-3,4-dihydro-1H-isoquinolin-2-yl)ethyl]benzenesulfonamide

Using an appropriate starting material and following the procedure of Example 21, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.84 (3H, s), 1.14 (3H, t, J = 7.0 Hz), 1.52 (3H, s), 2.10-2.24 (2H, m), 3.01 (2H, t, J = 6.5 Hz), 3.39 (3H, s), 3.59-3.87 (9H, m), 3.99 (2H, t, J = 5.9 Hz), 4.08-4.23 (1H, m), 6.69 (1H, d, J = 2.9 Hz), 6.74 (1H, dd, J = 2.7 and 8.8 Hz), 7.17 (2H, d, J = 9.0 Hz), 7.29-7.48 (2H, m), 7.57-7.69 (3H, m), 8.00-8.05 (2H, m).

Example 36

Synthesis of 1-ethyl-3,3,5-trimethyl-7-{3-[2-(1-oxo-3,4-dihydro-1H-isoquinolin-2-yl)ethylamino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 18, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.85 (3H, s), 1.14 (3H, t, J = 7.0 Hz), 1.52 (3H, s), 1.91-2.06 (2H, m), 2.82-3.02 (6H, m), 3.38 (3H, s), 3.53-3.78 (5H, m), 4.06 (2H, t, J = 6.1 Hz), 4.09-4.25 (1H, m), 6.72 (1H, d, J = 2.7 Hz), 6.78 (1H, dd, J = 2.7 and 9.0 Hz), 7.16 (2H, d, J = 8.9 Hz), 7.28-7.48 (2H, m), 8.05 (1H, d, J = 7.6 Hz).

Example 37

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{[2-(1-oxo-3,4-dihydro-

1H-isoquinolin-2-yl)ethyl]pyridin-4-ylmethylamino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using appropriate starting materials and following the procedures of Examples 7 and 6, the object compound was synthesized.

^{1}H-NMR (DMSO-D_6) δppm:

0.75 (3H, s), 1.01 (3H, t, J = 7.0 Hz), 1.32 (3H, s), 2.22-2.43 (2H, m), 2.98-3.10 (2H, m), 3.20-3.49 (4H, m), 3.32 (3H, s), 3.57-3.75 (3H, m), 3.90-4.08 (3H, m), 4.08-4.20 (2H, m), 4.65-4.90 (2H, m), 6.80-6.97 (2H, m), 7.28-7.45 (3H, m), 7.45-7.55 (1H, m), 7.87 (1H, d, J = 7.6 Hz), 8.38 (2H, d, J = 5.7 Hz), 8.99 (2H, d, J = 6.1 Hz).

Example 38

Synthesis of 2-nitro-N-[2-(1-oxo-1H-isoquinolin-2-yl)ethyl]-N-[3-(1,3,3,5-tetramethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]benzenesulfonamide

Using an appropriate starting material and following the procedure of Example 21, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.85 (3H, s), 1.53 (3H, s), 1.99-2.15 (2H, m), 3.39 (3H, s), 3.41 (3H, s), 3.61 (2H, t, J = 6.9 Hz), 3.74 (2H, t, J = 6.8 Hz), 3.94 (2H, t, J = 5.6 Hz), 4.24 (2H, t, J = 6.7 Hz), 6.45 (1H, d, J = 7.3 Hz), 6.60-6.74 (2H, m), 7.02-7.18 (2H, m), 7.41-7.70 (6H, m), 7.88-8.00 (1H, m), 8.35 (1H, d, J = 8.3 Hz).

Example 39

Synthesis of 1,3,3,5-tetramethyl-7-{3-[2-(1-oxo-1H-isoquinolin-2-yl)ethylamino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 18, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.86 (3H, s), 1.53 (3H, s), 1.89-2.04 (2H, m), 2.87 (2H, t, J = 6.8 Hz), 3.07 (2H, t, J = 6.2 Hz), 3.38 (3H, s), 3.39 (3H, s), 4.03 (2H, t, J = 6.1 Hz), 4.08-4.21 (2H, m), 6.47 (1H, d, J = 7.3 Hz), 6.70 (1H, d, J = 2.7 Hz), 6.75 (1H, dd, J = 2.7 and 9.0 Hz), 7.09 (1H, d, J = 8.9 Hz), 7.13 (1H, d, J = 7.4 Hz), 7.41-7.55 (2H, m), 7.60-7.70 (1H, m), 8.41 (1H, d, J = 8.0 Hz).

Example 40

Synthesis of 1,3,3,5-tetramethyl-7-(3-{[2-(1-oxo-1H-isoquinolin-2-yl)ethyl]pyridin-4-ylmethylamino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using appropriate starting materials and following the procedures of Examples 7 and 6, the object compound was synthesized.

^{1}H-NMR (DMSO-D_6) δppm:

0.75 (3H, s), 1.33 (3H, s), 2.09-2.38 (2H, m), 3.01-3.56 (6H, m), 3.30 (3H, s), 3.32 (3H, s), 3.93-4.18 (2H, m), 4.30-4.54 (2H, m), 6.62-6.73 (1H, m), 6.73-6.96 (2H, m), 7.34 (1H, d, J = 8.9 Hz), 7.48-7.62 (2H, m), 7.62-7.81 (2H, m), 8.12-8.38 (3H, m), 8.76-9.05 (2H, m).

Example 41

Synthesis of tert-butyl methyl-(2-{(2-nitrobenzenesulfonyl)-[3-(1,3,3,5-tetramethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]amino}ethyl)carbamate

Using an appropriate starting material and following the procedure of Example 21, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.86 (3H, s), 1.46 (9H, s), 1.53 (3H, s), 2.01-2.15 (2H, m), 2.87 (3H, s), 3.39 (3H, s), 3.41 (3H, s), 3.43 - 3.48 (4H, m), 3.58 (2H, t, J = 6.9 Hz), 3.99 (2H, t, J = 5.5 Hz), 6.69 (1H, d, J = 2.7 Hz), 6.75 (1H, dd, J = 2.7 and 8.9 Hz), 7.12 (1H, d, J = 9.1 Hz), 7.57-7.72 (3H, m), 7.98-8.08 (1H, m).

Example 42

Synthesis of tert-butyl methyl-{2-[3-(1,3,3,5-tetramethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl amino]ethyl}carbamate

Using an appropriate starting material and following the procedure of Example 18, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.87 (3H, s), 1.46 (9H, s), 1.53 (3H, s), 1.91-2.04 (2H, m), 2.80 (2H, t, J = 6.5 Hz), 2.84 (2H, t, J = 7.0 Hz), 2.88 (3H, s), 3.35 (2H, t, J = 6.5 Hz), 3.39 (3H, s), 3.41 (3H, s), 4.06 (2H, t, J = 6.2 Hz), 6.73 (1H, d, J = 2.7 Hz), 6.81 (1H, dd, J = 2.7 and 9.0 Hz), 7.13 (1H, d, J = 9.0 Hz).

Example 43

Synthesis of tert-butyl methyl-(2-{pyridin-4-ylmethyl-[3-(1,3,3,5-tetramethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]amino}ethyl)carbamate

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.87 (3H, s), 1.44 (9H, br), 1.53 (3H, s), 1.90-2.02 (2H, m), 2.63 (2H, t, J = 6.9 Hz), 2.67 (2H, t, J = 6.9 Hz), 2.79 (3H, br), 3.33 (2H, br), 3.40 (3H, s), 3.41 (3H, s), 3.65 (2H, s), 4.00 (2H, t, J = 6.1 Hz), 6.66 (1H, d, J = 2.7 Hz), 6.75 (1H, dd, J = 2.7 and 8.9 Hz), 7.13 (1H, d, J = 8.9 Hz), 7.25 (2H, d, J = 6.5 Hz), 8.48 (2H, d, J = 5.7 Hz).

Example 44

Synthesis of 1,3,3,5-tetramethyl-7-{3-[(2-methylaminoethyl)-pyridin-4-ylmethylamino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

A 4N-hydrogen chloride ethyl acetate solution (3.2 ml) was added to an ethyl acetate solution (30 ml) of tert-butyl methyl-(2-{pyridin-4-ylmethyl-[3-(1,3,3,5-tetramethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]amino}ethyl)carbamate (1.43 g, 2.5 mmol) and stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in dichloromethane, and trifluoroacetic acid (3 ml) was added thereto. Stirring was conducted at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in a dichloromethane-methanol mixture solvent. Polymer-bonded quaternary ammonium carbonate (PL-HCO3MP) was added thereto to neutralize the mixture. The resulting reaction mixture was filtered. The filtrate was concentrated under reduced pressure to thereby obtain 1.44 g (yield: quantitative) of 1,3,3,5-tetramethyl-7-{3-[(2-methylaminoethyl)pyridin-4-ylmethylamino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione as a pale brown oil.

^{1}H-NMR ($CDCl_3$) δppm:

0.85 (3H, s), 1.53 (3H, s), 1.92-2.06 (2H, m), 2.56 (3H, s), 2.72 (2H, t, J = 7.0 Hz), 2.89 (2H, t, J = 5.6 Hz), 3.03 (2H, t, J = 5.6 Hz), 3.38 (3H, s), 3.39 (3H, s), 3.68 (2H, s), 4.00 (2H, t, J = 5.6 Hz), 6.67 (1H, d, J = 2.7 Hz), 6.75 (1H, dd, J = 2.7 and 8.9 Hz), 7.12 (1H, d, J = 8.9 Hz), 7.30 (2H, d, J = 5.8 Hz), 8.51 (2H, d, J = 4.6 Hz).

Example 45

Synthesis of N-methyl-N-(2-{pyridin-4-ylmethyl-[3-(1,3,3,5-tetramethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]amino}ethyl)benzamide dihydrochloride

1-(3-Dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (WSC) (144 mg, 0.75 mmol) and 1-hydroxybenzotriazole (HOBt) (115 mg, 0.75 mmol) were added to a DMF solution (5 ml) of 1,3,3,5-tetramethyl-7-{3-[(2-methylaminoethyl)pyridin-4-ylmethyl amino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione (227 mg, 0.5 mmol) and benzoic acid (92 mg, 0.75 mmol), and stirred at room temperature overnight. Water was added to the reaction mixture, and extraction with ethyl acetate was performed. The organic layer was washed with water, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:methanol=1:0→10:1). The purified product was concentrated under reduced pressure, and a 4N-hydrogen chloride ethyl acetate solution (0.14 ml) was added to the residue (an ethyl acetate solution). The precipitated insoluble matter was collected by filtration, washed with ethyl acetate, and dried to thereby obtain 120.5 mg (yield: 40%) of N-methyl-N-(2-{pyridin-4-ylmethyl-[3-(1,3,3,5-tetramethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]amino}ethyl)benzamide dihydrochloride as a white powder.

^{1}H-NMR (DMSO-D_6) δppm:

0.76 (3H, s), 1.34 (3H, s), 2.08-2.31 (2H, m), 2.94 (3H, s), 2.99-3.38 (4H, m), 3.29 (3H, s), 3.32 (3H, s), 3.66-3.89 (2H, m), 4.00-4.15 (2H, m), 4.29-4.55 (2H, m), 6.80-6.89 (2H, m), 7.32 (1H, d, J = 8.7 Hz), 7.41 (5H, br-s), 8.02 (2H, br-s), 7.58-8.78 (2H, m).

Example 46

Synthesis of 2,3-dihydrobenzofuran-7-carboxylic acid

methyl-(2-{pyridin-4-ylmethyl-[3-(1,3,3,5-tetramethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]amino}ethyl)amide dihydrochloride

Using an appropriate starting material and following the procedure of Example 45, the object compound was synthesized.

^{1}H-NMR (DMSO-D_6) δppm:

0.77 (3H, s), 1.34 (3H, s), 2.08-2.34 (2H, m), 2.76-3.33 (8H, m), 3.29 (3H, s), 3.32 (3H, s), 3.69-3.92 (2H, m), 3.95-4.18 (3H, m), 4.39-4.63 (4H, m), 6.72-6.92 (3H, m), 6.92-7.10 (1H, m), 7.19-7.37 (2H, m), 7.80-8.18 (2H, m), 8.79 (2H, br-s).

Example 47

Synthesis of 2-nitro-N-(2-pyridin-3-ylethyl)-N-[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]benzenesulfonamide

Potassium carbonate (1.89 g, 13.7 mmol) was added to a DMF solution (50 ml) of 2-nitro-N-(2-pyridin-3-ylethyl)benzene sulfonamide (1.40 g, 4.56 mmol) and 1-ethyl-7-(3-iodopropoxy)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione (2.16 g, 5.0 mmol), and stirred at room temperature overnight. Water was added to the reaction mixture, and extraction with ethyl acetate was performed. The organic layer was washed with water and a saturated sodium chloride aqueous solution in this order, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:methanol=1:0→10:1). The purified product was concentrated under reduced pressure to thereby obtain 2.99 g (yield: quantitative) of 2-nitro-N-(2-pyridin-3-ylethyl)-N-[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]benzenesulfonamide as a yellow oil.

^{1}H-NMR ($CDCl_3$) δppm:

0.84 (3H, s), 1.15 (3H, t, J = 7.0 Hz), 1.52 (3H, s), 2.04-2.12 (2H, m), 2.88 - 2.96 (2H, m), 3.40 (3H, s), 3.55-3.62 (4H, m), 3.64-3.76 (1H, m), 4.01 (2H, t, J = 5.9 Hz), 4.08-4.23 (1H, m), 6.70 (1H, d, J = 2.7 Hz), 6.78 (1H, dd, J = 9.0 and 2.0 Hz), 7.17-7.22 (2H, m),

7.53 (1H, dt, J = 7.9 and 2.1 Hz), 7.59-7.70 (2H, m), 7.99-8.02 (2H, m), 8.42 (1H, d, J = 1.7 Hz), 8.46 (1H, dd, J = 4.8 and 1.7 Hz).

Example 48

Synthesis of 1-ethyl-7-{3-[(1H-imidazol-2-ylmethyl)-(2-pyridin-3-ylethyl)amino]propoxy}-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.85 (3H, s), 1.15 (3H, t, J = 7.0 Hz), 1.52 (3H, s), 1.91-1.99 (2H, m), 2.68-2.90 (6H, m), 3.39 (3H, s), 3.60-3.78 (1H, m), 3.78-4.02 (4H, m), 4.07-4.22 (1H, m), 6.67 (1H, d, J = 2.5 Hz), 6.76 (1H, dd, J = 2.5 and 9.0 Hz), 6.85 - 6.94 (2H, m), 7.12-7.28 (2H, m), 7.46 (1H, d, J = 7.8 Hz), 8.44 (1H, d, J = 4.5 Hz), 8.47 (1H, s).

Example 49

Synthesis of 1-ethyl-7-{3-[(3H-imidazol-4-ylmethyl)-(2-pyridin-3-ylethyl)amino]propoxy}-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using appropriate starting materials and following the procedures of Examples 7 and 6, the object compound was synthesized.

^{1}H-NMR (DMSO-D_6) δppm:

0.76 (3H, s), 1.01 (3H, t, J = 6.9 Hz), 1.32 (3H, s), 2.18-2.38 (2H, m), 3.17-3.42 (6H, m), 3.33 (3H, s), 3.58-3.72 (1H, m), 4.00-4.19 (3H, m), 4.40-4.52 (2H, m), 6.88-6.98 (2H, m), 7.42 (1H, d, J = 8.8 Hz), 7.73 (1H, dd, J = 5.3 and 7.5 Hz), 7.87 (1H, s), 8.21 (1H, d, J = 7.5 Hz), 8.67 (1H, d, J = 5.3 Hz), 8.78 (1H, s), 8.91 (1H, s).

Example 50

Synthesis of 1,3,3,5-tetramethyl-7-{3-[(2-methylbenzyl)-(2-pyridin-3-ylethyl)amino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using appropriate starting materials and following the procedures of Examples 7 and 6, the object compound was synthesized.

^{1}H-NMR (DMSO-D_6) δppm:

0.76 (3H, s), 1.33 (3H, s), 2.20-2.42 (2H, m), 2.50 (3H, s), 3.08-3.40 (2H, m), 3.30 (3H, s), 3.33 (3H, s), 3.49-3.62 (4H, m), 4.08-4.21 (2H,

m), 4.37-4.61 (2H, m), 6.82-6.96 (2H, m), 7.17-7.41 (4H, m), 7.78 (1H, d, J = 7.3 Hz), 7.99 (1H, dd, J = 5.7 and 7.6 Hz), 8.49 (1H, d, J = 8.0 Hz), 8.82 (1H, d, J = 5.3 Hz), 8.94 (1H, s).

Example 51

Synthesis of 1,3,3,5-tetramethyl-7-{3-[(2-pyridin-3-ylethyl)-(quinolin-4-ylmethyl)amino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione trihydrochloride

Using appropriate starting materials and following the procedures of Examples 7 and 6, the object compound was synthesized.

^{1}H-NMR (DMSO-D_6) δppm:

0.74 (3H, s), 1.32 (3H, s), 2.13-2.45 (2H, m), 3.14-3.78 (6H, m), 3.29 (3H, s), 3.31 (3H, s), 3.98-4.17 (4H, m), 6.73-6.89 (2H, m), 7.33 (1H, d, J = 8.8 Hz), 7.90 (1H, t, J = 7.7Hz), 7.98-8.12 (2H, m), 8.37 (1H, d, J = 8.4 Hz), 8.53 (1H, d, J = 8.2 Hz), 8.38-8.69 (2H, m), 8.83 (1H, d, J = 5.6 Hz), 8.95 (1H, s), 9.22 (1H, d, J = 4.9 Hz).

Example 52

Synthesis of 1,3,3,5-tetramethyl-7-{3-[(2-methylpyridin-4-yl methyl)(2-pyridin-3-ylethyl)amino]propoxy}-1,5-dihydrobenzo [b][1,4]diazepine-2,4-dione trihydrochloride

Using appropriate starting materials and following the procedures of Examples 7 and 6, the object compound was synthesized.

^{1}H-NMR (DMSO-D_6) δppm:

0.76 (3H, s), 1.33 (3H, s), 2.10-2.37(2H, m), 2.69 (3H, s), 3.00-3.98 (6H, m), 3.30 (3H, s), 3.33 (3H, s), 3.98-4.22 (2H, m), 4.41-4.78 (2H, m), 6.82-6.95 (3H, m), 7.37 (1H, d, J = 8.6 Hz), 7.88-8.26 (3H, m), 8.68-8.82 (2H, m), 8.85 (1H, s).

Example 53

Synthesis of 7-{3-[(3,5-dichloropyridin-4-ylmethyl)-(2-pyridin-3-ylethyl)amino]propoxy}-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione trihydrochloride

Using appropriate starting materials and following the procedures of Examples 7 and 6, the object compound was synthesized.

^{1}H-NMR (DMSO-D_6) δppm:

0.76 (3H, s), 1.02 (3H, t, J = 7.0 Hz), 1.33 (3H, s), 2.09-2.44 (2H, m), 2.98-3.60 (6H, m), 3.33 (3H, s), 3.60-3.77 (1H, m), 3.98-4.18 (3H,

m), 4.20-4.62 (2H, m), 6.80-7.00 (2H, m), 7.41 (1H, d, J = 8.7 Hz), 7.97-8.10 (1H, m), 8.49-8.78 (3H, m), 8.84 (1H, d, J = 5.4 Hz), 8.96 (1H, s).

Example 54

Synthesis of 1-ethyl-3,3,5-trimethyl-7-{3-[(3-methylpyridin-4-ylmethyl)-(2-pyridin-3-ylethyl)amino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione trihydrochloride

Using appropriate starting materials and following the procedures of Examples 7 and 6, the object compound was synthesized.

^{1}H-NMR (DMSO-D_6) δppm:

0.75 (3H, s), 1.01 (3H, t, J = 6.9 Hz), 1.32 (3H, s), 2.11-2.42 (2H, m), 2.56 (3H, s), 3.08-3.59 (8H, m), 3.59-3.77 (1H, m), 3.95-4.18 (2H, m), 4.41-4.90 (4H, m), 6.82-6.97 (2H, m), 7.41 (1H, d, J = 8.8 Hz), 8.03 (1H, dd, J = 5.7 and 7.8 Hz), 8.30-8.69 (1H, m), 8.56 (1H, d, J = 8.1 Hz), 8.72-8.88 (3H, m), 8.96 (1H, s).

Example 55

Synthesis of 1-ethyl-3,3,5-trimethyl-7-{3-[(2-pyridin-3-ylethyl) pyridin-3-ylmethylamino]propoxy}-1,5-dihydrobenzo[b][1,4] diazepine-2,4-dione trihydrochloride

Using appropriate starting materials and following the procedures of Examples 7 and 6, the object compound was synthesized.

^{1}H-NMR (DMSO-D_6) δppm:

0.76 (3H, s), 1.01 (3H, t, J = 6.9 Hz), 1.32 (3H, s), 2.27-2.41 (2H, m), 3.20-3.36 (2H, m), 3.33 (3H, s), 3.38-3.57 (4H, m), 3.67-3.76 (1H, m), 4.00-4.18 (3H, m), 4.52-4.75 (2H, m), 6.87-6.97 (2H, m), 7.42 (1H, d, J = 8.8 Hz), 7.83 (1H, dd, J = 5.3 and 7.9 Hz), 7.99 (1H, dd, J = 5.7 and 8.0 Hz), 8.51 (1H, d, J = 8.1 Hz), 8.65 (1H, d, J = 7.9 Hz), 8.78-8.87 (2H, m), 8.95 (1H, s), 9.13 (1H, s).

Example 56

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{[2-(1-oxo-1H-isoquinolin-2-yl)ethyl]pyridin-3-ylmethylamino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using appropriate starting materials and following the procedures of Examples 7 and 6, the object compound was synthesized.

^{1}H-NMR (DMSO-D_6) δppm:

0.75 (3H, s), 1.01 (3H, t, J = 7.0 Hz), 1.32 (3H, s), 2.19-2.40 (2H, m), 3.20-3.57 (4H, m), 3.32 (3H, s), 3.61-3.72 (1H, m), 3.99-4.10 (3H, m), 4.35-4.85 (4H, m), 6.70 (1H, d, J = 7.4 Hz), 6.81-6.97 (2H, m), 7.39 (1H, d, J = 9.0 Hz), 7.50-7.57 (2H, m), 7.66-7.92 (3H, m), 8.22 (1H, d, J = 8.0 Hz), 8.50-8.71 (1H, m), 8.78-8.90 (1H, m), 9.02-9.18 (1H, m).

Example 57

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{[2-(1-oxo-1H-isoquinolin-2-yl)ethyl]thiazol-2-ylmethylamino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.84 (s, 3H), 1.15 (t, J = 7.1 Hz, 3H), 1.53 (s, 3H), 1.88-2.00 (m, 2H), 2.82 (t, J = 6.3 Hz, 2H), 3.01 (t, J = 6.3 Hz, 2H), 3.36 (s, 3H), 3.61-3.74 (m, 1H), 3.88 (t, J = 6.1 Hz, 2H), 4.07 (s, 2H), 4.08-4.23 (m, 3H), 6.42 (d, J = 7.3 Hz, 1H), 6.60-6.68 (m, 2H), 7.06 (d, J = 7.3 Hz, 1H), 7.12-7.15 (m, 2H), 7.48-7.49 (m, 2H), 7.64 (d, J = 7.4 Hz, 1H), 7.67 (d, J = 3.3 Hz, 1H), 8.39 (d, J = 7.4 Hz, 1H).

Example 58

Synthesis of 1-ethyl-7-(3-{(3-fluorobenzyl)-[2-(1-oxo-1H-isoquinolin-2-yl)ethyl]amino}propoxy)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.85 (s, 3H), 1.15 (t, J = 7.0 Hz, 3H), 1.53 (s, 3H), 1.80-1.96 (m, 2H), 2.70 (t, J = 6.4 Hz, 2H), 2.70 (t, J = 6.4 Hz, 2H), 3.35 (s, 3H), 3.67 (s, 2H), 3.66-3.76 (m, 1H), 3.83 (t, J = 6.0 Hz, 2H), 4.08 (t, J = 6.0 Hz, 2H), 4.00-4.21 (m, 1H), 6.40 (d, J = 7.4 Hz, 1H), 6.55-6.61 (m, 2H), 6.80-6.95 (m, 1H), 6.88-7.00 (m, 3H), 7.05-7.18 (m, 2H), 8.41-8.50 (m, 2H), 7.64 (t, J = 8.0 Hz, 1H), 8.39 (d, J = 8.0 Hz, 1H).

Example 59

Synthesis of 1-ethyl-7-(3-{(3-methoxybenzyl)-[2-(1-oxo-1H-isoquinolin-2-yl)ethyl]amino}propoxy)-3,3,5-trimethyl-1,5-dihydro

benzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.84 (s, 3H), 1.15 (t, J = 7.1 Hz, 3H), 1.52 (s, 3H), 1.80-1.96 (m, 2H), 2.70 (t, J = 6.8 Hz, 2H), 2.90 (t, J = 6.2 Hz, 2H), 3.36 (s, 3H), 3.65 (s, 2H), 3.68 (s, 3H), 3.65-3.72 (m, 1H), 3.84 (t, J = 6.2 Hz, 2H), 4.06 (t, J = 6.2 Hz, 2H), 4.10-4.20 (m, 1H), 6.38 (d, J = 7.3 Hz, 1H), 6.55-6.60 (m, 2H), 6.67 - 6.73 (m, 1H), 6.79-6.81 (m, 2H), 6.95-7.30 (m, 3H), 7.39-7.50 (m, 2H), 7.60-7.67 (m, 1H), 8.40 (d, J = 1.2 Hz, 1H).

Example 60

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{[2-(1-oxo-1H-isoquinolin-2-yl)ethyl]thiophen-2-ylmethylamino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.85 (s, 3H), 1.14 (t, J = 7.1 Hz, 3H), 1.52 (s, 3H), 1.80-1.96 (m, 2H), 2.69 (t, J = 6.8 Hz, 2H), 2.91 (t, J = 6.2 Hz, 2H), 3.35 (s, 3H), 3.65-3.78 (m, 1H), 3.82 (t, J = 6.2 Hz, 2H), 3.89 (s, 2H), 4.07 (t, J = 6.2 Hz, 2H), 4.10-4.25 (m, 1H), 6.40 (d, J = 7.3 Hz, 1H), 6.38-6.49 (m, 2H), 6.87-6.89 (m, 2H), 7.02-7.28 (m, 3H), 7.42-7.50 (m, 2H), 7.60-7.64 (m, 1H), 8.40 (d, J = 1.2 Hz, 1H).

Example 61

Synthesis of 7-(3-{bis-[2-(1-oxo-1H-isoquinolin-2-yl)ethyl]amino}propoxy)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

(1-Oxo-1H-isoquinolin-2-yl)acetaldehyde (207 mg, 1.1 mmol) was added to a 1,2-dichloroethane solution (4 ml) of 7-(3-aminopropoxy)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione (329 mg, 1.0 mmol) and sodium triacetoxyhydroborate (381 mg, 1.8 mmol), and stirred at room temperature overnight. Water was added to the reaction mixture, and extraction with ethyl acetate was performed. The organic layer was

washed with water, and a saturated sodium chloride aqueous solution, in this order, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane:methanol=20:1). The purified product was concentrated under reduced pressure to thereby obtain 7-(3-{bis-[2-(1-oxo-1H-isoquinolin-2-yl)ethyl] amino}propoxy)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4] diazepine-2,4-dione.

^{1}H-NMR ($CDCl_3$) δppm:

0.84 (s, 3H), 1.14 (t, J = 7.1 Hz, 3H), 1.52 (s, 3H), 1.74-1.82 (m, 2H), 2.75 (t, J = 7.3 Hz, 2H), 2.94 (t, J = 6.2 Hz, 4H), 3.34 (s, 3H), 3.62-3.75 (m, 3H), 4.02 (t, J = 6.2 Hz, 4H), 4.12-4.23 (m, 1H), 6.16 (d, J = 7.3 Hz, 2H), 6.50 (dd, J = 8.9 and 2.7 Hz, 1H), 6.56 (d, J = 2.7 Hz, 1H), 6.91 (d, J = 7.3 Hz, 2H), 7.09 (d, J = 8.9 Hz, 1H), 7.39-7.62 (m, 4H), 7.59-7.68 (m, 2H), 8.41 (d, J = 7.9 Hz, 2H).

Example 62

Synthesis of 1-ethyl-7-(3-{[2-(7-methoxy-2-oxo-3,4-dihydro-2H-quinolin-1-yl)ethyl]pyridin-4-ylmethylamino}propoxy)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.84 (s, 3H), 1.14 (t, J = 7.1 Hz, 3H), 1.51 (s, 3H), 1.90-2.00 (m, 4H), 2.58 (t, J = 6.8 Hz, 2H), 2.68 (t, J = 6.8 Hz, 2H), 3.38 (s, 3H), 3.61 (s, 2H), 3.62-3.72 (m, 1H), 3.95-4.00 (m, 4H), 4.08-4.22 (m, 1H), 6.44 (d, J = 7.3 Hz, 1H), 6.68 (d, J = 2.7 Hz, 1H), 6.75 (dd, J = 9.0 and 2.7 Hz, 1H), 6.95 (d, J = 7.3 Hz, 1H), 7.17 (d, J = 9.0 Hz, 1H), 7.25-7.27 (m, 2H), 7.45-7.52 (m, 2H), 7.60-7.70 (m, 1H), 8.40 (d, J = 7.9 Hz, 1H), 8.48 (d, J = 1.5 Hz, 2H).

Example 63

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{[2-(2-oxo-2H-quinolin-1-yl)ethyl]pyridin-4-ylmethylamino}propoxy)-1,5-dihydrobenzo [b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.87 (s, 3H), 1.17 (t, J = 7.0 Hz, 3H), 1.54 (s, 3H), 1.92-2.04 (m, 2H), 2.80-2.86 (m, 4H), 3.41 (s, 3H), 3.76 (s, 2H), 3.68-3.78 (m, 1H), 4.01 (t, J = 6.0 Hz, 2H), 4.10-4.22 (m, 1H), 4.44 (t, J = 7.0 Hz, 2H), 6.66-6.70 (m, 2H), 6.76 (dd, J = 8.9 and 2.9 Hz, 1H), 7.09 (d, J = 8.3 Hz, 1H), 7.07-7.11 (m, 4H), 7.38-7.46 (m, 1H), 7.57 (d, J = 6.5 Hz, 1H), 7.68 (d, J = 9.5 Hz, 1H), 8.44 (d, J = 5.9 Hz, 2H).

Example 64

Synthesis of 1-ethyl-7-{3-[(2-(6-methoxy-2-oxo-2H-quinolin-1-yl)ethyl)pyridin-4-ylmethylamino]propoxy}-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.85 (s, 3H), 1.15 (t, J = 7.1 Hz, 3H), 1.52 (s, 3H), 1.89-2.00 (m, 2H), 2.81 (m, 4H), 3.39 (s, 3H), 3.74 (s, 2H), 3.65-3.77 (m, 1H), 3.85 (s, 3H), 3.99 (t, J = 6.0Hz, 2H), 4.11-4.28 (m, 1H), 4.40 (t, J = 6.9 Hz, 2H), 6.64-6.70 (m, 2H), 6.74 (dd, J = 8.9 and 2.9 Hz, 1H), 6.96-7.04 (m, 3H), 7.16-7.20 (m, 3H), 7.60 (d, J = 9.5 Hz, 1H), 8.43 (d, J = 5.9 Hz, 2H).

Example 65

Synthesis of 1-ethyl-7-(3-{[2-(6-methoxyquinolin-2-yloxy)ethyl]pyridin-4-ylmethylamino}propoxy)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.82 (s, 3H), 1.12 (t, J = 7.1 Hz, 3H), 1.51 (s, 3H), 1.90-2.05 (m, 2H), 2.77 (t, J = 7.0 Hz, 2H), 2.97 (t, J = 7.0 Hz, 2H), 3.34 (s, 3H), 4.58-5.59 (m, 1H), 3.77 (s, 2H), 3.90 (s, 3H), 3.95-4.04 (m, 2H), 4.04-4.19 (m, 1H), 4.50-4.63 (m, 2H), 6.59-6.66 (m, 2H), 6.83 (d, J = 8.8 Hz, 1H), 7.04 (d, J = 2.8 Hz, 1H), 7.11 (d, J = 8.9 Hz, 1H), 7.24-7.27 (m, 3H), 7.67 (d, J = 9.1 Hz, 1H), 7.89 (d, J = 8.8 Hz, 1H), 8.42 (d, J = 5.9 Hz, 2H).

Example 66

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{[2-(2-oxo-3,4-dihydro-2H-quinolin-1-yl)ethyl]pyridin-4-ylmethylamino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.85 (s, 3H), 1.14 (t, J = 7.1 Hz, 3H), 1.52 (s, 3H), 1.89-1.97 (m, 2H), 2.53-2.64 (m, 2H), 2.68-2.77 (m, 4H), 2.86 (t, J = 8.0 Hz, 2H), 3.38 (s, 3H), 3.69 (s, 2H), 3.60-3.78 (m, 1H), 3.93-4.20 (m, 5H), 6.67 (d, J = 2.7 Hz, 1H), 6.72-6.84 (m, 2H), 6.79 (t, J = 8.2 Hz, 1H), 7.10-7.22 (m, 5H), 8.44 (d, J = 6.0 Hz, 2H).

Example 67

Synthesis of 1-ethyl-3,3,5-trimethyl-7-{3-[(2-(4-oxo-4H-thieno[3,2-c]pyridin-5-yl)ethyl)pyridin-4-ylmethylamino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.88 (s, 3H), 1.17 (t, J = 7.1 Hz, 3H), 1.54 (s, 3H), 1.89-1.97 (m, 2H), 2.74 (t, J = 6.8 Hz, 2H), 2.83-2.95 (m, 2H), 3.39 (s, 3H), 3.69 (s, 2H), 3.68-3.74 (m, 1H), 3.89 (t, J = 6.0 Hz, 2H), 4.12 (t, J = 6.0 Hz, 2H), 4.11-4.21 (m, 1H), 6.53-6.70 (m, 3H), 7.05 (d, J = 7.2 Hz, 1H), 7.10 (d, J = 5.9 Hz, 2H), 7.20 (d, J = 8.9 Hz, 1H), 7.32 (d, J = 5.3 Hz, 1H), 7.63 (d, J = 5.3 Hz, 1H), 8.32 (d, J = 5.9 Hz, 2H).

Example 68

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{[2-(7-oxo-7H-thieno[2,3-c]pyridin-6-yl)ethyl]pyridin-4-ylmethylamino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.88 (s, 3H), 1.17 (t, J = 7.1 Hz, 3H), 1.54 (s, 3H), 1.89-1.97 (m, 2H), 2.74 (t, J = 6.8 Hz, 2H), 2.83-2.95 (m, 2H), 3.39 (s, 3H), 3.68 (s, 2H), 3.68-3.74 (m, 1H), 3.90 (t, J = 6.0 Hz, 2H), 4.05-4.21 (m, 3H), 6.56 (d, J = 7.1 Hz, 1H), 6.60-6.70 (m, 2H), 7.03-7.10 (m, 3H),

7.16-7.23 (m, 2H), 7.73 (d, J = 5.2 Hz, 1H), 8.31 (d, J = 5.9 Hz, 2H).

Example 69

Synthesis of 1-ethyl-7-(3-{[2-(8-methoxy-2-oxo-2H-quinolin-1-yl)ethyl]pyridin-4-ylmethylamino}propoxy)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.87 (s, 3H), 1.17 (t, J = 7.1 Hz, 3H), 1.54 (s, 3H), 1.89-1.97 (m, 2H), 2.78 (t, J = 6.7 Hz, 2H), 2.88 (t, J = 7.2 Hz, 2H), 3.41 (s, 3H), 3.75 (s, 3H), 3.68-3.79 (m, 3H), 3.98 (t, J = 6.2 Hz, 2H), 4.05-4.21 (m, 1H), 4.80 (t, J = 7.7 Hz, 2H), 6.65-6.78 (m, 3H), 6.96-7.03 (m, 1H), 7.11-7.23 (m, 5H), 7.62 (d, J = 9.4 Hz, 1H), 8.41 (d, J = 6.0 Hz, 2H).

Example 70

Synthesis of 1-ethyl-7-(3-{[2-(6-methoxyquinolin-2-yloxy)ethyl]pyridin-4-ylmethylamino}propoxy)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.83 (s, 3H), 1.14 (t, J = 7.1 Hz, 3H), 1.51 (s, 3H), 1.89-2.03 (m, 2H), 2.76 (t, J = 6.7 Hz, 2H), 3.00 (t, J = 7.2 Hz, 2H), 3.35 (s, 3H), 3.59-3.67 (m, 1H), 3.80 (s, 2H), 3.99 (s, 3H), 3.95-4.07 (m, 2H), 4.10-4.19 (m, 1H), 4.70 (t, J = 7.0 Hz, 2H), 6.58-6.70 (m, 2H), 6.89 (d, J = 8.8 Hz, 1H), 6.95-7.05 (m, 1H), 7.11 (d, J = 8.9 Hz, 1H), 7.23-7.38 (m, 4H), 7.97 (d, J = 8.8 Hz, 1H), 8.41 (d, J = 6.0 Hz, 2H).

Example 71

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]pyridin-4-ylmethylamino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.87 (s, 3H), 1.16 (t, J = 7.1 Hz, 3H), 1.53 (s, 3H), 1.82-1.95 (m,

2H), 2.72 (t, J = 6.8 Hz, 2H), 2.76-2.89 (m, 2H), 3.38 (s, 3H), 3.68 (s, 2H), 3.63-3.78 (m, 1H), 3.87 (t, J = 6.0 Hz, 2H), 4.10 (t, J = 6.0 Hz, 2H), 4.11-4.20 (m, 1H), 6.43 (d, J = 7.4 Hz, 1H), 6.60 (d, J = 2.8 Hz, 1H), 6.67 (dd, J = 9.0 and 2.8 Hz, 1H), 6.96 (d, J = 2.9 Hz, 1H), 7.05-7.11 (m, 3H), 7.19 (d, J = 9.0 Hz, 1H), 7.50 (d, J = 2.9 Hz, 1H), 8.35 (d, J = 6.0 Hz, 2H).

Example 72

Synthesis of 1-ethyl-7-(3-{[2-(6-methoxy-2-oxo-3,4-dihydro-2H-quinolin-1-yl)ethyl]pyridin-4-ylmethylamino}propoxy)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.87 (s, 3H), 1.16 (t, J = 7.1 Hz, 3H), 1.53 (s, 3H), 1.86-1.96 (m, 2H), 1.87-2.01 (m, 2H), 2.55-2.61 (m, 2H), 2.70-2.85 (m, 6H), 3.40 (s, 3H), 3.62-3.78 (m, 1H), 3.71 (s, 2H), 3.75 (s, 3H), 3.98-4.21 (m, 3H), 6.48 (d, J = 2.3 Hz, 1H), 6.49 (dd, J = 8.2 and 2.3 Hz, 1H), 6.69 (d, J = 2.7 Hz, 1H), 6.76 (dd, J = 8.0 and 2.7Hz , 1H), 7.06 (d, J = 8.2 Hz, 1H), 7.18-7.23 (m, 3H), 8.44 (d, J = 6.0 Hz, 2H).

Example 73

Synthesis of 1-ethyl-7-(3-{[2-(7-methoxy-2-oxo-3,4-dihydro-2H-quinolin-1-yl)ethyl]pyridin-4-ylmethylamino}propoxy)-3,3,5-tri-methyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.85 (s, 3H), 1.14 (t, J = 7.1 Hz, 3H), 1.52 (s, 3H), 1.84-1.96 (m, 2H), 2.55-2.63 (m, 2H), 2.62-2.71 (m, 4H), 2.75-2.84 (m, 2H), 3.38 (s, 3H), 3.68 (s, 2H), 3.77 (s, 3H), 3.64-3.76 (m, 1H), 3.96-4.23 (m, 5H), 6.61-6.75 (m, 5H), 7.16-7.22 (m, 3H), 8.45 (d, J = 6.0 Hz, 2H).

Example 74

Synthesis of N-(3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl)-N-(2-(7-methyl-1-oxo-1H-isoquinolin-2-yl)ethyl)-2-nitrobenzenesulfonamide

N,N,N',N'-Tetra methyl azodicarboxamide (TMAD) (118 mg) and

tri-n-butyl phosphine (0.17 ml) were added to a THF solution (5 ml) of N-[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]-2-nitrobenzenesulfonamide (231 mg) and 2-(2-hydroxyethyl)-7-methyl-2H-isoquinolin-1-one (93 mg), and stirred at room temperature overnight. Water was added to the reaction mixture, and extraction with dichloromethane was performed. The organic layer was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:methanol=20:1→10:1). The purified product was concentrated to dryness under reduced pressure to thereby obtain 205 mg (yield: 65%) of N-(3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl)-N-(2-(7-methyl-1-oxo-1H-isoquinolin-2-yl)ethyl)-2-nitrobenzenesulfonamide as a white amorphous solid.

^{1}H-NMR ($CDCl_3$) δppm:

0.84 (3H, s), 1.14 (3H, t, J = 7.1 Hz), 1.52 (3H, s), 2.04-2.19 (2H, m), 2.49 (3H, s), 3.39 (3H, s), 3.62 (2H, t, J = 6.7 Hz), 3.60-3.78 (1H, m), 3.73 (2H, t, J = 6.7 Hz), 3.94 (2H, t, J = 5.7 Hz), 4.10-4.26 (1H, m), 4.23 (2H, t, J = 6.7 Hz), 6.43 (1H, d, J = 7.3 Hz), 6.68 (1H, d, J = 2.7 Hz), 6.72 (1H, dd, J = 2.7 and 8.9 Hz), 7.08 (1H, d, J = 7.3 Hz), 7.17 (1H, d, J = 8.9 Hz), 7.39 (1H, d, J = 8.1 Hz), 7.46-7.54 (1H, m), 7.54-7.62 (3H, m), 7.93-8.03 (1H, m), 8.16 (1H, s).

Example 75

Synthesis of 1-ethyl-3,3,5-trimethyl-7-{3-[2-(7-methyl-1-oxo-1H-isoquinolin-2-yl)ethylamino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 18, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.84 (3H, s), 1.14 (3H, t, J = 7.0 Hz), 1.52 (3H, s), 1.89-2.05 (2H, m), 2.48 (3H, s), 2.87 (2H, t, J = 6.7 Hz), 3.06 (2H, t, J = 6.2 Hz), 3.38 (3H, s), 3.61-3.76 (1H, m), 4.02 (2H, t, J = 6.1 Hz), 4.14 (2H, t, J = 6.2 Hz), 4.10-4.22 (1H, m), 6.44 (1H, d, J = 7.3 Hz), 6.69 (1H, d, J = 2.7 Hz), 6.75 (1H, dd, J = 2.7 and 8.9 Hz), 7.06 (1H, d, J =

7.3 Hz), 7.15 (1H, d, J = 8.9 Hz), 7.40 (1H, d, J = 8.0 Hz), 7.45-7.50 (1H, m), 8.22 (1H, s).

Example 76

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{[2-(7-methyl-1-oxo-1H-isoquinolin-2-yl)ethyl]pyridin-4-ylmethylamino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using appropriate starting materials and following the procedures of Examples 7 and 6, the object compound was synthesized. ^{1}H-NMR (DMSO-D_6) δppm:0.74 (3H, s), 1.01 (3H, t, J = 6.9Hz), 1.32 (3H, s), 2.00-2.24 (2H, m), 2.44 (3H, s), 2.89-4.60 (10H, m), 3.30 (3H, s), 4.81 (2H, s), 6.62 (1H, d, J = 7.1 Hz), 6.78 (1H, d, J = 9.1 Hz), 6.85 (1H, s), 7.36 (1H, d, J = 9.1 Hz), 7.45 (1H, d, J = 7.1 Hz), 7.95-8.13 (5H, m), 8.86 (2H, d, J = 6.0 Hz).

Example 77

Synthesis of 1-ethyl-3,3,5-trimethyl-7-{3-[(pyridin-4-ylmethyl)amino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

4-Pyridinecarbaldehyde (0.64 ml, 6.8 mmol) was added to a methanol solution (10 ml) of 7-(3-aminopropoxy)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione (2.18 g, 6.8 mmol), and stirred under a nitrogen atmosphere at room temperature for 1.5 hours. The reaction mixture was cooled in an ice water bath, and sodium borohydride (257 mg, 6.8 mmol) was added thereto at 0°C. The mixture was then stirred at room temperature overnight. Water was added to the reaction mixture, and extraction with ethyl acetate was performed. The organic layer was washed with water and a saturated sodium chloride aqueous solution, in this order, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:methanol=9:1→3:2). The purified product was concentrated under reduced pressure to thereby obtain 2.35 g (yield: 84%) of 1-ethyl-3,3,5-trimethyl-7-{3-[(pyridin-4-ylmethyl)amino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δppm:

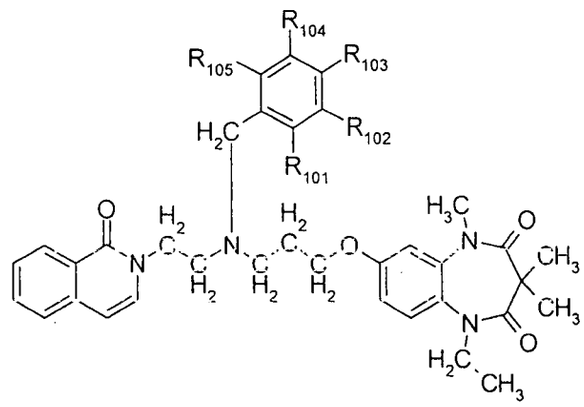
0.86 (s, 3H), 1.12 (t, J = 7.1 Hz, 3H), 1.52 (s, 3H), 1.97-2.09 (m, 2H), 2.84 (t, J = 6.8 Hz, 2H), 3.39 (s, 3H), 3.62-3.78 (m, 1H), 3.85

(s, 2H), 4.09 (t, J = 6.1 Hz, 2H), 4.06-4.24 (m, 1H), 6.71 (d, J = 2.8 Hz, 1H), 6.80 (dd, J = 9.0 and 2.8 Hz, 1H), 7.20 (d, J = 9.0 Hz, 1H), 7.26-7.27 (m, 2H), 8.53 (d, J = 6.0 Hz, 2H).

Examples 78 to 456

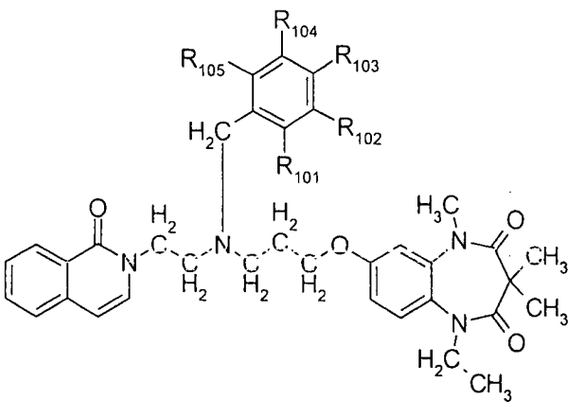
Using appropriate starting materials and following the procedures of the above-mentioned Examples, the compounds shown in Tables 1 to 33 were prepared.

Table 1



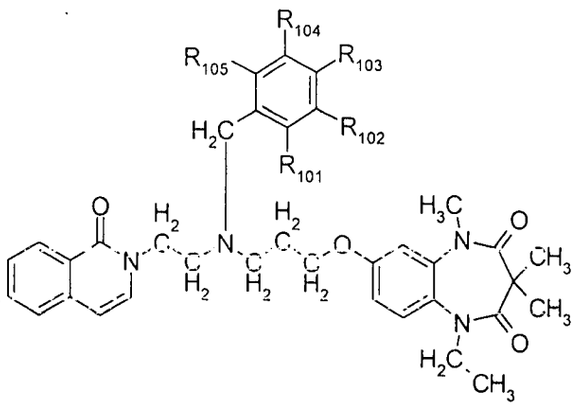
Example	R101	R102	R103	R104	R105	MS(M+1)
78	-H	-H	-H	-H	-H	581
79	-H	-H	$-CO_2H$	-H	-H	625
80	-H	-H	$-C_6H_5$	-H	-H	657
81	-H	-H	$-OCH_3$	-H	-H	611
82	-H	-H	-OH	-H	-H	597
83	-H	-H	$-CH_3$	-H	-H	595
84	-H	-H	$-CH(CH_3)_2$	-H	-H	623
85	-H	-H	-CN	-H	-H	606
86	-H	-H	$-OC_2H_5$	-H	-H	625
87	-H	-OH	-H	-H	-H	597
88	-H	-H	$-NHCOCH_3$	-H	-H	638
89	-Cl	-H	-H	-H	-H	615
90	-H	-Cl	-H	-H	-H	615
91	-H	-H	-Cl	-H	-H	615
92	-F	-H	-H	-H	-H	599
93	-CN	-H	-H	-H	-H	606
94	$-CF_3$	-H	-H	-H	-H	649
95	-H	$-CF_3$	-H	-H	-H	649
96	-H	$-CH_3$	-H	-H	-H	595
97	-H	-H	$-CF_3$	-H	-H	649
98	-H	-H	$-C_2H_5$	-H	-H	609
99	-H	-H	-F	-H	-H	599
100	$-CH_3$	-H	-H	-H	-H	595
101	-H	-CN	-H	-H	-H	606
102	$-OCH_3$	-H	-H	-H	-H	611
103	-H	-H	$-SCH_3$	-H	-H	627
104	-H	-H	$-OCH(CH_3)_2$	-H	-H	639

Table 2



Example	R101	R102	R103	R104	R105	MS(M+1)
105	-H	$-C_6H_5$	-H	-H	-H	657
106	-H	-H	-2-THIENYL	-H	-H	663
107	-OH	-H	-H	-H	-H	597
108	-H	-H	-3-PYRIDYL	-H	-H	658
109	-H	-3-PYRIDYL	-H	-H	-H	658
110	-3-PYRIDYL	-H	-H	-H	-H	658
111	-2-THIENYL	-H	-H	-H	-H	663
112	-H	-H	-2-FURYL	-H	-H	647

Table 3



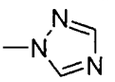
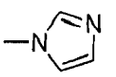
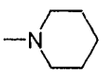
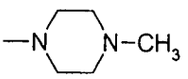
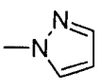
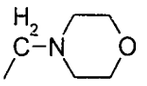
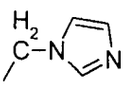
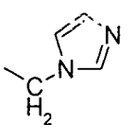
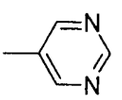
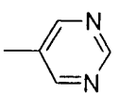
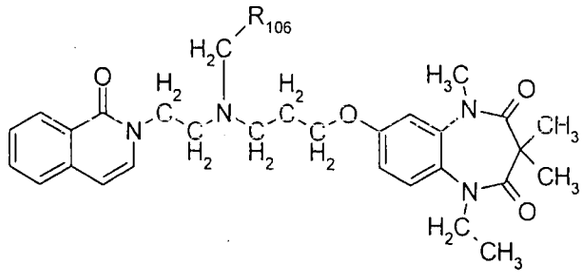
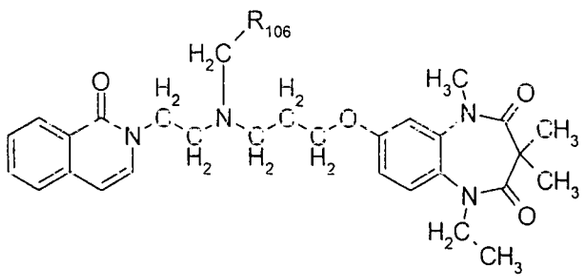
Example	R101	R102	R103	R104	R105	MS(M+1)
113	-H	-H		-H	-H	648
114	-H	-H		-H	-H	647
115	-H	-H		-H	-H	664
116		-H	-H	-H	-H	679
117	-H		-H	-H	-H	647
118	-H	-H		-H	-H	680
119	-H	-H		-H	-H	661
120	-H		-H	-H	-H	661
121	-H	-H		-H	-H	659
122	-H		-H	-H	-H	659

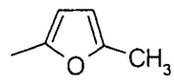
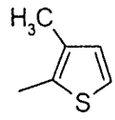
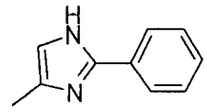
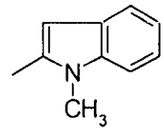
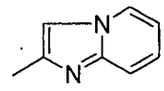
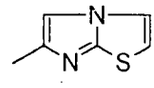
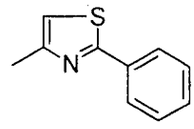
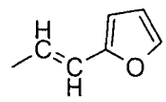
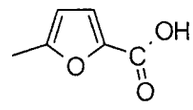
Table 4



Example	R106	MS(M+1)
123	-2-IMIDAZOLYL	571
124	-2-PYRIDYL	582
125	-3-THIENYL	587
126	-3-INDOLYL	620
127	-2-BENZOFURANYL	621
128	-4-QUINOLYL	632
129	-2-QUINOLYL	632
130	-CH=CHC$_6$H$_5$(trans)	607
131	-4-IMIDAZOLYL	571
132	-2-FURYL	571
133	-2-NAPHTHYL	631
134	-5-BENZOFURANYL	621
135	-3-QUINOLYL	632
136	-CH$_2$C$_6$H$_5$	595
137	-8-QUINOLYL	632
138	-CH(CH$_3$)C$_6$H$_5$	609
139	-(CH$_2$)$_2$C$_6$H$_5$	609

Table 5



Example	R106	MS(M+1)
140		585
141		601
142		647
143		634
144		621
145		627
146		664
147		597
148		615

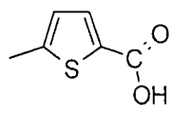
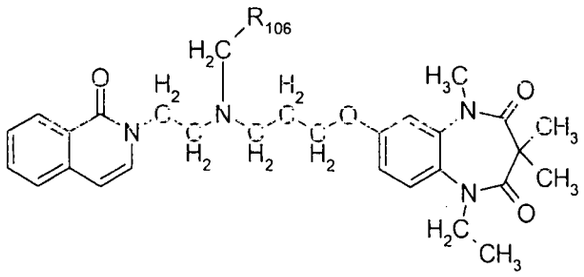
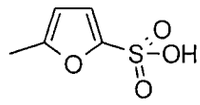
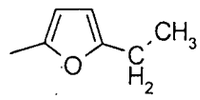
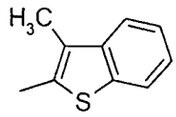
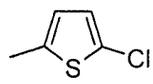
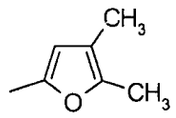
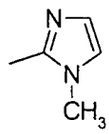
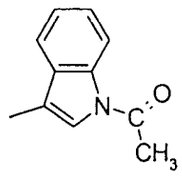
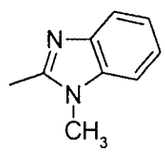
149		631

Table 6



Example	R106	MS(M+1)
150		651
151		599
152		651
153		621
154		599
155		585
156		662
157		635

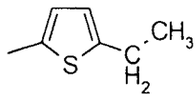
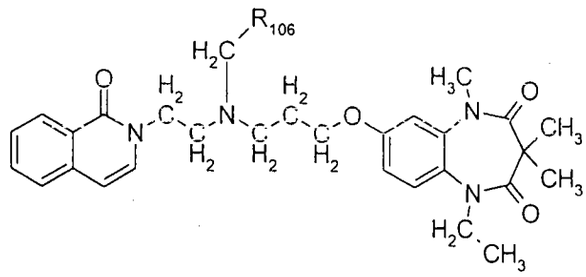
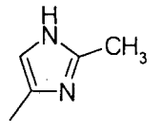
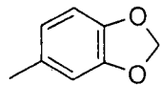
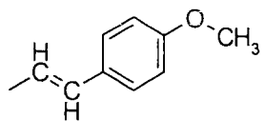
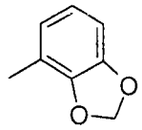
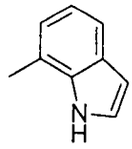
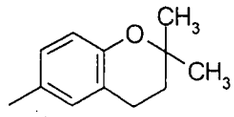
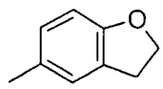
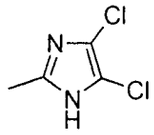
158		615

Table 7



Example	R106	MS(M+1)
159		585
160		625
161		637
162		625
163		620
164		665
165		623
166		639

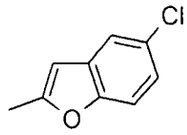
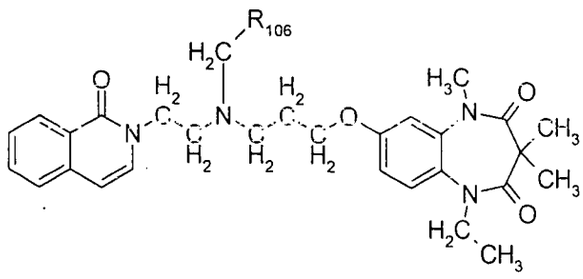
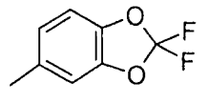
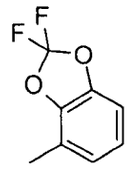
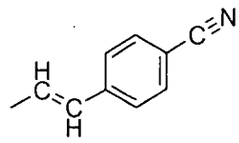
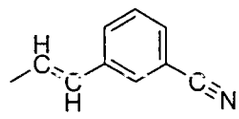
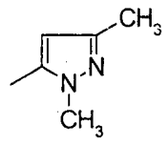
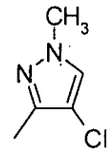
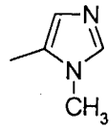
167		655

Table 8



Example	R106	MS(M+1)
168		661
169		661
170		632
171		632
172		599
173		619
174		585

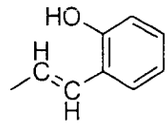
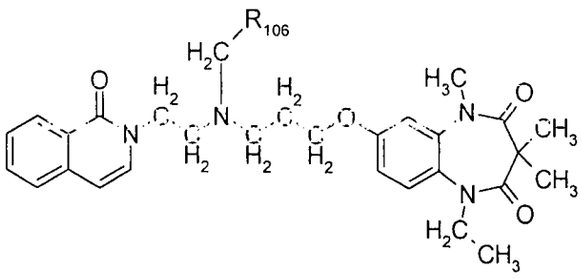
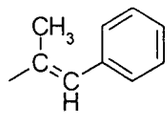
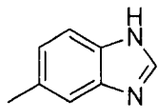
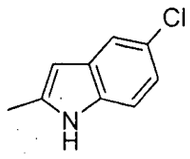
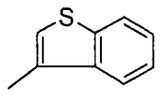
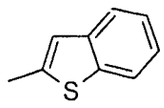
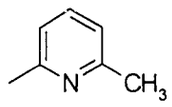
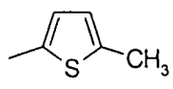
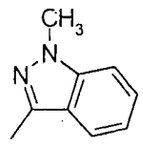
175		623

Table 9



Example	R106	MS(M+1)
176		621
177		621
178		654
179		637
180		637
181		596
182		601
183		635

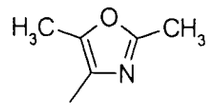
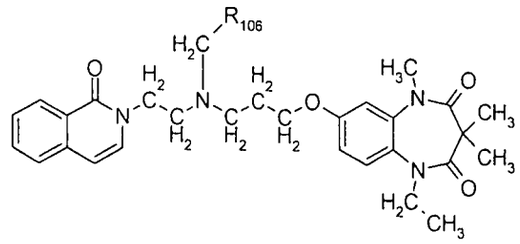
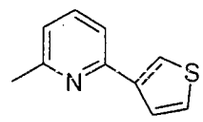
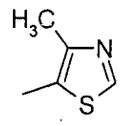
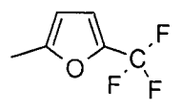
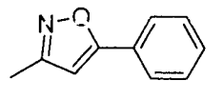
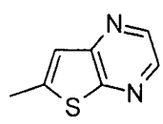
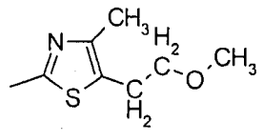
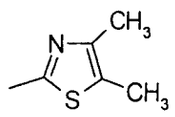
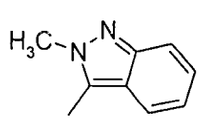
184		600

Table 10



Example	R106	MS(M+1)
185		664
186		602
187		639
188		648
189		639
190		660
191		616
192		635

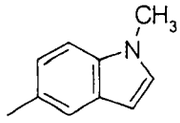
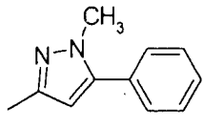
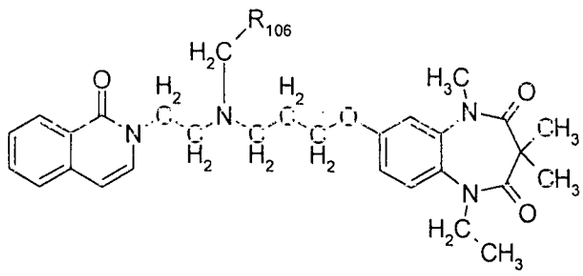
193		634
194		661

Table 11



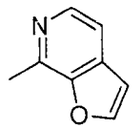
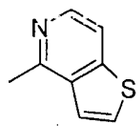
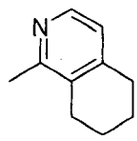
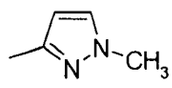
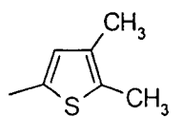
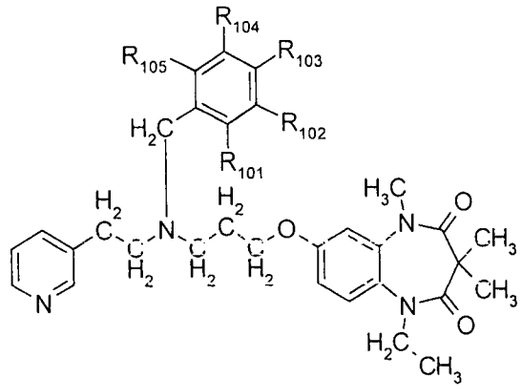
Example	R106	MS(M+1)
195		622
196		638
197		636
198		585
199		615

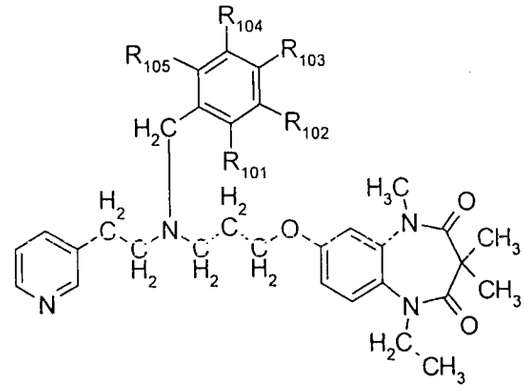
Table 12



Example	R101	R102	R103	R104	R105	MS(M+1)
200	-H	-H	-H	-H	-H	515
201	-H	-H	$-CO_2H$	-H	-H	559
202	-H	-H	$-C_6H_5$	-H	-H	591
203	-H	-H	$-OCH_3$	-H	-H	545
204	-H	-H	-H	$-OCH_3$	-H	545
205	-H	-H	-OH	-H	-H	531
206	-H	-H	$-CH_3$	-H	-H	529
207	-H	-H	$-CH(CH_3)_2$	-H	-H	557
208	-H	-H	-CN	-H	-H	540
209	-H	-H	$-OC_2H_5$	-H	-H	559
210	-H	-H	-H	-OH	-H	531
211	-H	-H	-OH	-OH	-H	547
212	-H	-H	-H	-H	$-CO_2H$	559
213	-H	-H	$-NHCOCH_3$	-H	-H	572
214	-H	-H	$-O(CH_2)_3N(CH_3)_2$	-H	-H	616
215	-H	-H	-H	-H	-Cl	549
216	-H	-H	-H	-Cl	-H	549
217	-H	-H	-Cl	-H	-H	549
218	-H	-H	-H	-H	-F	533
219	-H	-H	-H	-H	-CN	540
220	-H	-H	-H	-H	$-CF_3$	583
221	-H	-H	-H	$-CF_3$	-H	583
222	-H	-H	-H	$-CH_3$	-H	529
223	-H	-H	$-CF_3$	-H	-H	583
224	-H	-H	$-C_2H_5$	-H	-H	543
225	-H	-H	-F	-H	-H	533
226	-H	-H	-H	-H	$-CH_3$	529

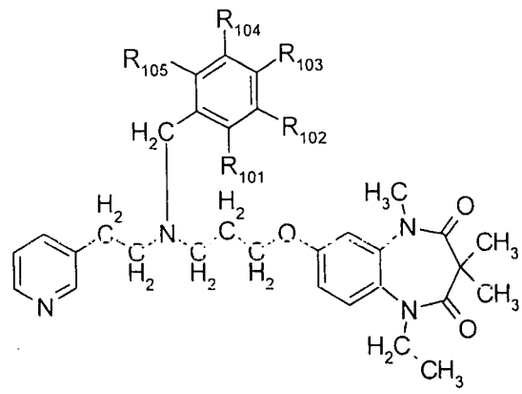
227	-H	-H	$-CO_2CH_3$	-H	-H	573

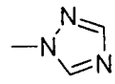
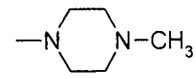
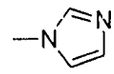
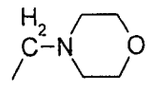
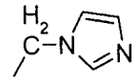
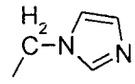
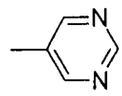
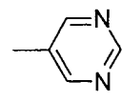
Table 13

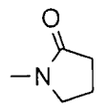


Example	R101	R102	R103	R104	R105	MS(M+1)
228	-H	-H	-H	-F	-H	533
229	-H	-H	-H	-CN	-H	540
230	-H	-H	-H	-H	$-OCH_3$	545
231	-H	-H	$-SCH_3$	-H	-H	561
232	-H	-H	-H	-H	$-CO_2CH_3$	573
233	-H	-H	$-SO_2CH_3$	-H	-H	593
234	-H	-H	$-OCH(CH_3)_2$	-H	-H	573
235	-H	-H	-H	$-C_6H_5$	-H	591
236	-H	-H	-H	-H	$-NHSO_2CH_3$	608
237	-H	-H	-1-IMIDAZOLYL	-H	-H	581
238	-H	-H	-2-THIENYL	-H	-H	597
239	-H	-H	-H	-H	-OH	531
240	-H	-H	-3-PYRIDYL	-H	-H	592
241	-H	-H	-H	-3-PYRIDYL	-H	592
242	-H	-H	-H	-H	-3-PYRIDYL	592
243	-H	-H	-H	-H	-2-THIENYL	597
244	-H	-H	-2-FURYL	-H	-H	581

Table 14

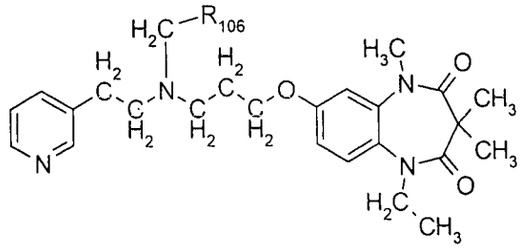


Example	R101	R102	R103	R104	R105	MS(M+1)
245	-H	-H		-H	-H	582
246	-H	-H	-H	-H		613
247	-H	-H	-H		-H	581
248	-H	-H		-H	-H	614
249	-H	-H		-H	-H	595
250	-H	-H	-H		-H	595
251	-H	-H		-H	-H	593
252	-H	-H	-H		-H	593

253	-H	-H		-H	-H	598

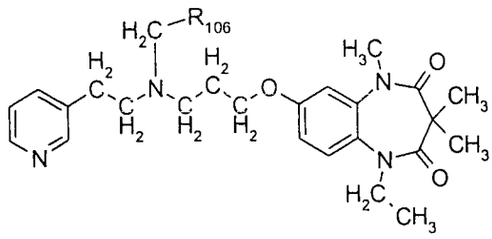
148

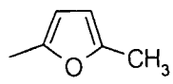
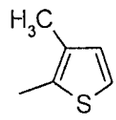
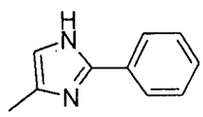
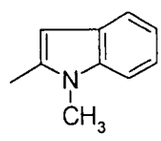
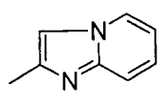
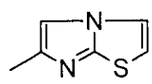
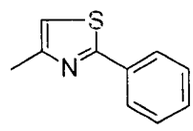
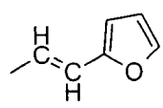
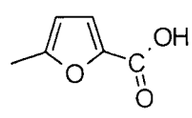
Table 15



Example	R106	MS(M+1)
254	-3-FURYL	505
255	-2-PYRIDYL	516
256	-2-THIENYL	521
257	-3-THIENYL	521
258	-2-BENZOFURANYL	555
259	-4-QUINOLYL	566
260	-2-QUINOLYL	566
261	-CH=CHC$_6$H$_5$(trans)	541
262	-2-THIAZOLYL	522
263	-1-NAPHTHYL	565
264	-2-FURYL	505
265	-2-NAPHTHYL	565
266	-5-BENZOFURANYL	555
267	-3-QUINOLYL	566
268	-CH$_2$C$_6$H$_5$	529
269	-8-QUINOLYL	566
270	-CH(CH$_3$)C$_6$H$_5$	543
271	-(CH$_2$)$_2$C$_6$H$_5$	543
272	-6-QUINOLYL	566
273	-2-BENZTHIAZOLYL	572

Table 16



Example	R106	MS(M+1)
274		519
275		535
276		581
277		568
278		555
279		561
280		598
281		531
282		549

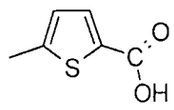
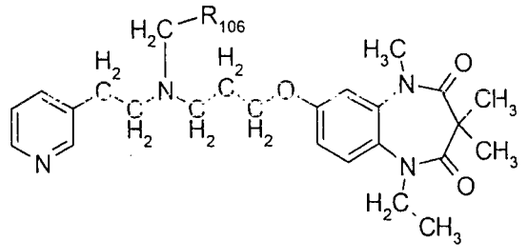
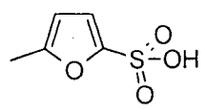
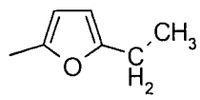
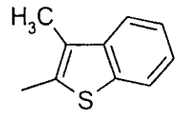
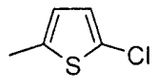
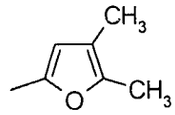
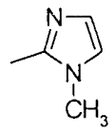
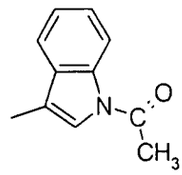
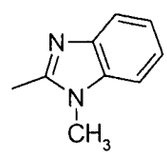
283		565

Table 17



Example	R106	MS(M+1)
284		585
285		533
286		585
287		555
288		533
289		519
290		596
291		569

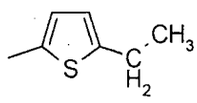
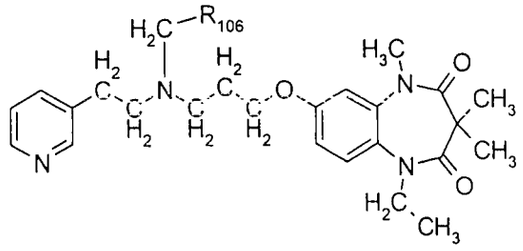
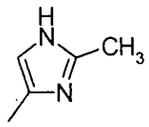
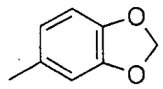
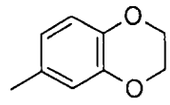
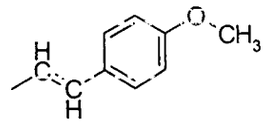
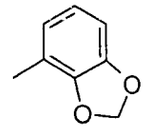
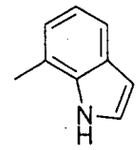
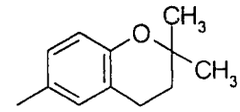
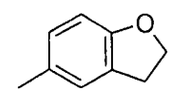
292		549

Table 18



Example	R106	MS(M+1)
293		519
294		559
295		573
296		571
297		559
298		554
299		599
300		557

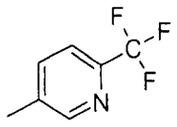
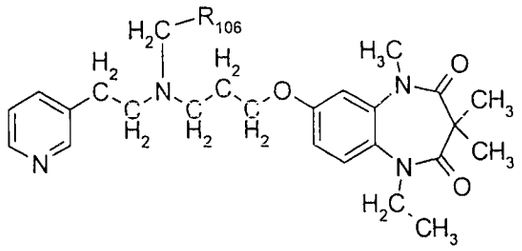
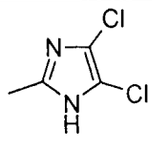
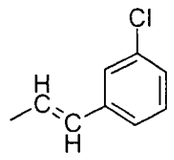
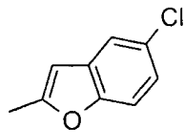
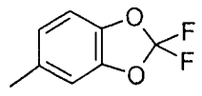
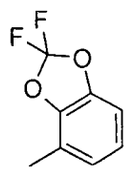
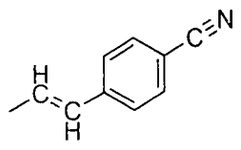
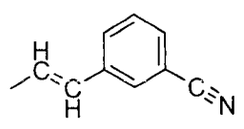
301		584

Table 19



Example	R106	MS(M+1)
302		573
303		575
304		589
305		595
306		595
307		566
308		566

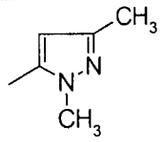
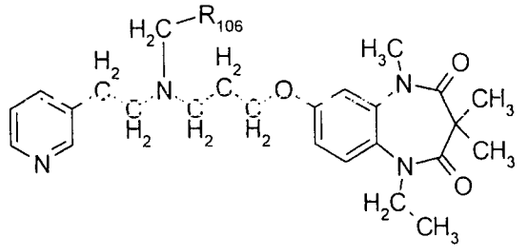
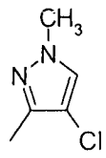
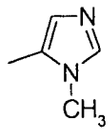
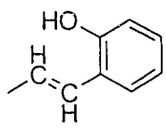
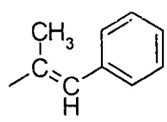
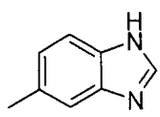
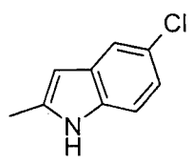
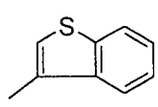
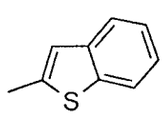
309		533

Table 20



Example	R106	MS(M+1)
310		553
311		519
312		557
313		555
314		555
315		588
316		571
317		571

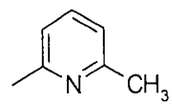
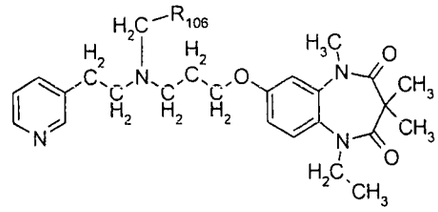
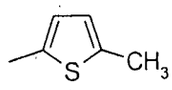
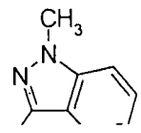
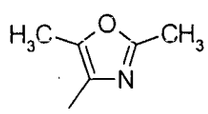
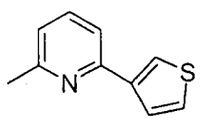
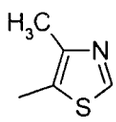
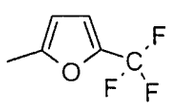
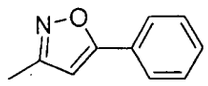
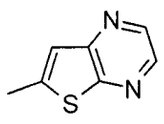
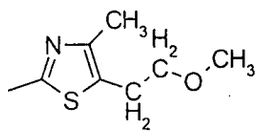
318		530

Table 21



Example	R106	MS(M+1)
319		535
320		569
321		534
322		598
323		536
324		573
325		582
326		573
327		594

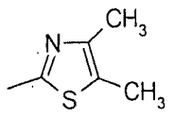
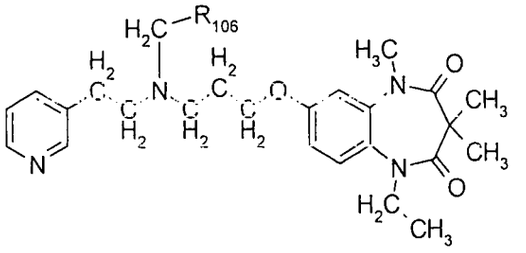
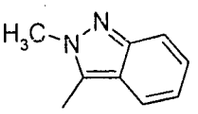
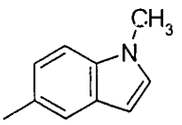
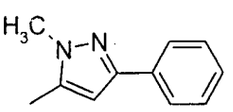
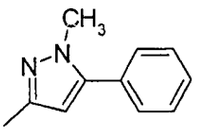
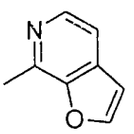
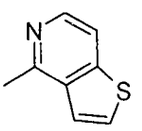
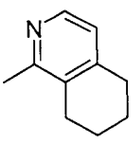
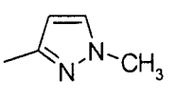
328		550

Table 22



Example	R106	MS(M+1)
329		569
330		568
331		595
332		595
333		556
334		572
335		570
336		519

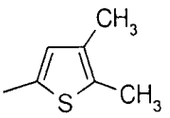
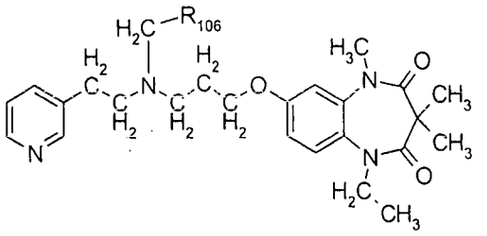
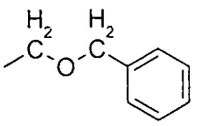
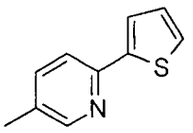
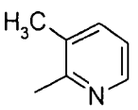
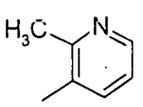
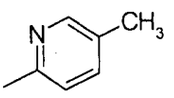
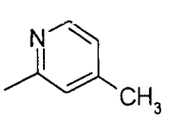
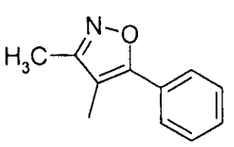
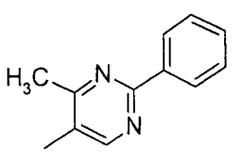
337		549

Table 23



Example	R106	MS(M+1)
338		559
339		598
340		530
341		530
342		530
343		530
344		596
345		607

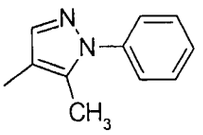
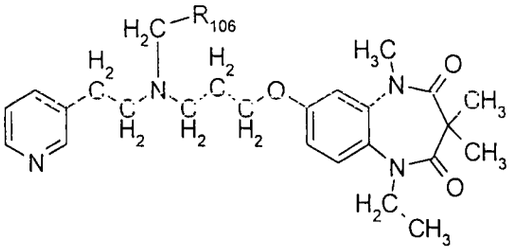
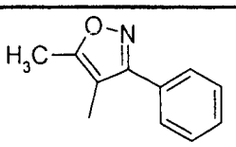
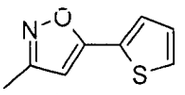
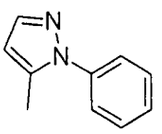
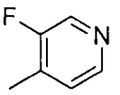
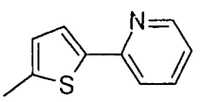
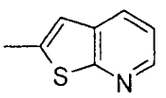
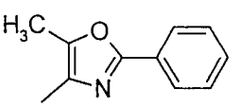
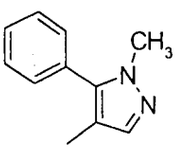
346		595

Table 24



Example	R106	MS(M+1)
347		596
348		588
349		581
350		534
351		598
352		572
353		596
354		595

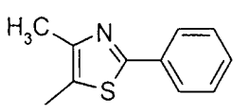
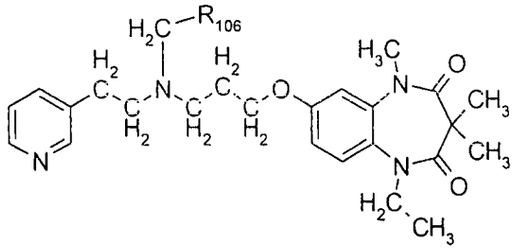
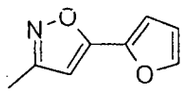
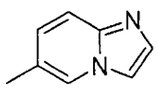
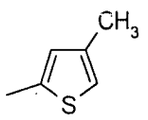
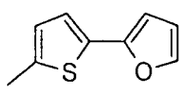
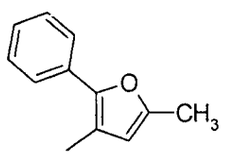
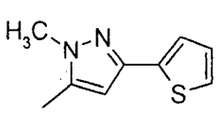
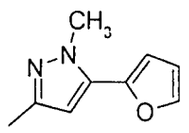
355		612

Table 25



Example	R106	MS(M+1)
356		572
357		555
358		535
359		587
360		595
361		601
362		585

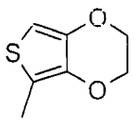
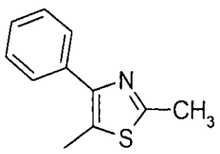
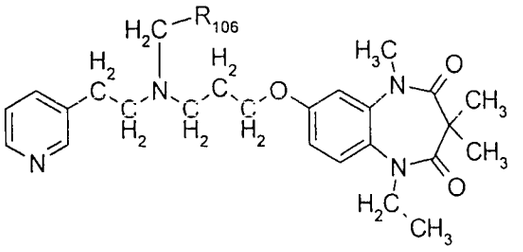
363		579
364		612

Table 26



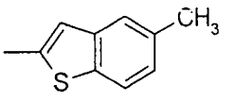
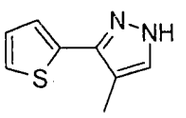
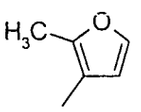
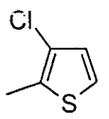
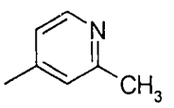
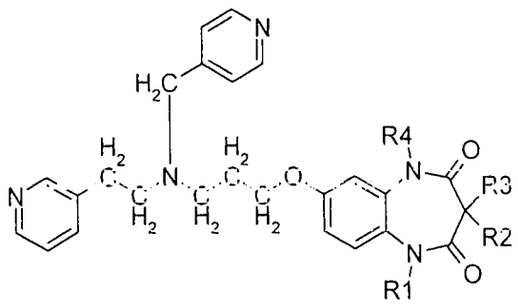
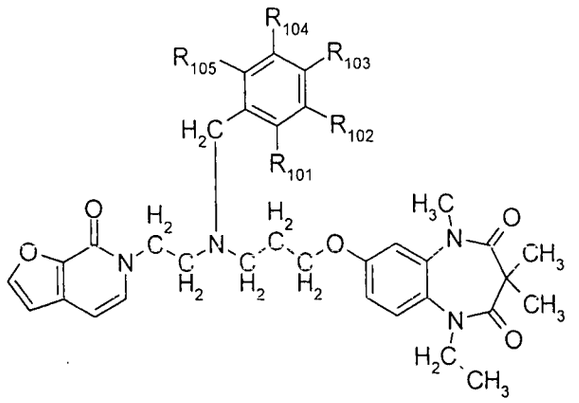
Example	R106	MS(M+1)
365		585
366		587
367		519
368		555
369		530

Table 27



Example	R1	R2	R3	R4	MS(M+1)
370	$-CH_3$	-H	-H	$-CH_3$	474
371	-H	-H	-H	-H	446

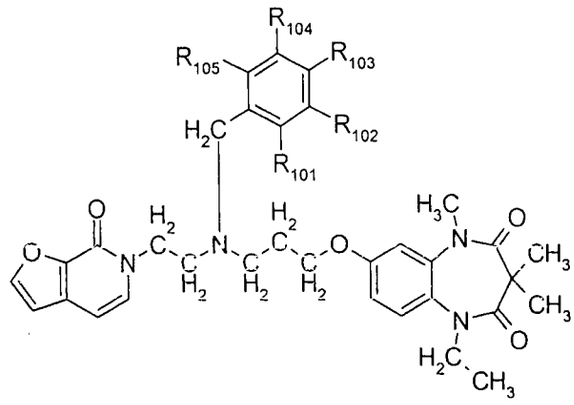
Table 28



Example	R101	R102	R103	R104	R105	MS(M+1)
372	-H	-H	-H	-H	-H	571
373	-H	-H	$-CO_2H$	-H	-H	615
374	-H	-H	$-C_6H_5$	-H	-H	647
375	-H	-H	$-OCH_3$	-H	-H	601
376	-H	-H	-H	$-OCH_3$	-H	601
377	-H	-H	-OH	-H	-H	587
378	-H	-H	$-CH_3$	-H	-H	585
379	-H	-H	$-CH(CH_3)_2$	-H	-H	613
380	-H	-H	-CN	-H	-H	596
381	-H	-H	$-OC_2H_5$	-H	-H	615
382	-H	-H	-H	-OH	-H	587
383	-H	-H	-OH	-OH	-H	603
384	-H	-H	-H	-H	$-CO_2H$	615
385	-H	-H	$-NHCOCH_3$	-H	-H	628
386	-H	-H	$-O(CH_2)_3N(CH_3)_2$	-H	-H	672
387	-H	-H	-H	-H	-Cl	605
388	-H	-H	-H	-Cl	-H	605
389	-H	-H	-Cl	-H	-H	605
390	-H	-H	-H	-H	-F	589
391	-H	-H	-H	-H	-CN	596
392	-H	-H	-H	-H	$-CF_3$	639
393	-H	-H	-H	$-CF_3$	-H	639
394	-H	-H	-H	$-CH_3$	-H	585
395	-H	-H	$-CF_3$	-H	-H	639
396	-H	-H	$-C_2H_5$	-H	-H	599
397	-H	-H	-F	-H	-H	589
398	-H	-H	-H	-H	$-CH_3$	585

399	-H	-H	$-CO_2CH_3$	-H	-H	629

Table 29



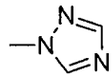
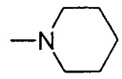
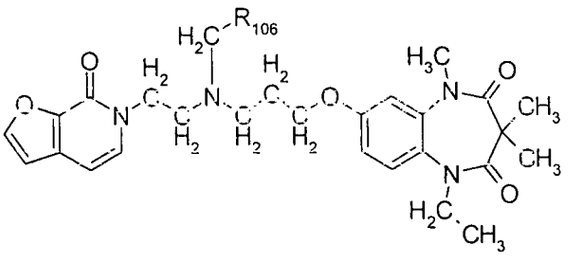
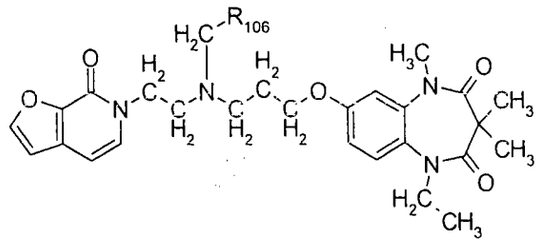
Example	R101	R102	R103	R104	R105	MS(M+1)
400	-H	-H	-H	-F	-H	589
401	-H	-H	-H	-CN	-H	596
402	-H	-H	-H	-H	$-OCH_3$	601
403	-H	-H	$-SCH_3$	-H	-H	617
404	-H	-H	-H	-H	$-CO_2CH_3$	629
405	-H	-H	$-SO_2CH_3$	-H	-H	649
406	-H	-H	$-OCH(CH_3)_2$	-H	-H	629
407	-H	-H	-H	$-C_6H_5$	-H	647
408	-H	-H	-H	-H	$-NHSO_2CH_3$	664
409	-H	-H	-1-IMIDAZOLYL	-H	-H	637
410	-H	-H	-2-THIENYL	-H	-H	653
411	-H	-H		-H	-H	638
412	-H	-H		-H	-H	654

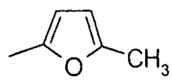
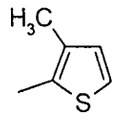
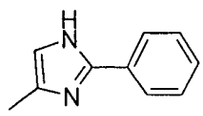
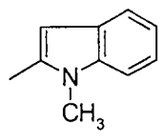
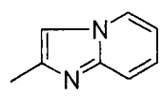
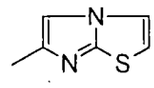
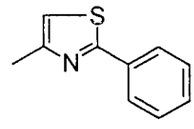
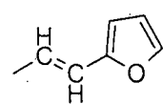
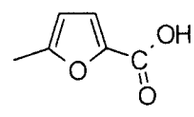
Table 30



Example	R106	MS(M+1)
413	-3-FURYL	561
414	-2-IMIDAZOLYL	561
415	-2-PYRIDYL	572
416	-3-PYRIDYL	572
417	-2-THIENYL	577
418	-3-THIENYL	577
419	-2-BENZOFURANYL	611
420	-4-QUINOLYL	622
421	-2-QUINOLYL	622
422	-CH=CHC$_6$H$_5$(trans)	597
423	-2-THIAZOLYL	578
424	-4-IMIDAZOLYL	561
425	-1-NAPHTHYL	621
426	-2-FURYL	561
427	-2-NAPHTHYL	621
428	-5-BENZOFURANYL	611

Table 31



Example	R106	MS(M+1)
429		575
430		591
431		637
432		624
433		611
434		617
435		654
436		587
437		605

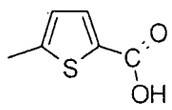
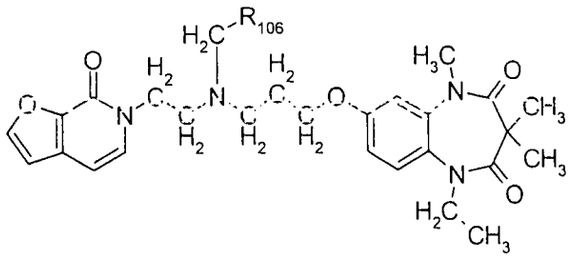
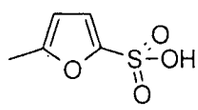
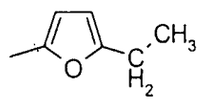
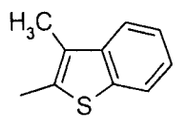
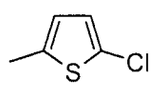
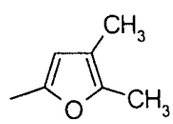
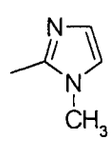
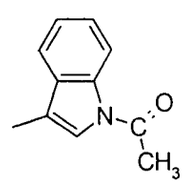
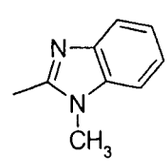
438		621

Table 32



Example	R106	MS(M+1)
439		641
440		589
441		641
442		611
443		589
444		575
445		652
446		625

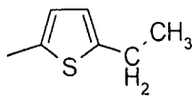
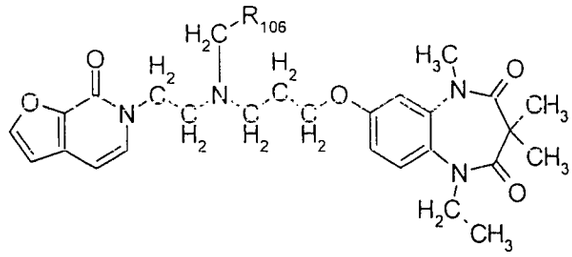
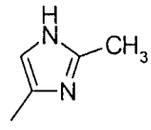
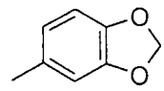
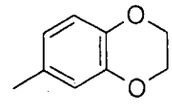
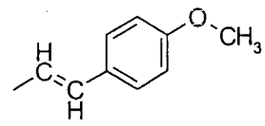
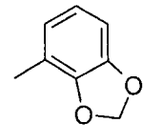
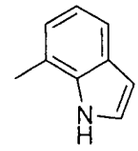
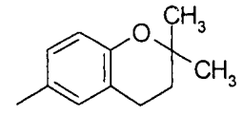
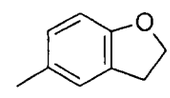
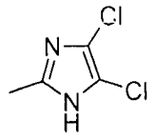
447		605

Table 33



Example	R106	MS(M+1)
448		575
449		615
450		629
451		627
452		615
453		610
454		655
455		613

456		629

Using appropriate starting materials and following the procedures of Reference Examples 1 to 62, the following object compounds were synthesized.

Reference Example 63

(1-Oxo-1H-isoquinolin-2-yl)acetaldehyde

^{1}H-NMR ($CDCl_3$) δppm:

4.78 (s, 2H), 6.59 (d, J=7.3 Hz, 1H), 7.00 (d, J=7.3 Hz, 1H), 7.52-7.59 (m, 2H), 7.68-7.73 (m, 1H), 8.44 (d, J=8.9 Hz, 1H), 9.76 (s, 1H).

Reference Example 64

(2-Oxo-2H-quinolin-1-yl)acetaldehyde

^{1}H-NMR ($CDCl_3$) δppm:

5.15 (s, 2H), 6.76 (d, J=9.5 Hz, 1H), 7.05 (d, J=8.5 Hz, 1H), 7.24-7.29 (m, 1H), 7.54-7.60 (m, 1H), 7.61 (dd, J=7.7 and 1.5 Hz, 1H), 7.77 (d, J=9.5 Hz, 1H), 9.70 (s, 1H).

Reference Example 65

6-(2,2-Dihydroxyethyl)-6H-thieno[2,3-c]pyridin-7-one

^{1}H-NMR (DMSO-d_6) δppm:

3.98 (d, J=5.3 Hz, 2H), 5.11-5.16 (m, 1H), 6.04 (d, J=6.4 Hz, 1H), 6.66 (d, J=7.1 Hz, 2H), 7.27 (d, J=5.2 Hz, 1H), 7.41 (d, J=7.1 Hz, 1H), 7.84 (d, J=5.2 H, 1H).

Reference Example 66

5-(2,2-Dihydroxyethyl)-5H-furo[3,2-c]pyridin-4-one

^{1}H-NMR (DMSO-d_6) δppm:

3.88 (d, J=5.4 Hz, 2H), 4.95-5.03 (m, 1H), 6.08 (d, J=6.4 Hz, 2H), 6.69 (dd, J=7.4, 0.8 Hz, 1H), 6.94 (dd, J=2.1 and 0.8 Hz, 1H), 7.50 (d, J=7.4 Hz, 1H), 7.86 (d, J=2.1 Hz, 1H).

Reference Example 67

5-(2,2-Dihydroxyethyl)-5H-thieno[3,2-c]pyridin-4-one

^{1}H-NMR (DMSO-d_6) δppm:

3.90 (d, J=6.3 Hz, 2H), 4.99-5.04 (m, 1H), 6.07 (d, J=6.3 Hz, 2H), 6.86 (d, J=7.2 Hz, 1H), 7.41-7.49 (m, 2H), 7.57-7.64 (m, 1H).

Reference Example 68

2-Bromo-5-(2,2-dihydroxyethyl)-5H-furo[3,2-c]pyridin-4-one

^{1}H-NMR (DMSO-d_6) δppm:

3.86 (d, J=5.4 Hz, 2H), 4.95-5.03 (m, 1H), 6.07 (d, J=6.4 Hz, 2H), 6.69 (dd, J=7.4 and 0.8 Hz, 1H), 7.08 (d, J=0.8 Hz, 1H), 7.51 (d, J=7.4 Hz, 1H).

Reference Example 69

5-(2,2-Dihydroxyethyl)-2-methyl-5H-furo[3,2-c]pyridin-4-one

^{1}H-NMR (DMSO-d_6) δppm:

2.36 (s, 3H), 3.86 (d, J=5.4 Hz, 2H), 4.94-4.98 (m, 1H), 6.04 (d, J=6.4 Hz, 2H), 6.52 (s, 1H), 6.59 (d, J=7.4 Hz, 1H), 7.41 (d, J=7.4 H, 1H).

Reference Example 70

5-(2,2-Dihydroxyethyl)-2-ethyl-5H-thieno[3,2-c]pyridin-4-one

^{1}H-NMR (DMSO-d_6) δppm:

1.73 (t, J=7.5z, 3H), 3.31 (q, J=7.5 Hz, 2H), 4.32 (d, J=6.8 Hz, 2H), 5.40-5.51 (m, 1H), 6.53 (d, J=6.2 Hz, 2H), 7.22 (d, J=7.2 Hz, 1H), 7.65 (s, 1H), 7.82 (d, J=7.2 Hz, 1Hz).

Reference Example 71

(7-Bromo-1-oxo-1H-isoquinolin-2-yl)acetaldehyde

^{1}H-NMR ($CDCl_3$) δppm:

4.77 (s, 2H), 6.52 (d, J=7.4 Hz, 1H), 6.97 (d, J=7.4 Hz, 1H), 7.43 (d, J=8.5 Hz, 1H), 7.76 (dd, J=8.5 and 2.1 Hz, 1H), 8.55 (d, J=2.1 Hz, 1H), 9.73 (s, 1H).

Reference Example 72

(1-Oxo-5,6,7,8-tetrahydro-1H-isoquinolin-2-yl)acetaldehyde

^{1}H-NMR ($CDCl_3$) δppm:

1.73-1.94 (4H, m), 2.64-2.81 (2H, m), 2.81-2.98 (2H, m), 5.04-5.17 (2H, m), 6.72-6.84 (1H, m), 7.08 (1H, d, J=6.5 Hz), 8.31 (1H, d, J=6.5 Hz).

Reference Example 73

2-Butylpyridine-3-carbaldehyde

^{1}H-NMR ($CDCl_3$) δppm:

0.96 (3H, t, J=7.4 Hz), 1.41-1.48 (2H, m), 1.67-1.76 (2H, m), 3.21 (2H, t, J=8.0 Hz), 7.31 (1H, dd, J=7.8 and 4.8 Hz), 8.13 (1H, dd, J=7.8

and 1.9 Hz), 8.72 (1H, dd, J=4.8 and 1.9 Hz), 10.36 (1H, s).

Reference Example 74

1-(Ethoxycarbonyl)cyclobutanecarboxylic acid

^{1}H-NMR ($CDCl_3$) δppm:

1.27 (t, J=7.1 Hz, 3H), 2.00-2.07 (m, 2H), 2.60 (t, J=8.2 Hz, 4H), 4.25 (q, J=7.1 Hz, 1H).

Reference Example 75

Ethyl 1-(2-aminophenylcarbamoyl)cyclobutanecarboxylate

^{1}H-NMR ($CDCl_3$) δppm:

1.34 (t, J=7.1 Hz, 3H), 1.97-2.08 (m, 2H), 2.60-2.68 (m, 2H), 2.71-2.82 (m, 2H), 3.80 (br, 2H), 4.29 (q, J=7.1 Hz, 2H), 6.77-6.83 (m, 2H), 7.02-7.08 (m, 1H), 7.95 (br, 1H).

Reference Example 76

Spiro[benzo[b][1,4]diazepine-3,1'-cyclobutane]-2,4(1H,5H)-dione

^{1}H-NMR (DMSO-d_6) δppm:

1.59-1.70 (m, 2H), 3.29-3.44 (m, 4H), 7.07-7.14 (m, 4H), 10.4 (br, 2H).

Reference Example 77

1,5-Dimethylspiro[benzo[b][1,4]diazepine-3,1'-cyclobutane]-2,4(1H,5H)-dione

^{1}H-NMR ($CDCl_3$) δppm:

1.26-1.68 (m, 4H), 2.83-2.89 (m, 2H), 3.44 (s, 6H), 7.23-7.30 (m, 4H).

Reference Example 78

1,5-Dimethyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)spiro[benzo[b][1,4]diazepine-3,1'-cyclobutane]-2,4(1H,5H)-dione

^{1}H-NMR ($CDCl_3$) δppm:

1.26 (s, 6H), 1.60 (s, 6H), 1.62-1.69 (m, 4H), 2.06-2.89 (m, 2H), 3.45 (s, 3H), 3.48 (s, 3H), 7.26-7.28 (m, 1H), 7.65-7.70 (m, 2H).

Reference Example 79

7-Hydroxy-1,5-dimethylspiro[benzo[b][1,4]diazepine-3,1'-cyclobutane]-2,4(1H,5H)-dione

^{1}H-NMR ($CDCl_3$) δppm:

1.58-1.62 (m, 4H), 2.83-2.88 (m, 2H), 3.41 (s, 3H), 3.44 (s, 3H), 7.14 (d, J=8.7 Hz, 1H), 7.36 (dd, J=8.7 and 2.1 Hz, 1H), 7.41 (d, J=2.1

Hz, 1H).

Example 457

Synthesis of 1-ethyl-3,3,5-trimethyl-7-{3-[(pyridin-4-ylmethyl)amino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione sulfate

Sulfuric acid (13 µl) was added to an ethyl acetate solution (5 ml) of 1-ethyl-3,3,5-trimethyl-7-{3-[(pyridin-4-ylmethyl)amino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione (100 mg, 0.24 mmol), and stirred at room temperature for 15 minutes. The resultant mixture was concentrated to dryness under reduced pressure to thereby obtain 1-ethyl-3,3,5-trimethyl-7-{3-[(pyridin-4-ylmethyl)amino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione sulfate as a white amorphous solid.

^{1}H-NMR (DMSO-d_6) δppm:

0.74 (s, 3H), 0.99 (t, J = 7.0 Hz, 3H), 1.31 (s, 3H), 2.14-2.18 (m, 2H), 3.14-3.18 (m, 2H), 3.31 (s, 3H), 3.61-3.69 (m, 1H), 4.00-4.09 (m, 1H), 4.10-4.14 (m, 2H), 4.27 (s, 2H).6.94-6.95 (m, 2H), 7.40 (d, J = 9.0 Hz, 1H), 7.55-7.57 (m, 2H), 8.62-8.64 (m, 2H).

Example 458

Synthesis of 1,3,3,5-tetramethyl-7-(3-{[2-(1-oxo-3,4-dihydro-1H-isoquinolin-2-yl)ethyl]pyridin-4-ylmethylamino}-propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione tris phosphate

85% phosphoric acid aqueous solution (0.34ml) was added to an ethanol solution (19ml) of 1,3,3,5-Tetramethyl-7-(3-{[2-(1-oxo-3,4-dihydro-1H-isoquinolin-2-yl)ethyl]pyridin-4-ylmethylamino}-propoxy)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione (1.05g, 1.84mmol), and stirred at 50℃ for 15 minutes. The reaction mixture was cooled to room temperature. The precipitated insoluble matter was collected by filtration, washed with ethanol, and dried to thereby obtain 1.59 g (yield: 73%) of 1,3,3,5-Tetramethyl-7-(3-{[2-(1-oxo-3,4-dihydro-1H-isoquinolin-2-yl)ethyl]pyridin-4-ylmethylamino}-propoxy)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione tris(phosphate) as a white solid.

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (3H, s), 1.32 (3H, s), 1.78-1.98 (2H, m), 2.55-2.77 (4H, m),

2.81-2.98 (2H, m), 3.28 (3H, s), 3.29 (3H, s), 3.51 (2H, t, 6.6 Hz), 3.62 (2H, m), 3.68(s, 2 H), 3.99 (2H, t, J = 6.0 Hz), 6.75 (2H, dd, J=2.6 and 9.0 Hz), 6.82 (2H, d, 2.6 Hz), 7.21-7.38 (5H, m), 7.41-7.51 (1H, m), 8.34 (2H, d, J=5.8Hz)

Example 459

Synthesis of N-[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]-N-(2-pyridin-3-ylethyl)isonicotinamide

N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (WSC) (0.16 g, 0.85 mmol) was added to an acetonitrile solution (6 ml) of 1-ethyl-3,3,5-trimethyl-7-[3-(2-pyridin-3-ylethylamino)propoxy]-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione (0.3 g, 0.71 mmol), isonicotinic acid (96 mg, 0.78 mmol), and 1-hydroxybenzotriazole (HOBT) (0.138 g, 0.85 mmol), and then stirred at room temperature for 2 days. The solvent was concentrated under reduced pressure. Ethyl acetate and a sodium hydrogen carbonate aqueous solution were added to the reaction mixture, and stirred for 1 hour. Water was added to the reaction mixture, and extraction with ethyl acetate was conducted. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue thus obtained was purified by medium pressure liquid chromatography (silica gel, dichloromethane:methanol=92:8). The purified product was concentrated under reduced pressure and crystallized from ethyl acetate, diethylether and n-hexane. The precipitated crystals were collected by filtration and dried to thereby obtain 0.21 g (yield:56%) of N-[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]-N-(2-pyridin-3-ylethyl)isonicotinamide as a white powder.

Melting Point 88.1 to 92.2°C

Example 460

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{[2-(4-oxo-4H-thieno[3,2-c]pyridin-5-yl)ethyl]pyridin-4-ylmethylamino}-propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.88 (s, 3H), 1.17 (t, J=7.1 Hz, 3H), 1.54 (s, 3H), 1.89-1.97 (m, 2H), 2.74 (t, J=6.8 Hz, 2H), 2.83-2.95 (m, 2H), 3.39 (s, 3H), 3.69 (s, 2H), 3.68-3.74 (m, 1H), 3.89 (t, J=6.0 Hz, 2H), 4.12 (t, J=6.0 Hz, 2H), 4.11-4.21 (m, 1H), 6.53-6.70 (m, 3H), 7.05 (d, J=7.2 Hz, 1H), 7.10 (d, J=5.9 Hz, 2H), 7.20 (d, J=8.9 Hz, 1H), 7.32 (d, J=5.3 Hz, 1H), 7.63 (d, J=5.3 Hz, 1H), 8.32 (d, J=5.9 Hz, 2H).

Example 461

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{[2-(7-oxo-7H-thieno[2,3-c]pyridin-6-yl)ethyl]pyridin-4-ylmethylamino}-propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.88 (s, 3H), 1.17 (t, J=7.1 Hz, 3H), 1.54 (s, 3H), 1.89-1.97 (m, 2H), 2.74 (t, J=6.8 Hz, 2H), 2.83-2.95 (m, 2H), 3.39 (s, 3H), 3.68-3.74 (m, 3H), 3.90 (t, J=6.0 Hz, 2H), 4.05-4.21 (m, 3H), 6.56 (d, J=7.1 Hz, 1H), 6.60-6.70 (m, 2H), 7.03-7.10 (m, 3H), 7.16-7.23 (m, 2H), 7.73 (d, J=5.2 Hz, 1H), 8.31 (d, J=5.9 Hz, 2H).

Example 462

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]pyridin-4-ylmethylamino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

White powder

Melting Point 93.8°C

^{1}H-NMR ($CDCl_3$) δppm:

0.87 (s, 3H), 1.16 (t, J=7.1 Hz, 3H), 1.53 (s, 3H), 1.82-1.95 (m, 2H), 2.72 (t, J=6.8 Hz, 2H), 2.76-2.89 (m, 2H), 3.38 (s, 3H), 3.68 (s, 2H), 3.63-3.78 (m, 1H), 3.87 (t, J=6.0 Hz, 2H), 4.10 (t, J=6.0 Hz, 2H), 4.11-4.20 (m, 1H), 6.43 (d, J=7.4 Hz, 1H), 6.60 (d, J=2.8 Hz, 1H), 6.67 (dd, J=9.0 and 2.8 Hz, 1H), 6.96 (d, J=2.9 Hz, 1H), 7.05-7.11 (m, 3H), 7.19 (d, J=9.0 Hz, 1H), 7.50 (d, J=2.9 Hz, 1H), 8.35 (d, J=6.0 Hz, 2H).

Example 463

Synthesis of 7-(3-{[2-(2-bromo-4-oxo-4H-furo[3,2-c]pyridine-5-yl) ethyl]pyridin-4-ylmethylamino}propoxy)-1-ethyl-3,3,5-trimethyl-1, 5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 7 and Example 6, the object compound was synthesized.

amorphous

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (s, 3H), 1.01 (t, J = 7.1 Hz, 3H), 1.32 (s, 3H), 2.15 (br, 2H), 2.95-3.40 (m, 2H), 3.32 (s, 3H), 3.61-3.73 (m, 3H), 4.01-4.09 (m, 3H), 4.34 (br, 4H), 6.81 (br, 2H), 6.88 (br, 1H), 7.10 (s, 1H), 7.39 (d, J = 9.0 Hz, 1H), 7.74 (br, 1H), 8.13 (br, 2H), 8.86 (br, 2H).

Example 464

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]pyridin-4-ylmethyl-amino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 6, the object compound was synthesized.

amorphous

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (s, 3H), 1.01 (t, J = 7.1 Hz, 3H), 1.32 (s, 3H), 2.00-2.22 (m, 2H), 2.22 (s, 3H), 3.11-3.39 (m, 7H), 3.60-3.71 (m, 1H), 4.02-4.07 (m, 3H), 4.30-4.45 (m, 2H), 4.51-4.71(m, 2H), 6.55 (s, 1H), 6.72 (d, J = 7.3 Hz, 1H), 6.84-6.90 (m, 2H), 7.40 (d, J = 9.0 Hz, 1H), 7.64 (d, J = 7.3 Hz, 1H), 8.21 (br, 2H), 8.89 (br, 2H).

Example 465

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]pyridin-4-ylmethyl-amino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.87 (s, 3H), 1.16 (t, J=7.1 Hz, 3H), 1.53 (s, 3H), 1.83-1.96 (m, 2H),

2.42 (s, 3H), 2.72 (t, J=6.2 Hz, 2H), 2.85 (t, J=6.0 Hz, 2H), 3.39 (s, 3H), 3.68 (s, 2H), 3.66-3.79 (m, 1H), 3.89 (t, J=6.1 Hz, 2H), 4.08-4.23 (m, 3H), 6.37 (d, J=7.3 Hz, 1H), 6.49-6.54 (m, 1H), 6.63-6.69 (m, 2H), 7.01 (d, J=7.3 Hz, 1H), 7.08-7.12 (m, 2H), 7.19 (d, J=8.3 Hz, 1H), 8.35-8.37 (m, 2H).

Example 466

Synthesis of 1-ethyl-7-(3-{[2-(2-ethyl-4-oxo-4H-thieno [3,2-c]pyridin-5-yl)-ethyl]-pyridin-4-ylmethyl-amino}-propoxy)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 7 and Example 6, the object compound was synthesized.

amorphous

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (s, 3H), 1.01 (t, J = 7.0 Hz, 3H), 1.28 (t, J = 7.5 Hz, 3H), 1.32 (s, 3H), 2.09 (br, 2H), 2.87 (q, J = 7.5 Hz, 2H), 3.10-3.21 (m, 2H), 3.30 (s, 3H), 3.51-3.69 (m, 3H), 3.90-4.09 (m, 5H), 4.30 (br, 2H), 6.71-6.88 (m, 3H), 7.18-7.20 (m, 1H), 7.36-7.43 (m, 1H), 7.52 (br, 1H), 7.86 (br, 2H), 8.69 (br, 2H).

Example 467

Synthesis of 7-(3-{[2-(2,3-dimethyl-4-oxo-4H-furo[3,2-c] pyridin-5-yl)ethyl]pyridin-4-ylmethylamino}propoxy)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 7 and Example 6, the object compound was synthesized.

pale yellow amorphous

^{1}H-NMR (DMSO-d_6) δppm:

0.74 (s, 3H), 1.01 (t, J = 7.0 Hz, 3H), 1.32 (s, 3H), 2.05-2.20 (m, 2H), 2.17 (s, 3H), 2.29 (s, 3H), 3.05-3.20 (m, 2H), 3.31 (s, 3H), 3.61-3.73 (m, 3H), 3.95-4.05 (m, 3H), 4.31 (br, 4H), 6.63 (br, 1H), 6.81-6.88 (m, 2H), 7.39 (d, J = 9.0 Hz, 1H), 7.56 (d, J = 7.3 Hz, 1H), 8.04 (br, 2H), 8.79 (br, 2H).

Example 468

Synthesis of 1-ethyl-7-(3-{[2-(2-furan-3-yl-4-oxo-4H-furo [3,2-c]pyridin-5-yl)ethyl]pyridin-4-ylmethylamino}propoxy)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

A 2N-Sodium carbonate aqueous solution (0.3 ml) and tetrakis(triphenylphosphine)palladium(0) (37.2 mg, 0.03 mmol) were added to a dimethoxyethane solution (2 ml) of 7-(3-{[2-(2-bromo -4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]pyridin-4-ylmethylamino} propoxy)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepin e-2,4-dione (0.20 g, 0.31 mmol) and furan-3-boronic acid (39.2 mg, 0.035 mmol), and stirred under argon atmosphere at 80°C for 6.5 hours. The reaction mixture was cooled to room temperature, and purified by silica gel column chromatography (ethyl acetate:methanol=100:0→93:7). The purified product was concentrated under reduced pressure and the resultant residue was dissolved in ethyl acetate (10 ml). A 4N-HCl ethyl acetate solution (0.5 ml) was added to the solution, and concentrated to dryness under reduced pressure to thereby obtain 0.10 g (yield:51%) of 1-ethyl-7-(3-{[2-(2-furan-3-yl-4-oxo-4H-furo [3,2-c]pyridin-5-yl)ethyl]pyridin-4-ylmethylamino}propoxy)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride as a pale yellow amorphous solid.

^{1}H-NMR (DMSO-d_6) δppm:

0.73 (s, 3H), 1.00 (t, J = 7.0 Hz, 3H), 1.32 (s, 3H), 2.09 (br, 2H), 3.21-3.40 (m, 2H), 3.29 (s, 3H), 3.51-3.64 (m, 3H), 3.81-4.01 (m, 5H), 4.30 (br, 2H), 6.78 (br, 2H), 6.84 (br, 1H), 6.98 (d, J = 0.74 Hz, 1H), 7.16 (s, 1H), 7.33 (d, J = 8.5 Hz, 1H), 7.69 (d, J = 5.9 Hz, 1H), 7.82 (s, 1H), 7.93 (br, 2H), 8.19 (s, 1H), 8.74 (br, 2H).

Example 469

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{[2-(4-oxo-2-pyridin-3-yl-4H-furo[3,2-c]pyridin-5-yl)ethyl]pyridin-4-ylmethylamino)-propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione trihydrochloride

Using an appropriate starting material and following the

procedure of Example 468, the object compound was synthesized.

pale yellow amorphous

^{1}H-NMR (DMSO-d_6) δppm:

0.73 (s, 3H), 0.99 (t, J = 7.0 Hz, 3H), 1.31 (s, 3H), 2.13 (br, 2H), 3.10-3.30 (m, 2H), 3.30 (s, 3H), 3.70-3.85 (m, 1H), 3.92-4.03 (m, 5H), 4.38 (br, 4H), 6.80-6.87 (m, 3H), 7.35 (d, J = 9.0 Hz, 1H), 7.79-7.84 (m, 3H), 8.07 (br, 2H), 8.55 (d, J = 8.0 Hz, 1H), 8.72 (dd, J = 1.3, 5.2 Hz, 1H), 8.82 (br, 2H), 9.23 (d, J = 1.8 Hz, 1H).

Example 470

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{[2-(4-oxo-2-pyridin-4-yl-4H-furo[3,2-c]pyridin-5-yl)ethyl]pyridin-4-yl methylamino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione trihydrochloride

Using an appropriate starting material and following the procedure of Example 468, the object compound was synthesized.

yellow powder

^{1}H-NMR (DMSO-d_6) δppm:

0.74 (s, 3H), 0.99 (t, J = 7.0 Hz, 3H), 1.31 (s, 3H), 2.11 (br, 2H), 3.12-3.30 (m, 2H), 3.29 (s, 3H), 3.55-3.69 (m, 1H), 3.91-4.08 (m, 5H), 4.36 (br, 4H), 6.77-6.90 (m, 3H), 7.35 (d, J = 8.9 Hz, 1H), 7.93 (br, 3H), 8.30 (br, 3H), 8.76 (br, 2H), 8.91 (d, J = 5.6 Hz, 2H).

Example 471

Synthesis of 7-[3-({2-[2-(3-amino-henyl)-4-oxo-4H-furo [3,2-c]pyridin-5-yl]ethyl}pyridin-4-ylmethylamino)propoxy]-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione trihydrochloride

Using an appropriate starting material and following the procedure of Example 468, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

0.73 (s, 3H), 0.99 (t, J = 7.0 Hz, 3H), 1.31 (s, 3H), 2.10 (br, 2H), 3.02-3.20 (m, 2H), 3.30 (s, 3H), 3.55-3.70 (m, 1H), 3.95-4.03 (m, 5H), 4.39 (br, 4H), 6.78-6.88 (m, 3H), 7.15-7.80 (m, 2H), 7.53 (br, 2H), 7.62-7.81 (m, 3H), 8.06 (br, 2H), 8.82 (br, 2H).

Example 472

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{[2-(7-oxo-7H-

furo[2,3-c]pyridin-6-yl)ethyl]pyridin-3-ylmethylamino}-propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

White powder

Melting Point 125°C

Example 473

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{[2-(7-oxo-7H-furo[2,3-c]pyridin-6-yl)ethyl]quinolin-4-ylmethylamino}-propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 7 and Example 6, the object compound was synthesized.

White powder

^{1}H-NMR (DMSO-D_6) δppm:

0.74 (3H, s), 1.01 (3H, t, J= 7.0 Hz), 1.32 (3H, s), 2.00-2.28 (2H, m), 2.70-5.31 (15H, m), 6.45-6.59 (1H, m), 6.76-6.80 (1H, m), 6.83-6.87 (2H, m), 7.37 (1H, d, J= 9.0 Hz) 7.42-7.58 (1H, m), 7.72-7.88 (1H, m), 7.95-8.19 (3H, m), 8.31 (1H, d, J= 8.6 Hz), 8.43-8.50 (1H, m), 9.03-9.19 (1H, m)

Example 474

Synthesis of 1-ethyl-7-(3-{(3-hydroxybenzyl)-[2-(7-oxo-7H-furo[2,3-c]pyridin-6-yl)ethyl]amino}propoxy)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione hydrochloride

Using an appropriate starting material and following the procedure of Example 7 and Example 6, the object compound was synthesized.

White powder

^{1}H-NMR (DMSO-D_6) δppm:

0.75 (3H, s), 1.01 (3H, t, J= 7.0 Hz), 1.32 (3H, s), 2.12-2.27 (2H, m), 3.20-3.44 (7H, m) 3.45-3.43 (2H, m), 3.63-3.70 (1H, m), 3.99-4.09 (3H, m), 4.35-4.37 (1H, m), 4.43-4.53 (1H, m) 6.68-6.71 (1H, m), 6.84-6.93 (4H, m), 6.99-7.10 (2H, m), 7.20-7.26 (1H, m), 7.40 (1H, d, J= 7.7Hz), 7.54-7.58 (1H, m), 8.17(1H, s), 9.72-9.80(1H, m)

Example 475

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{[2-(7-oxo-7H-furo[2,3-c]pyridin-6-yl)ethyl]thiazol-2-ylmethylamino}-propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 7 and Example 6, the object compound was synthesized.

White powder

^{1}H-NMR (DMSO-D_6) δppm:

0.75 (3H, s), 1.00 (3H, t, J= 7.1 Hz), 1.32 (3H, s), 2.05-2.28 (2H, m), 3.10-3.84(8H, m), 3.99-4.09 (3H, m), 4.40-4.50 (2H, m), 4.72-4.88 (2H, m), 6.64-6.67 (1H, m), 6.84-6.92 (3H, m), 7.39 (1H, d, J= 9.0Hz) 7.52-7.59 (1H, m), 7.65-7.91 (2H, m), 8.14 (1H, d, J= 1.9Hz)

Example 476

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{[2-(4-oxo-2-phenyl-4H-furo[3,2-c]pyridin-5-yl)ethyl]pyridin-4-ylmethyl-amino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 468, the object compound was synthesized.

amorphous

^{1}H-NMR (DMSO-d6) δppm:

0.72 (s, 3H), 0.99 (t, J = 7.0 Hz, 3H), 1.31 (s, 3H), 2.09 (br, 2H), 3.11-3.30 (m, 2H), 3.29 (s, 3H), 3.61-3.72 (m, 1H), 3.60-4.04 (m, 5H), 4.38 (br, 4H), 6.71-6.88 (m, 3H), 7.32 (d, J = 8.6 Hz, 1H), 7.37-7.41 (m, 1H), 7.46-7.51 (m, 3H), 7.74 (br, 1H), 7.86 (d, J = 7.4 Hz, 2H), 8.03 (br, 2H), 8.81 (br, 2H).

Example 477

Synthesis of 1-ethyl-7-[3-({2-[2-(4-methoxyphenyl)-4-oxo-4H-furo[3,2-c]pyridin-5-yl]ethyl}pyridin-4-ylmethylamino)-propoxy]-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the

procedure of Example 468, the object compound was synthesized.

amorphous

^{1}H-NMR (DMSO-d6) δppm:

0.71 (s, 3H), 0.98 (t, J = 7.0 Hz, 3H), 1.31 (s, 3H), 2.00 (br, 2H), 3.28 (s, 3H), 3.20-3.38 (m, 2H), 3.50-3.70 (m, 1H), 3.82 (s, 3H), 3.90-4.02 (m, 5H), 4.40 (br, 4H), 6.82 (br, 3H), 7.05 (d, J = 8.8 Hz, 2H), 7.30 (br, 2H), 7.66 (br, 1H), 7.79 (d, J = 8.8 Hz, 2H), 7.92 (br, 2H), 8.68 (br, 2H).

Example 478

Synthesis of 1-ethyl-3,3,5-trimethyl-7-[3-(pyridin-4-ylmethylpyridin-2-ylmethylamino)propoxy]-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

Colorless oil

^{1}H-NMR ($CDCl_3$) δppm:

0.86 (s, 3H), 1.15 (t, J=7.1 Hz, 3H), 1.53 (s, 3H), 1.91-2.08 (m, 2H), 2.66 (t, J=6.9 Hz, 2H), 3.39 (s, 3H), 3.61 (s, 2H), 3.63 (s, 2H), 3.61-3.78 (m, 1H), 3.97 (t, J=6.1 Hz, 2H), 4.03-4.20 (m, 1H), 6.60 (d, J=2.7 Hz, 1H), 6.70 (dd, J=2.7 and 9.0 Hz, 1H), 7.16-7.26 (m, 4H), 7.64-7.68 (m, 1H), 8.46-8.52 (m, 3H), 8.60 (br, 1H).

Example 479

Synthesis of 1-ethyl-3,3,5-trimethyl-7-[3-(pyridin-4-ylmethyl pyridin-2-ylmethylamino)propoxy]-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione trihydrochloride

Using an appropriate starting material and following the procedure of Example 6, the object compound was synthesized.

White solid

^{1}H-NMR (DMSO-d_6) δppm:

0.76 (s, 3H), 1.05 (t, J=7.0 Hz, 3H), 1.33 (s, 3H), 2.09 (br, 2H), 2.75 (br, 2H), 3.31 (s, 3H), 3.61-3.73 (m, 1H), 4.03 - 4.30 (m, 5H), 4.53 (br, 2H), 6.81-6.82 (m, 2H), 7.34-7.37 (m, 1H), 7.94 (br, 1H), 8.15 (br, 2H), 8.64 (br, 1H), 8.80-8.87 (m, 3H), 9.01(Br, 1H).

Example 480

Synthesis of 1-ethyl-3,3,5-trimethyl-7-[3-(pyridin-4-

ylmethylpyridin-3-ylmethylamino)propoxy]-1,5-dihydrobenzo [b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

colorless oil

^{1}H-NMR ($CDCl_3$) δppm:

0.86 (s, 3H), 1.15 (t, J=7.1 Hz, 3H), 1.53 (s, 3H), 1.91-2.04 (m, 2H), 2.71 (t, J=6.9 Hz, 2H), 3.38 (s, 3H), 3.67 (s, 2H), 3.61-3.72 (m, 1H), 3.80 (s, 2H), 3.99 (t, J=6.1 Hz, 2H), 4.05-4.20 (m, 1H), 6.61 (d, J=2.8 Hz, 1H), 6.71 (dd, J=2.8 and 9.0 Hz, 1H), 7.14-7.19 (m, 2H), 7.26-7.31 (m, 2H), 7.46 (d, J=7.8 Hz, 1H), 7.57-7.68 (m, 1H), 8.47-8.54 (m, 3H).

Example 481

Synthesis of 1-ethyl-3,3,5-trimethyl-7-[3-(pyridin-4-ylmethylpyridin-3-ylmethylamino)propoxy]-1,5-dihydrobenzo [b][1,4]diazepine-2,4-dione trihydrochloride

Using an appropriate starting material and following the procedure of Example 6, the object compound was synthesized.

White amorphous

^{1}H-NMR (DMSO-d_6) δppm:

0.76 (s, 3H), 1.01 (t, J=7.0 Hz, 3H), 1.32 (s, 3H), 2.14 (br, 2H), 2.96 (br, 2H), 3.30 (s, 3H), 3.61-3.73 (m, 1H), 4.03-4.10 (m, 3H), 4.27-4.32 (m, 4H), 6.81-6.85 (m, 2H), 7.38 (d, J=9.0 Hz, 1H), 7.64 (br, 1H), 7.81 (br, 1H), 8.07 (br, 3H), 8.81 (br, 3H).

Example 482

Synthesis of 7-[3-(bis-pyridin-4-ylmethylamino)propoxy]-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

colorless oil

^{1}H-NMR ($CDCl_3$) δppm:

0.86 (s, 3H), 1.15 (t, J=7.1 Hz, 3H), 1.53 (s, 3H), 1.91-2.02 (m, 2H), 2.66 (t, J=6.6 Hz, 2H), 3.38 (s, 3H), 3.62 (s, 4H), 3.61-3.78 (m, 1H), 3.92-3.99 (m, 2H), 4.01-4.20 (m, 1H), 6.61 (d, J=2.8 Hz, 1H), 6.70 (dd, J=2.8 and 9.0 Hz, 1H), 7.20 (d, J=9.0 Hz, 1H), 7.28-7.30 (m, 4H), 8.50-8.53 (m, 4H).

Example 483

Synthesis of 7-[3-(bis-pyridin-4-ylmethylamino)propoxy]-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione trihydrochloride

Using an appropriate starting material and following the procedure of Example 6, the object compound was synthesized.

White amorphous

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (s, 3H), 1.02 (t, J=7.0 Hz, 3H), 1.32 (s, 3H), 2.01 (br, 2H), 2.67 (br, 2H), 3.30 (s, 3H), 3.63-3.72 (m, 1H), 4.03-4.10 (m, 7H), 6.81-6.85 (m, 2H), 7.37 (d, J=9.0 Hz, 1H), 8.10 (br, 4H), 8.84 (br, 4H).

Example 484

Synthesis of 1-ethyl-3,3,5-trimethyl-7-{3-[(5-methylfuran-2-ylmethyl)pyridin-4-ylmethylamino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

pale yellow oil

^{1}H-NMR ($CDCl_3$) δppm:

0.86 (s, 3H), 1.15 (t, J=7.1 Hz, 3H), 1.53 (s, 3H), 1.91-2.05 (m, 2H), 2.27 (s, 3H), 2.67 (t, J=6.6 Hz, 2H), 3.39 (s, 3H), 3.63 (s, 2H), 3.64 (s, 2H), 3.62-3.79 (m, 1H), 4.02 (t, J=6.2 Hz, 2H), 4.07-4.22 (m, 1H), 5.87 (br, 1H), 6.04 (br, 1H), 6.66 (d, J=2.8 Hz, 1H), 6.75 (dd, J=2.8 and 9.0 Hz, 1H), 7.20 (d, J=9.0 Hz, 1H), 7.24-7.26 (m, 2H), 8.46-8.50 (m, 2H).

Example 485

Synthesis of 1-ethyl-3,3,5-trimethyl-7-{3-[(5-methylfuran-2-ylmethyl)pyridin-4-ylmethylamino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 6, the object compound was synthesized.

pale yellow amorphous

^{1}H-NMR (DMSO-d_6) δppm:

0.76 (s, 3H), 1.01 (t, J=7.0 Hz, 3H), 1.32 (s, 3H), 2.21-2.30 (m, 5H),

3.05 (br, 2H), 3.32 (s, 3H), 3.62-3.72 (m, 1H), 4.02-4.11 (m, 3H), 4.23-4.58 (m, 4H), 6.10 (br, 1H), 6.57 (br, 1H), 6.87-6.91 (m, 2H), 7.40 (d, J=9.0 Hz, 1H), 8.20 (br, 2H), 8.90 (br, 2H).

Example 486

Synthesis of 1-ethyl-3,3,5-trimethyl-7-{3-[(2-methylaminoethyl)pyridin-4-ylmethylamino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione trihydrochloride

Using an appropriate starting material and following the procedure of Example 44, the object compound was synthesized.

^{1}H-NMR (DMSO-d6) δppm:

0.76 (s, 3H), 1.01 (t, J = 7.0 Hz, 3H), 1.32 (s, 3H), 2.21 (br, 2H), 2.51 (s, 3H), 3.10 (br, 2H), 3.33 (s, 3H), 3.35 (br, 2H), 3.61-3.72 (m, 1H), 4.00-4.12 (m, 5H), 4.55 (br, 2H), 6.90 (dd, J = 2.6, 9.0 Hz, 1H), 6.94 (d, J = 2.6 Hz, 1H), 7.40 (d, J = 9.0 Hz, 1H), 8.35 (br, 2H), 8.95 (br, 2H), 9.50 (br, 2H).

Example 487

Synthesis of N-(2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)-N-methylbenzamide

Diethyl phosphorocyanidate (0.15 g, 1.0 mmol) was added to a THF solution (5 ml) of 1-ethyl-3,3,5-trimethyl-7-{3-[(2-methylaminoethyl)pyridin-4-ylmethylamino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione (0.39 g, 0.83 mmol), benzoic acid (0.14 g, 1.1 mmol), and triethylamine (0.15 ml, 1.1 mmol), and the mixture was stirred at room temperature overnight. The reaction mixture was purified by silica gel column chromatography (ethyl acetate:methanol=100:0→80:20). The purified product was concentrated under reduced pressure to thereby obtain 0.41g (yield: 86%) of N-(2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)-N-methyl-benzamide as a colorless oil.

^{1}H-NMR ($CDCl_3$) δppm:

0.84 (s, 3H), 1.15 (t, J=7.1 Hz, 3H), 1.52 (s, 3H), 1.86-1.98 (m, 2H), 2.72 (br, 4H), 2.93 (br, 3H), 3.36 (s, 3H), 3.40-3.69 (m, 5H), 3.98 (br, 2H), 4.13-4.23 (m, 1H), 6.66 (d, J=2.8 Hz, 1H), 6.70 (dd, J=2.8

and 9.0 Hz, 1H), 7.15 (d, J=9.0 Hz, 1H), 7.17-7.27 (m, 2H), 7.30-7.39 (m, 5H), 8.47-8.50 (m, 2H).

Example 488

Synthesis of N-(2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)-N-methylbenzamide dihydrochloride

Using an appropriate starting material and following the procedure of Example 6, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (s, 3H), 1.01 (t, J=7.0 Hz, 3H), 1.33 (s, 3H), 2.38 (br, 2H), 2.97 (s, 3H), 3.32 (br, 5H), 3.40-3.49 (m, 2H), 3.61-3.70 (m, 1H), 3.97 (br, 2H), 4.01-4.10 (m, 1H), 4.15 (br, 2H), 4.87 (br, 2H), 6.90-6.95 (m, 2H), 7.40-7.49 (m, 6H), 8.50 (br, 2H), 9.05 (br, 2H).

Example 489

Synthesis of N-(2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)-3-methoxy-N-methylbenzamide

Using an appropriate starting material and following the procedure of Example 487, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.84 (s, 3H), 1.13 (t, J=7.1 Hz, 3H), 1.52 (s, 3H), 1.92 (br, 2H), 2.71 (br, 4H), 2.93 (br, 3H), 3.36 (s, 3H), 3.40-3.80 (m, 5H), 3.79 (s, 3H), 3.99 (br, 2H), 4.08-4.25 (m, 1H), 6.67 (d, J=2.8 Hz, 1H), 6.72 (dd, J=2.8 and 9.0 Hz, 1H), 6.85-6.94 (m, 3H), 7.16 (d, J=9.0 Hz, 1H), 7.12-7.30 (m, 3H), 8.47-8.50 (m, 2H).

Example 490

Synthesis of N-(2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)-3-methoxy-N-methylbenzamide dihydrochloride

Using an appropriate starting material and following the procedure of Example 6, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (br, 3H), 1.00 (br, 3H), 1.32 (s, 3H), 2.33 (br, 2H), 2.94 (s, 3H), 3.30 (br, 7H), 3.61-3.70 (m, 1H), 3.77 (s, 3H), 4.01-4.15 (m,

5H), 4.71 (br, 2H), 6.91 (br, 2H), 7.02 (br, 3H), 7.32-7.41 (m, 2H), 8.17 (br, 2H), 8.89 (br, 2H).

Example 491

Synthesis of N-(2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)-4-methoxy-N-methylbenzamide

Using an appropriate starting material and following the procedure of Example 487, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.84 (s, 3H), 1.13 (t, J=7.1 Hz, 3H), 1.51 (s, 3H), 1.84-1.97 (m, 2H), 2.60-2.78 (m, 4H), 2.95 (s, 3H), 3.37 (s, 3H), 3.50-3.75 (m, 5H), 3.82 (s, 3H), 4.00 (t, J=6.2 Hz, 2H), 4.08-4.21 (m, 1H), 6.67 (d, J=2.8 Hz, 1H), 6.86 (dd, J=2.8 and 9.0 Hz, 1H), 6.85-6.88 (m, 2H), 7.16 (d, J=9.0 Hz, 1H), 7.17-7.21 (m, 2H), 7.32-7.33 (m, 2H), 8.47-8.50 (m, 2H).

Example 492

Synthesis of N-(2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)-4-methoxy-N-methylbenzamide dihydrochloride

Using an appropriate starting material and following the procedure of Example 6, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (br, 3H), 1.00 (br, 3H), 1.32 (s, 3H), 2.32 (br, 2H), 2.99 (s, 3H), 3.30 (br, 5H), 3.66 (br, 2H), 3.78 (s, 3H), 3.88 (br, 3H), 4.10 (br, 3H), 4.64 (br, 2H), 6.87-6.97 (m, 4H), 7.38-7.45 (m, 3H), 8.12 (br, 2H), 8.95 (br, 2H).

Example 493

Synthesis of N-(2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)-2-fluoro-N-methylbenzamide

Using an appropriate starting material and following the procedure of Example 487, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.84 (s, 3H), 1.13 (t, J=7.1 Hz, 3H), 1.51 (s, 3H), 1.95-2.04 (m, 2H),

2.43-2.59 (m, 2H), 2.81-2.95 (m, 2H), 2.83 (s, 3H), 3.35 (s, 3H), 3.62-3.79 (m, 5H), 4.02-4.21 (m, 3H), 6.61-6.79 (m, 3H), 7.00-7.39 (m, 6H), 8.46-8.49 (m, 2H).

Example 494

Synthesis of N-(2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)-2-fluoro-N-methylbenzamide

Using an appropriate starting material and following the procedure of Example 6, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (br, 3H), 1.00 (br, 3H), 1.32 (s, 3H), 2.32 (br, 2H), 2.88 (s, 3H), 3.30 (br, 5H), 3.68 (br, 3H), 4.12 (br, 5H), 4.72 (br, 2H), 6.89-6.93 (m, 2H), 7.29 (br, 2H), 7.38-7.42 (m, 1H), 7.51 (br, 2H), 8.29 (br, 2H), 8.96 (br, 2H).

Example 495

Synthesis of N-(2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)-2,N-dimethylbenzamide

Using an appropriate starting material and following the procedure of Example 487, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.84 (s, 3H), 1.13 (t, J=7.1 Hz, 3H), 1.49 (s, 3H), 1.95-2.04 (m, 2H), 2.26 (s, 3H), 2.43-2.59 (m, 2H), 2.73 (s, 3H), 2.72-2.81 (m, 2H), 3.35 (s, 3H), 3.62-3.79 (m, 5H), 4.02-4.27 (m, 3H), 6.60-6.79 (m, 2H), 7.00-7.35 (m, 7H), 8.46-8.52 (m, 2H).

Example 496

Synthesis of N-(2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)-2,N-dimethylbenzamide dihydrochloride

Using an appropriate starting material and following the procedure of Example 6, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (s, 3H), 1.00 (br, 3H), 1.32 (s, 3H), 2.18 (s, 3H), 2.33 (br, 2H), 2.78 (s, 3H), 3.30 (br, 5H), 3.60 - 3.75 (m, 3H), 4.04-4.08 (m,

3H), 4.13(br, 2H), 4.71 (br, 2H), 6.87-6.93 (m, 2H), 7.15-7.31 (m, 4H), 7.40-7.42 (m, 1H), 8.23 (br, 2H), 8.92 (br, 2H).

Example 497

Synthesis of N-(2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)-4,N-dimethylbenzamide

Using an appropriate starting material and following the procedure of Example 487, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.84 (s, 3H), 1.13 (t, J=7.1 Hz, 3H), 1.51 (s, 3H), 1.84-1.98 (m, 2H), 2.35 (s, 3H), 2.60-2.78 (m, 4H), 2.93 (s, 3H), 3.36 (s, 3H), 3.53-3.78 (m, 5H), 4.00 (br, 2H), 4.07-4.22 (m, 1H), 6.67 (d, J=2.8 Hz, 1H), 6.70 (dd, J=2.8 and 9.0 Hz, 1H), 7.10-7.17 (m, 3H), 7.20-7.27 (m, 4H), 8.47-8.50 (m, 2H).

Example 498

Synthesis of N-(2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)-4,N-dimethylbenzamide dihydrochloride

Using an appropriate starting material and following the procedure of Example 6, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

0.74 (s, 3H), 1.00 (br, 3H), 1.32 (s, 3H), 2.32 (br, 5H), 2.95 (s, 3H), 3.30 (br, 5H), 3.60 -3.75 (m, 3H), 3.80 - 4.15 (m, 5H), 4.68 (br, 2H), 6.91(br, 2H), 7.23 (br, 2H), 7.40-7.42 (m, 3H), 8.23 (br, 2H), 8.91 (br, 2H).

Example 499

Synthesis of N-(2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)-2-(2-methoxyphenyl)-N-methyl acetamide

Using an appropriate starting material and following the procedure of Example 487, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.84 (s, 3H), 1.13 (t, J=7.1 Hz, 3H), 1.52 (s, 3H), 1.84-1.99 (m, 2H),

2.60-2.73 (m, 4H), 3.04 (s, 3H), 3.37 (s, 3H), 3.41-3.53 (m, 2H), 3.65 (br, 2H), 3.61-3.70 (m, 1H), 3.83 (s, 3H), 3.93-4.00 (m, 2H), 4.06-4.21 (m, 1H), 4.68 (s, 2H), 6.63-6.73 (m, 2H), 6.80-6.97(m, 4H), 7.10-7.24 (m, 3H), 8.47-8.49 (m, 2H).

Example 500

Synthesis of N-(2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)-2-(2-methoxyphenyl)-N-methyl acetamide dihydrochloride

Using an appropriate starting material and following the procedure of Example 6, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

0.74 (s, 3H), 1.01 (t, J=7.0 Hz, 3H), 1.31 (s, 3H), 2.25 (br, 2H), 3.04 (s, 3H), 3.30 (br, 5H), 3.40-3.49 (m, 2H), 3.75 (s, 3H), 3.75 (br, 1H), 3.94-4.08 (m, 5H), 4.67 (br, 2H), 4.83 (s, 2H), 6.79-6.99 (m, 6H), 3.78 (d, J=9.0 Hz, 1H), 8.05 (br, 2H), 8.83 (br, 2H).

Example 501

Synthesis of N-(2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)-2-(3-methoxyphenyl)-N-methylacetamide

Using an appropriate starting material and following the procedure of Example 487, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.84 (s, 3H), 1.13 (t, J=7.1 Hz, 3H), 1.52 (s, 3H), 1.82-1.93 (m, 2H), 2.60-2.73 (m, 4H), 2.91 (s, 3H), 3.37 (s, 3H), 3.41-3.54 (m, 2H), 3.59-3.70 (m, 5H), 3.76 (s, 3H), 3.97 (t, J=6.1 Hz, 2H), 4.06-4.21 (m, 1H), 6.65-6.81 (m, 5H), 7.13-7.25 (m, 4H), 8.44-8.50 (m, 2H).

Example 502

Synthesis of N-(2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)-2-(3-methoxyphenyl)-N-methyl acetamide dihydrochloride

Using an appropriate starting material and following the procedure of Example 6, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

0.74 (s, 3H), 1.00 (t, J=7.0 Hz, 3H), 1.32 (s, 3H), 2.24 (br, 2H), 3.03 (s, 3H), 3.23 (br, 2H), 3.30 (s, 3H), 3.63-3.72 (m, 6H), 4.01-4.08 (m, 5H), 4.62 (br, 4H), 6.78 - 6.91 (m, 5H), 7.20 (t, J = 7.8 Hz, 1H), 7.39 (d, J=8.9 Hz, 1H), 8.22 (br, 2H), 8.90 (br, 2H).

Example 503

Synthesis of N-(2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)-2-(4-methoxyphenyl)-N-methyl acetamide

Using an appropriate starting material and following the procedure of Example 487, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.84 (s, 3H), 1.13 (t, J=7.1 Hz, 3H), 1.52 (s, 3H), 1.82-1.93 (m, 2H), 2.57-2.73 (m, 4H), 2.91 (s, 3H), 3.37 (s, 3H), 3.43-3.54 (m, 2H), 3.59 (s, 2H), 3.60-3.75 (m, 3H), 3.76 (s, 3H), 3.97 (t, J=6.1 Hz, 2H), 4.06-4.21 (m, 1H), 6.65 (br, 1H), 6.73 (dd, J=8.9 and 2.8 Hz, 1H), 6.83 (d, J=8.4 Hz, 2H), 7.05-7.21 (m, 5H), 8.44-8.50 (m, 2H).

Example 504

Synthesis of N-(2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)-2-(4-methoxyphenyl)-N-methyl acetamide dihydrochloride

Using an appropriate starting material and following the procedure of Example 6, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

0.74 (s, 3H), 1.00 (t, J = 7.0 Hz, 3H), 1.31 (s, 3H), 2.27 (br, 2H), 3.04 (s, 3H), 3.23 (br, 2H), 3.30 (s, 3H), 3.63 - 3.72 (m, 6H), 4.01 - 4.08 (m, 5H), 4.62 (br, 4H), 6.78 - 6.89 (m, 4H), 7.12 - 7.14 (m, 2H), 7.39 (d, J = 9.0 Hz, 1H), 7.96 (br, 2H), 8.81 (br, 2H).

Example 505

Synthesis of 2-benzo[1,3]dioxol-5-yl-N-(2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)-N-methyl acetamide

Using an appropriate starting material and following the procedure of Example 487, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.84 (s, 3H), 1.13 (t, J=7.1 Hz, 3H), 1.52 (s, 3H), 1.82-1.93 (m, 2H), 2.57-2.73 (m, 4H), 2.92 (s, 3H), 3.37 (s, 3H), 3.41-3.50 (m, 2H), 3.57 (s, 2H), 3.59-3.73 (m, 3H), 3.98 (t, J=6.1 Hz, 2H), 4.07-4.20 (m, 1H), 5.89 (s, 2H), 6.64-6.77 (m, 5H), 7.07-7.25 (m, 3H), 8.44-8.49 (m, 2H).

Example 506

Synthesis of 2-benzo[1,3]dioxol-5-yl-N-(2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)-N-methylacetamide dihydrochloride

Using an appropriate starting material and following the procedure of Example 6, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

0.74 (s, 3H), 1.00 (t, J = 7.0 Hz, 3H), 1.32 (s, 3H), 2.25 (br, 2H), 3.03 (s, 3H), 3.23 (br, 2H), 3.30 (s, 3H), 3.63 - 3.71 (m, 3H), 4.01 - 4.08 (m, 5H), 4.58 (br, 2H), 4.69 (br, 2H), 5.97 (s, 2H), 6.67 - 6.69 (m, 1H), 6.80 - 6.83 (m, 2H), 6.89 - 6.91 (m, 2H), 7.39 (d, J = 8.9 Hz, 1H), 8.14 (br, 2H), 8.87 (br, 2H).

Example 507

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{(3-methylpyridin-4-ylmethyl)-[2-(7-oxo-7H-furo[2,3-c]pyridin-6-yl)ethyl]-amino}-propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 7 and Example 6, the object compound was synthesized.

White powder

^{1}H-NMR (DMSO-D_6) δppm:

0.75 (3H, s), 1.02 (3H, t, J= 7.1 Hz), 1.32 (3H, s), 1.90-2.01 (2H, m), 2.35-2.45 (3H, m), 2.61-3.95 (8H, m), 3.96-4.32 (7H, m), 6.49-6.61 (1H, m), 6.81-6.89 (3H, m), 7.39 (1H, d, J= 9.0 Hz), 7.41-7.51 (1H, m), 7.52-8.02 (1H, m), 8.11 (1H, s), 8.41-8.49 (1H, m), 8.65 (1H, s)

Example 508

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{(2-methylpyridin-4-ylmethyl)-[2-(7-oxo-7H-furo[2,3-c]pyridin-6-yl)ethyl]-amino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 7 and Example 6, the object compound was synthesized.

White powder

^{1}H-NMR (DMSO-D_6) δppm:

0.75 (3H, s), 1.01 (3H, t, J= 7.1 Hz), 1.32 (3H, s), 1.82-2.11 (2H, m), 2.61-3.81 (8H, m), 3.89-4.41 (10H, m), 6.54-6.59 (1H, m), 6.78-6.91 (3H, m), 7.39 (1H, d, J= 9.0 Hz), 7.48-7.53 (1H, m), 7.52-7.99 (2H, m), 8.12 (1H, s), 8.52-8.68 (1H, m)

Example 509

Synthesis of 1-ethyl-7-(3-{(3-fluoropyridin-4-ylmethyl)-[2-(7-oxo-7H-furo[2,3-c]pyridin-6-yl)ethyl]amino}propoxy)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 7 and Example 6, the object compound was synthesized.

White powder

^{1}H-NMR (DMSO-D_6) δppm:

0.75 (3H, s), 1.01 (3H, t, J= 7.1 Hz), 1.32 (3H, s), 1.99-2.27 (2H, m), 3.31 (3H, s), 3.33-3.81 (5H, m), 3.96-4.20 (3H, m), 4.25-4.45 (4H, m), 6.60-6.64 (1H, m), 6.80-6.92 (3H, m), 7.39 (1H, d, J= 9.0 Hz), 7.52-7.56 (1H, m), 7.57-8.12 (1H, m), 8.14 (1H, s), 8.15-8.57 (1H, m), 8.60-8.66 (1H, m)

Example 510

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{(2-methylpyridin-3-ylmethyl)-[2-(7-oxo-7H-furo[2,3-c]pyridin-6-yl)ethyl]-amino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 7 and Example 6, the object compound was

synthesized.

White powder

^{1}H-NMR (DMSO-D_6) δppm:

0.75 (3H, s), 1.01 (3H, t, J= 7.1 Hz), 1.32 (3H, s), 1.90-2.17 (2H, m), 2.52-3.00 (4H, m), 3.25-3.94 (9H, m), 4.01-4.35 (5H, m), 6.52-6.60 (1H, m), 6.82-6.91 (3H, m), 6.93-7.38 (1H, m), 7.40 (1H, d, J= 9.0 Hz), 7.47-7.94 (2H, m), 8.12 (1H, s), 8.60-8.68 (1H, m)

Example 511

Synthesis of 1-ethyl-3,3,5-trimethyl-7-{3-[[2-(7-oxo-7H-furo [2,3-c]pyridin-6-yl)ethyl]-(4-trifluoromethylpyridin-3-ylmethyl)amino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

White powder

Melting Point 137 to 138°C

Example 512

Synthesis of 1-ethyl-3,3,5-trimethyl-7-{3-[[2-(7-oxo-7H-furo [2,3-c]pyridin-6-yl)ethyl]-(2-pyrrolidin-1-ylpyridin-4-ylmethyl)amino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione trihydrochloride

Using an appropriate starting material and following the procedure of Example 7 and Example 6, the object compound was synthesized.

White powder

^{1}H-NMR (DMSO-D_6) δppm:

0.75 (3H, s), 1.01 (3H, t, J= 7.1 Hz), 1.32 (3H, s), 1.91-2.03 (5H, m), 3.27-3.76 (13H, m), 3.99-4.61 (7H, m), 6.58-6.62 (1H, m), 6.91-7.24 (4H, m), 7.40 (1H, d, J= 9.1 Hz), 7.43-8.09 (3H, m), 8.13 (1H, s)

Example 513

Synthesis of 2-({[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]-[2-(7-oxo-7H-furo[2,3-c]pyridin-6-yl)ethyl]amino}methyl)-benzonitrile phosphate

Using an appropriate starting material and following the

procedure of Example 7 and Example 458, the object compound was synthesized.

^{1}H-NMR (DMSO-D_6) δppm:

0.75 (3H, s), 1.02 (3H, t, J= 7.0 Hz), 1.32 (3H, s), 1.78-1.90 (2H, m), 2.65 (2H, t, J= 6.5 Hz), 2.77 (2H, t, J= 5.7 Hz), 3.30 (3H, s), 3.34-4.13 (8H, m), 6.46 (1H, d, J= 6.7 Hz), 6.74 (1H, dd, J= 2.7 and 9.0 Hz), 6.81 (1H, d, J= 2.7 Hz), 6.85 (1H, d, J= 2.0 Hz), 7.21-7.32 (3H, m), 7.35-7.40 (2H, m), 7.63 (1H, m), 8.07 (1H, d, J= 2.0 Hz)

Example 514

Synthesis of 7-(3-{(3,5-dihydroxybenzyl)-[2-(7-oxo-7H-furo [2,3-c]pyridin-6-yl)ethyl]amino}propoxy)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione hydrochloride

Using an appropriate starting material and following the procedure of Example 7 and Example 6, the object compound was synthesized.

White powder

^{1}H-NMR (DMSO-D_6) δppm:

0.75 (3H, s), 1.00 (3H, t, J= 7.0 Hz), 1.32 (3H, s), 2.20-2.35 (2H, m), 3.08-3.62 (7H, m), 3.63-3.72 (1H, m), 3.99-4.17(3H, m), 4.18-4.28 (1H, m), 4.30-4.72 (3H, m), 6.34 (1H, s), 6.45 (2H, s), 6.70 (1H, d, J= 7.0 Hz), 6.86-6.96 (3H, m), 7.39 (1H, d, J= 8.9 Hz), 7.56 (1H, d, J= 7.1 Hz), 8.16 (1H, s), 9.47 (2H, br s)

Example 515

Synthesis of 1-ethyl-7-(3-{(5-fluoropyridin-3-ylmethyl)-[2-(7-oxo-7H-furo[2,3-c]pyridin-6-yl)ethyl]amino}propoxy)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione hydrochloride

Using an appropriate starting material and following the procedure of Example 7 and Example 6, the object compound was synthesized.

White powder

^{1}H-NMR (DMSO-D_6) δppm:

0.75 (3H, s), 1.00 (3H, t, J= 7.1 Hz), 1.32 (3H, s), 2.17-2.32 (2H, m), 3.22-3.73 (8H, m), 3.99-4.10 (3H, m), 4.44-4.66(4H, m), 6.68 (1H,

d, J= 7.0 Hz), 6.85-6.93 (3H, m), 7.41 (1H, d, J= 9.0 Hz), 7.58 (1H, d, J= 7.0 Hz), 8.05-8.21 (2H, m), 8.64-8.71 (2H, m)

Example 516

Synthesis of 1-ethyl-7-(2-hydroxy-3-{[2-(1-oxo-1H-isoquinolin-2-yl)ethyl]pyridin-4-ylmethylamino}propoxy)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

Colorless solid

Melting Point 67 to 74°C

Example 517

Synthesis of 1-ethyl-7-(2-hydroxy-3-{[2-(1-oxo-1H-isoquinolin-2-yl)ethyl]pyridin-3-ylmethylamino}propoxy)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

colorless solid

^{1}H-NMR (DMSO-D_6) δppm:

0.74 (3H, s), 1.03 (3H, t, J= 7.0 Hz), 1.32 (3H, s), 2.54-3.08 (3H, m), 3.23-3.30 (3H, m), 3.49-3.92 (6H, m), 3.92-4.27 (3H, m), 4.84-4.99 (1H, m), 6.45-6.56 (1H, m), 6.56-6.79 (2H, m), 6.88-7.06 (1H, m), 7.22-7.38 (1H, m), 7.38-7.73 (5H, m), 8.16 (1H, d, J= 8.1 Hz), 8.23-8.35 (1H, m), 8.42 (1H, s).

Example 518

Synthesis of N-(2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)-3-fluoro-N-methylbenzamide

Using an appropriate starting material and following the procedure of Example 487, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.84 (s, 3H), 1.13 (t, J = 7.1 Hz, 3H), 1.52 (s, 3H), 2.02 (br, 2H), 2.73 (br, 4H), 2.92 (s, 3H), 3.36 (s, 3H), 3.41 - 3.73 (m, 5H), 3.99 (br, 2H), 4.07 - 4.20 (m, 1H), 6.67 (d, J = 2.8 Hz, 1H), 6.72 (dd, J = 2.8 and 9.0 Hz, 1H), 7.03 - 7.40 (m, 7H), 8.48 - 8.51 (m, 2H).

Example 519

Synthesis of N-(2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)-3-fluoro-N-methylbenzamide dihydrochloride

Using an appropriate starting material and following the procedure of Example 6, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (s, 3H), 1.00 (t, J = 7.0 Hz, 3H), 1.32 (s, 3H), 2.33 (br, 2H), 2.93 (s, 3H), 3.30 (br, 5H), 3.61 - 3.71 (m, 3H), 4.01 - 4.11 (m, 5H), 4.66 (br, 2H), 6.88 - 6.91 (m, 2H), 7.28 - 7.33 (m, 2H), 7.39 - 7.40 (m, 2H), 7.46 - 7.52 (m, 1H), 8.14 (br, 2H), 8.91 (br, 2H).

Example 520

Synthesis of N-(2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)-4-fluoro-N-methylbenzamide

Using an appropriate starting material and following the procedure of Example 487, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.84 (s, 3H), 1.13 (t, J=7.1 Hz, 3H), 1.52 (s, 3H), 1.95 (br, 2H), 2.73 (br, 4H), 2.94 (s, 3H), 3.37 (s, 3H), 3.42-3.77 (m, 5H), 3.98 (br, 2H), 4.07-4.20 (m, 1H), 6.67 (d, J=2.8 Hz, 1H), 6.72 (dd, J=2.8 and 9.0 Hz, 1H), 7.05 (t, J=8.6 Hz, 2H), 7.16 (d, J=9.0 Hz, 1H), 7.26 (br, 2H), 7.32-7.38 (m, 2H), 8.48-8.51 (m, 2H).

Example 521

Synthesis of N-(2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)-4-fluoro-N-methylbenzamide dihydrochloride

Using an appropriate starting material and following the procedure of Example 6, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

0.74 (s, 3H), 1.00 (t, J=7.0 Hz, 3H), 1.32 (s, 3H), 2.27 (br, 2H), 2.94 (s, 3H), 3.30 (br, 5H), 3.61-3.91 (m, 5H), 4.03-4.10 (m, 3H), 4.62 (br, 2H), 6.86-6.90 (m, 2H), 7.24-7.26 (m, 2H), 7.39 (d, J=8.9 Hz, 1H), 7.56 (br, 2H), 8.00 (br, 2H), 8.82 (br, 2H).

Example 522

Synthesis of N-(2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)-3,N-dimethylbenzamide

Using an appropriate starting material and following the procedure of Example 487, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.84 (s, 3H), 1.13 (t, J=7.1 Hz, 3H), 1.52 (s, 3H), 1.97 (br, 2H), 2.34 (s, 3H), 2.78 (br, 4H), 2.94 (s, 3H), 3.36 (s, 3H), 3.43-3.81 (m, 5H), 4.04 (br, 2H), 4.07-4.20 (m, 1H), 6.67 (d, J=2.8 Hz, 1H), 6.73 (dd, J=2.8 and 9.0 Hz, 1H), 7.09-7.26 (m, 5H), 7.32 (br, 2H), 8.48-8.51 (m, 2H).

Example 523

Synthesis of N-(2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)-3,N-dimethylbenzamide dihydrochloride

Using an appropriate starting material and following the procedure of Example 6, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (s, 3H), 1.00 (t, J=7.0 Hz, 3H), 1.32 (s, 3H), 2.32 (br, 5H), 2.94 (s, 3H), 3.30 (br, 5H), 3.61-3.91 (m, 5H), 4.02-4.11 (m, 3H), 4.62 (br, 2H), 6.89-6.90 (m, 2H), 7.20-7.31 (m, 4H), 7.39 (d, J=8.9 Hz, 1H), 8.05 (br, 2H), 8.83 (br, 2H).

Example 524

Synthesis of 2-dimethylamino-N-(2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)-N-methylbenzamide

Using an appropriate starting material and following the procedure of Example 487, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.84 (s, 3H), 1.13 (t, J=7.1 Hz, 3H), 1.52 (s, 3H), 1.99 (br, 2H), 2.76 (s, 6H), 2.74-2.89 (m, 4H), 3.06 (s, 3H), 3.36 (s, 3H), 3.53-3.83 (m, 5H), 3.95-4.21 (m, 3H), 6.67-6.75 (m, 2H), 6.85-6.97 (m, 2H),

7.10-7.24 (m, 3H), 7.40-7.42 (m, 2H), 8.53-8.55 (m, 2H).

Example 525

Synthesis of 2-dimethylamino-N-(2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)-N-methylbenzamide trihydrochloride

Using an appropriate starting material and following the procedure of Example 6, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

0.74 (s, 3H), 1.00 (t, J = 7.0 Hz, 3H), 1.32 (s, 3H), 2.32 (br, 2H), 2.84 (s, 6H), 2.94 (s, 3H), 3.01 (br, 7H), 3.64 - 3.70 (m, 1H), 3.93 (br, 2H), 4.03-4.14 (m, 3H), 4.69 (br, 2H), 6.85 - 6.93 (m, 2H), 7.12 (br, 1H), 7.23 (br, 2H), 7.39 - 7.42 (m, 2H), 8.22 (br, 2H), 8.92 (br, 2H).

Example 526

Synthesis of 3-dimethylamino-N-(2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)-N-methylbenzamide trihydrochloride

Using an appropriate starting material and following the procedure of Example 487, the object compound was synthesized.

White powder

^{1}H-NMR (DMSO-d6) δppm:

0.75 (s, 3H), 1.00 (t, J = 7.0 Hz, 3H), 1.32 (s, 3H), 2.34 (br, 2H), 2.96 (s, 3H), 3.05 (s, 6H), 3.31 (s, 3H), 3.43 (br, 2H), 3.58-3.69 (m, 1H), 3.94 (br, 2H), 4.01-4.10 (m, 1H), 4.13 (br, 2H), 4.68 (br, 2H), 4.81 (br, 2H), 6.88-6.93 (m, 2H), 7.18 (br, 1H), 7.40 (d, J = 9.0 Hz, 1H), 7.47 (br, 3H), 8.47 (br, 2H), 9.03 (br, 2H).

Example 527

Synthesis of 4-dimethylamino-N-(2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)-N-methylbenzamide trihydrochloride

Using an appropriate starting material and following the procedure of Example 487, the object compound was synthesized.

White solid

^{1}H-NMR (DMSO-d6) δppm:

0.75 (s, 3H), 1.00 (t, J = 7.0 Hz, 3H), 1.32 (s, 3H), 2.31 (br, 2H), 3.00 (br, 9H), 3.22-3.48 (m, 4H), 3.31 (s, 3H), 3.61-3.70 (m, 1H), 3.89 (br, 2H), 3.99-4.14 (m, 3H), 4.80 (br, 2H), 6.87-6.93 (m, 2H), 7.12 (br, 2H), 7.40 (d, J = 9.0 Hz, 1H), 7.48 (br, 2H), 8.46 (br, 2H), 9.03 (br, 2H).

Example 528

Synthesis of furan-2-carboxylic acid (2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)methylamide

Using an appropriate starting material and following the procedure of Example 487, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.86 (s, 3H), 1.15 (t, J=7.1 Hz, 3H), 1.54 (s, 3H), 1.88-1.96 (m, 2H), 2.65-2.80 (m, 4H), 3.14 (s, 3H), 3.39 (s, 3H), 3.61-3.75 (m, 5H), 4.01 (t, J=6.2 Hz, 2H), 4.04-4.22 (m, 1H), 6.45-6.48 (m, 1H), 6.67-6.69 (m, 1H), 6.73 (dd, J=2.8 and 9.0 Hz, 1H), 6.99 (d, J=3.5 Hz, 1H), 7.18 (d, J=9.0 Hz, 1H), 7.24-7.26 (m, 2H), 7.60 (br, 1H), 8.49-8.50 (m, 2H).

Example 529

Synthesis of furan-2-carboxylic acid (2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)methylamide dihydrochloride

Using an appropriate starting material and following the procedure of Example 6, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (s, 3H), 1.00 (t, J = 7.0 Hz, 3H), 1.32 (s, 3H), 2.29 (br, 2H), 3.10-3.40 (m, 2H), 3.32 (s, 3H), 3.59-3.70 (m, 1H), 3.80-4.11 (m, 7H), 4.70 (br, 2H), 6.63 (d, J = 1.6 Hz, 1H), 6.88 (dd, J = 2.7, 9.0 Hz, 1H), 6.92 (d, J = 2.7 Hz, 1H), 6.96 (d, J = 3.3 Hz, 1H), 7.40 (d, J = 9.0 Hz, 1H), 7.86 (br, 1H), 8.38 (br, 2H), 8.94 (br, 2H).

Example 530

Synthesis of thiophene-2-carboxylic acid (2-{[3-(1-ethyl-

3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)methyl amide

Using an appropriate starting material and following the procedure of Example 487, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.86 (s, 3H), 1.15 (t, J=7.1 Hz, 3H), 1.54 (s, 3H), 1.86-1.96 (m, 2H), 2.63-2.80 (m, 4H), 3.14 (s, 3H), 3.38 (s, 3H), 3.62-3.77 (m, 5H), 4.01 (t, J=6.2 Hz, 2H), 4.03-4.20 (m, 1H), 6.67 (d, J=2.8 Hz, 1H), 6.73 (dd, J=2.8 and 9.0 Hz, 1H), 7.01-7.03 (m, 1H), 7.16 (d, J=9.0 Hz, 1H), 7.24-7.26 (m, 2H), 7.30-7.32 (m, 1H), 7.59-7.61 (m, 1H), 8.48-8.50 (m, 2H).

Example 531

Synthesis of thiophene-2-carboxylic acid (2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)methyl amide dihydrochloride

Using an appropriate starting material and following the procedure of Example 6, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (s, 3H), 1.00 (t, J = 7.0 Hz, 3H), 1.32 (s, 3H), 2.26 (br, 3H), 3.23 (br, 2H), 3.31 (s, 3H), 3.64 - 3.70 (m, 3H), 3.80 - 3.93 (m, 2H), 4.02 - 4.08 (m, 3H), 4.59 (br, 2H), 6.85 - 6.89 (m, 2H), 7.14 (br, 1H), 7.39 (d, J = 8.9 Hz, 1H), 7.58 (br, 1H), 7.79 (br, 1H), 7.95 (br, 2H), 8.80 (br, 2H).

Example 532

Synthesis of furan-3-carboxylic acid (2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)methyl amide

Using an appropriate starting material and following the procedure of Example 487, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.84 (s, 3H), 1.13 (t, J=7.1 Hz, 3H), 1.52 (s, 3H), 1.87-1.98 (m, 2H), 2.63-2.80 (m, 4H), 3.05 (s, 3H), 3.37 (s, 3H), 3.53-3.70 (m, 5H), 3.99

(t, J=6.2 Hz, 2H), 4.01-4.21 (m, 1H), 6.56 (s, 1H), 6.66 (d, J=2.8 Hz, 1H), 6.72 (dd, J=2.8 and 9.0 Hz, 1H), 7.16 (d, J=9.0 Hz, 1H), 7.24-7.26 (m, 2H), 7.39 (br, 1H), 7.66 (br, 1H), 8.47-8.50 (m, 2H).

Example 533

Synthesis of furan-3-carboxylic acid (2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)methyl amide dihydrochloride

Using an appropriate starting material and following the procedure of Example 6, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (s, 3H), 1.00 (t, J=7.0 Hz, 3H), 1.32 (s, 3H), 2.26 (br, 2H), 3.14 (br, 3H), 3.31 (s, 5H), 3.62-3.70 (m, 3H), 3.87 (br, 2H), 4.03-4.09 (m, 3H), 4.61 (br, 2H), 6.74 (br, 1H), 6.85-6.90 (m, 2H), 7.39 (d, J=8.9 Hz, 1H), 7.74 (s, 1H), 8.09 (br, 2H), 8.14 (br, 1H), 8.85 (br, 2H).

Example 534

Synthesis of thiophene-3-carboxylic acid (2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)methyl amide

Using an appropriate starting material and following the procedure of Example 487, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.84 (s, 3H), 1.13 (t, J=7.1 Hz, 3H), 1.52 (s, 3H), 1.88-1.97 (m, 2H), 2.62-2.78 (m, 4H), 3.00 (s, 3H), 3.37 (s, 3H), 3.51-3.73 (m, 5H), 3.99 (t, J=6.2 Hz, 2H), 4.01-4.21 (m, 1H), 6.66 (d, J=2.8 Hz, 1H), 6.71 (dd, J=2.8 and 9.0 Hz, 1H), 7.13-7.26 (m, 4H), 7.26-7.29 (m, 1H), 7.43-7.44 (m, 1H), 8.48-8.50 (m, 2H).

Example 535

Synthesis of thiophene-3-carboxylic acid (2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)methyl amide dihydrochloride

Using an appropriate starting material and following the

procedure of Example 6, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (s, 3H), 1.00 (t, J=7.0 Hz, 3H), 1.32 (s, 3H), 2.28 (br, 2H), 3.06 (br, 5H), 3.31 (s, 3H), 3.61-3.70 (m, 3H), 3.87 (br, 2H), 4.03-4.09 (m, 3H), 4.61 (br, 2H), 6.86-6.90 (m, 2H), 7.28 (br, 1H), 7.39 (d, J=8.9 Hz, 1H), 7.58-7.60 (m, 1H), 7.91 (br, 1H), 8.06 (br, 2H), 8.84 (br, 2H).

Example 536

Synthesis of cyclohexanecarboxylic acid (2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)methyl amide

Using an appropriate starting material and following the procedure of Example 487, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.83 (s, 3H), 1.13 (t, J=7.1 Hz, 3H), 1.52 (s, 3H), 1.50-1.81 (m, 10H), 1.88-2.00 (m, 2H), 2.39 (br, 1H), 2.60-2.78 (m, 4H), 2.93 (s, 3H), 3.37 (s, 3H), 3.43 (br, 2H), 3.61-3.74 (m, 3H), 3.91-4.21 (m, 3H), 6.67 (d, J=2.8 Hz, 1H), 6.73 (dd, J=2.8 and 9.0 Hz, 1H), 7.15 (d, J=9.0 Hz, 1H), 7.24-7.26 (m, 2H), 8.48 (br, 2H).

Example 537

Synthesis of cyclohexanecarboxylic acid (2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)methyl amide dihydrochloride

Using an appropriate starting material and following the procedure of Example 6, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (s, 3H), 1.00 (t, J=7.0 Hz, 3H), 1.08-1.28 (m, 6H), 1.32 (s, 3H), 1.66 (br, 4H), 2.26 (br, 2H), 2.55 (br, 1H), 3.03 (s, 3H), 3.21 (br, 2H), 3.32 (s, 3H), 3.64-3.71 (m, 3H), 4.02-4.10 (m, 5H), 4.59 (br, 2H), 6.87-6.92 (m, 2H), 7.40 (d, J=8.9 Hz, 1H), 8.09 (br, 2H), 8.86 (br, 2H).

Example 538

Synthesis of benzo[1,3]dioxole-5-carboxylic acid

(2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)methylamide

Using an appropriate starting material and following the procedure of Example 487, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.84 (s, 3H), 1.13 (t, J=7.1 Hz, 3H), 1.52 (s, 3H), 1.88-1.94 (m, 2H), 2.62-2.75 (m, 4H), 2.94 (s, 3H), 3.36 (s, 3H), 3.51 (br, 2H), 3.63 (s, 2H), 3.61-3.77 (m, 1H), 3.98 (t, J=6.2 Hz, 2H), 3.95-4.20 (m, 1H), 5.96 (s, 2H), 6.67 (d, J=2.8 Hz, 1H), 6.72-6.79 (m, 2H), 6.83-6.88 (m, 2H), 7.15 (d, J=9.0 Hz, 1H), 7.24-7.26 (m, 2H), 8.47-8.50 (m, 2H).

Example 539

Synthesis of benzo[1,3]dioxole-5-carboxylic acid (2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)methylamide dihydrochloride

Using an appropriate starting material and following the procedure of Example 6, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (s, 3H), 1.00 (t, J=7.0 Hz, 3H), 1.32 (s, 3H), 2.32 (br, 2H), 2.95 (s, 3H), 3.31 (br, 5H), 3.62-3.71 (m, 3H), 4.02-4.09 (m, 5H), 4.71 (br, 2H), 6.06 (s, 2H), 6.86-7.06 (m, 5H), 7.39 (d, J=8.9 Hz, 1H), 8.29 (br, 2H), 8.94 (br, 2H).

Example 540

Synthesis of 1-Ethyl-3,3,5-trimethyl-7-(3-{[2-(2-oxo-2H-pyridin-1-yl)ethyl]pyridin-4-ylmethylamino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

Light brown amorphous

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (s, 3H), 1.01 (t, J = 7.0 Hz, 3H), 1.32 (s, 3H), 2.26 (br, 2H), 3.24 (br, 2H), 3.32 (s, 3H), 3.64-3.73 (m, 1H), 4.01-4.09 (m, 5H), 4.37 (br, 2H), 4.70 (br, 2H), 6.28 (t, J = 6.5 Hz, 1H), 6.41 (d, J = 9.0 Hz, 1H), 6.89 (dd, J = 2.5, 9.0 Hz, 1H), 6.93 (d, J = 2.5 Hz,

1H), 7.41 (d, J = 9.0 Hz, 1H), 7.42-7.47 (m, 1H), 7.78 (d, J = 6.5 Hz, 1H), 8.34 (br, 2H), 8.98 (br, 2H).

Example 541

Synthesis of N-(2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)-2-methoxy-N-methylbenzamide dihydrochloride

Using an appropriate starting material and following the procedure of Example 487, the object compound was synthesized.

White powder

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (s, 3H), 1.01 (t, J = 7.0 Hz, 3H), 1.32 (s, 3H), 2.33 (br, 2H), 2.79 (s, 3H), 3.21-3.44 (m, 2H), 3.30 (s, 3H), 3.53-3.64 (m, 1H), 3.94 (s, 3H), 3.90-4.15 (m, 7H), 4.76 (br, 2H), 6.84-7.14 (m, 4H), 7.22 (d, J = 7.4 Hz, 1H), 7.38-7.44 (m, 2H), 8.36 (br, 2H), 8.99 (br, 2H).

Example 542

Synthesis of N-(2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)-N-methyl-2-trifluoromethyl-benzamide dihydrochloride

Using an appropriate starting material and following the procedure of Example 487, the object compound was synthesized.

Pale yellow powder

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (s, 3H), 1.00 (t, J = 7.0 Hz, 3H), 1.32 (s, 3H), 2.36 (br, 2H), 2.78 (s, 3H), 3.30-3.43 (m, 5H), 3.61-3.70 (m, 1H), 3.85 (br, 2H), 4.00-4.19 (m, 5H), 4.81 (br, 2H), 6.84-6.95 (m, 2H), 7.40 (d, J = 9.0 Hz, 1H), 7.62-7.69 (m, 2H), 7.76 (t, J = 7.7 Hz, 1H), 7.82 (d, J = 7.7 Hz, 1H), 8.44 (br, 2H), 9.01 (br, 2H).

Example 543

Synthesis of N-(2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)-N-methyl-3-trifluoromethyl-benzamide dihydrochloride

Using an appropriate starting material and following the

procedure of Example 487, the object compound was synthesized.

Pale yellow amorphous

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (s, 3H), 1.00 (t, J = 7.0 Hz, 3H), 1.32 (s, 3H), 2.36 (br, 2H), 2.95 (s, 3H), 3.25-3.33 (m, 2H), 3.31 (s, 3H), 3.37-3.45 (m, 2H), 3.61-3.73 (m, 1H), 3.97 (br, 2H), 4.00-4.13 (m, 1H), 4.13 (br, 2H), 4.82 (br, 2H), 6.89-6.94 (m, 2H), 7.40 (d, J = 9.0 Hz, 1H), 7.69 (t, J = 7.6 Hz, 1H), 7.82-7.86 (m, 2H), 7.91 (s, 1H), 8.47 (br, 2H), 9.02 (br, 2H).

Example 544

Synthesis of 2-cyano-N-(2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)-N-methyl-benzamide dihydrochloride

Using an appropriate starting material and following the procedure of Example 487, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (s, 3H), 1.00 (t, J = 7.0 Hz, 3H), 1.32 (s, 3H), 2.31 (br, 2H), 2.89 (s, 3H), 3.16-3.45 (m, 2H), 3.30 (s, 3H), 3.50-3.75 (m, 3H), 3.90-4.15 (m, 5H), 4.71 (br, 2H), 6.82-6.94 (m, 2H), 7.40 (d, J = 9.0 Hz, 1H), 7.62-7.67 (m, 1H), 7.74 (br, 1H), 7.78-7.80 (m, 1H), 7.95 (d, J = 7.7 Hz, 1H), 8.29 (br, 2H), 8.94 (br, 2H).

Example 545

Synthesis of 4-cyano-N-(2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)-N-methyl-benzamide dihydrochloride

Using an appropriate starting material and following the procedure of Example 487, the object compound was synthesized.

White solid

^{1}H-NMR (DMSO-d_6) δppm:

0.74 (s, 3H), 1.00 (t, J = 7.0 Hz, 3H), 1.32 (s, 3H), 2.31 (br, 2H), 2.91 (s, 3H), 3.21-3.40 (m, 4H), 3.30 (s, 3H), 3.50 - 3.75 (m, 1H), 3.93 (br, 2H), 4.00-4.13 (m, 3H), 4.69 (br, 2H), 6.87-6.92 (m, 2H), 7.39 (d, J = 9.0 Hz, 1H), 7.71 (d, J = 7.8 Hz, 2H), 7.92 (d, J = 7.8

Using an appropriate starting material and following the procedure of Example 7 and Example 6, the object compound was synthesized.

White amorphous

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (3H, s), 1.01 (3H, t, J= 7.1 Hz), 1.32 (3H, s), 2.20-2.32 (2H, m), 2.40 (3H, s), 3.31 (3H, s) 3.37-3.46 (2H, m), 3.49-3.58 (2H, m), 3.60-3.71 (1H, m), 3.99-4.69 (7H, m), 6.56 (1H, s), 6.78 (1H, d, J= 7.4 Hz), 6.86-6.90 (2H, m), 7.38-7.43 (1H, m), 7.64 (1H, d, J= 7.3 Hz), 7.68-7.73 (1H, m) 8.04-8.09 (1H, m), 8.54 (1H, s)

Example 572

Synthesis of 1-ethyl-7-(3-{(6-methoxy-pyridin-3-ylmethyl)-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}-propoxy)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

White powder

Melting Point 114 to 116°C

Example 573

Synthesis of 1-ethyl-3,3,5-trimethyl-7-{3-[[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-(4-methylpyridin-3-yl methyl)amino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

White powder

Melting Point 147 to 148°C

Example 574

Synthesis of 1-ethyl-7-(3-{(6-methoxy-pyridin-3-ylmethyl)-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}propoxy)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

White powder

Melting Point 111 to 113°C

Example 575

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{(2-methylpyridin-3-ylmethyl)-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-amino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

White powder

Melting Point 111 to 114°C

Example 576

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{[2-(1-oxo-1H-isoquinolin-2-yl)ethyl]pyridin-2-ylmethylamino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

White solid

Melting Point 94.6 to 95.4°C

Example 577

Synthesis of 1-ethyl-3,3,5-trimethyl-7-{3-[(2-pyridin-3-yl-ethyl)-quinolin-4-ylmethylamino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione trihydrochloride

Using an appropriate starting material and following the procedure of Example 7 and Example 6, the object compound was synthesized.

White powder

Melting Point 139 to 143°C

Example 578

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{(4-methylpyridin-3-ylmethyl)-[2-(7-oxo-7H-furo[2,3-c]pyridin-6-yl)ethyl]-amino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

White powder

Melting Point 123 to 124°C

Example 579

Synthesis of 1-ethyl-3,3,5-trimethyl-7-{3-[[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-(2-pyridin-3-yl-ethyl)amino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 7 and Example 6, the object compound was synthesized.

White amorphous

^{1}H-NMR (D_2O) δppm:

0.64 (3H, s), 0.96 (3H, t, J=7.0 Hz), 1.29(3H, s), 2.21(2H, quin, J=2.8 Hz), 3.25(3H, s), 3.27-3.35 (2H, m), 3.55 (2H, t, J=7.0 Hz), 3.57-3.69 (3H, m), 3.71 (2H, t, J=5.4 Hz), 4.02 (1H, dq, J= 7.0, 7.0 Hz), 4.12 (2H, t, J=5.4 Hz), 4.38-4.53 (2H,m), 6.75(1H, s), 6.81-6.93(3H, m), 7.33(1H, d, J=9.0Hz), 7.50(1H, d, 7.5Hz), 7.58-7.65(1H, m), 7.77-7.90(1H, m), 8.30-8.40(1H, m), 8.57(1H, d, J=5.6 Hz), 8.61(1H, s)

Example 580

Synthesis of 1-ethyl-7-(3-{(4-methoxy-benzyl)-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}propoxy)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione hydrochloride

Using an appropriate starting material and following the procedure of Example 7 and Example 6, the object compound was synthesized.

White powder

Melting Point 116.3 to 120°C (dec.)

Example 581

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{(6-methylpyridin-3-ylmethyl)-[2-(7-oxo-7H-furo[2,3-c]pyridin-6-yl)ethyl]-amino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

White powder

Melting Point 120 to 122°C

Example 582

Synthesis of 1-ethyl-3,3,5-trimethyl-7-{3-[[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-(6-methylpyridin-3-ylmethyl)amino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

White powder

Melting Point 136 to 138°C

Example 583

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{(6-methylpyridin-3-ylmethyl)-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-amino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

White powder

^{1}H-NMR ($CDCl_3$) δppm:

0.86 (3H, s), 1.15 (3H, t, J = 7.1 Hz), 1.53 (3H, s), 1.86 - 1.95 (2H, m), 2.48 (3H, s), 2.70 (2H, t, J = 6.8 Hz), 2.85 (2H, t, J = 6.2 Hz), 3.39 (3H, s), 3.63 (2H, s), 3.65 - 3.75 (1H, m), 3.86 (2H, t, J = 6.1 Hz), 4.06 (2H, t, J = 6.1 Hz), 4.14 - 4.22 (1H, m), 6.41 (1H, dd, J= 7.4, 0.8 Hz), 6.62 (1H, d, J = 2.7 Hz), 6.67 (1H, dd, J= 9.0, 2.4 Hz), 6.90-6.95 (2H, m), 7.07 (1H, d, J= 7.4 Hz), 7.18 (1H, d, J= 8.9 Hz), 7.35-7.42 (1H m), 7.47 (1H, d, J= 2.1 Hz), 8.31 (1H, d, J = 1.8Hz))

Example 584

Synthesis of 1-ethyl-3,3,5-trimethyl-7-{3-[(2-pyridin-3-yl-ethyl)-quinolin-5-ylmethylamino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione trihydrochloride

Using an appropriate starting material and following the procedure of Example 7 and Example 6, the object compound was synthesized.

pale yellow white amorphous

^{1}H-NMR (D_2O) δppm:

0.66 (3H, s), 0.97 (3H, t, J=7.1 Hz), 1.30(3H, s), 2.12-2.37(2H,m), 3.25(3H, s), 3.36-3.57 (4H, m), 3.57-3.74 (3H, m), 3.93-4.10 (3H, m), 5.08 (2H, s), 6.69(1H, dd, J=9.0 and 2.8 Hz), 6.71(1H, d, J=2.8 Hz), 7.30(1H, d, J=9.0Hz), 7.93(1H, dd, J=8.0 and 5.8Hz), 7.98-8.13(3H,

m), 8.23(1H, d, J=8.3 Hz), 8.43(1H, d, J=8.3 Hz), 8.63(1H, d, J=5.7 Hz), 8.67(1H, s), 9.04-9.13(1H, m), 9.23(1H, d, J=8.7 Hz)

Example 585

Synthesis of 5-Ethyl-1,3,3-trimethyl-7-(3-{[2-(1-oxo-5,6,7,8-tetrahydro-1H-isoquinolin-2-yl)ethyl]pyridin-4-yl methylamino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

White powder

^{1}H-NMR (DMSO-D_6) δppm:

0.75 (3H, s), 1.01 (3H, t, J=7.0 Hz), 1.32 (3H, s), 1.49-1.74 (4H, m), 2.03-2.40 (4H, m), 2.90-3.41(4H, m), 3.32 (3H, s), 3.56-4.84 (10H, m), 6.02 (1H, d, J=6.8 Hz), 6.79-7.00 (2H, m), 7.31-7.57 (2H, m), 7.93-8.25 (2H, m), 8.68-9.08 (2H, m).

Example 586

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{(2-methyl-2H-pyrazol-3-ylmethyl)-[2-(1-oxo-1H-isoquinolin-2-yl)ethyl]-amino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

White powder

Melting Point 96 to 99°C

Example 587

Synthesis of 7-{3-[benzothiazol-2-ylmethyl-(2-pyridin-3-yl-ethyl)amino]propoxy}-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 7 and Example 6, the object compound was synthesized.

White amorphous

^{1}H-NMR (D_2O) δppm:

0.60 (3H, s), 0.95 (3H, t, J=7.1 Hz), 1.28(3H, s), 2.06-2.37(2H,m), 3.07(3H, s), 3.34-3.43 (2H, m), 3.47-3.56 (2H, m), 3.59 (1H, dq, J= 7.0, 7.0 Hz), 3.63-3.73 (2H, m), 3.98 (1H, dq, J= 7.0, 7.0 Hz), 4.03-4.16

(2H,m), 4.85 (1H, d, J= 15.2 Hz), 4.89 (1H, d, J= 15.2 Hz), 6.51(1H, d, J=2.8 Hz), 6.71(1H, dd, J=9.1 and 2.8 Hz), 7.20(1H, d, J=9.1 Hz), 7.38-7.53(2H,m), 7.83(1H, d, J=8.0 Hz), 7.87(1H, dd, J=8.0 and 5.8Hz), 7.91(1H, d, J=8.0 Hz), 8.43(1H, d, J=8.0 Hz), 8.56(1H, d, J=5.8 Hz), 8.66(1H, s)

Example 588

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{(5-methylpyridin-3-ylmethyl)-[2-(7-oxo-7H-furo[2,3-c]pyridin-6-yl)ethyl]-amino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

White powder

Melting Point 130 to 131°C

Example 589

Synthesis of 1-ethyl-3,3,5-trimethyl-7-{3-[[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-(5-methylpyridin-3-ylmethyl)amino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

White powder

Melting Point 125 to 127°C

Example 590

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{(4-methylpyridin-3-ylmethyl)-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-amino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

White powder

^{1}H-NMR ($CDCl_3$) δppm:

0.86 (3H, s), 1.15 (3H, t, J= 7.0 Hz), 1.53 (3H, s), 1.91-2.01 (2H, m), 2.25 (3H, s), 2.76 (2H, t, J= 6.8 Hz), 2.87 (2H, t, J= 6.5 Hz), 3.39 (3H, s), 3.65-3.74 (3H, m), 3.91 (2H, t, J= 6.2 Hz), 4.02 (2H, t, J= 6.4 Hz) 4.11-4.22 (1H, m), 6.41 (1H, d, J= 7.3 Hz), 6.65 (1H, d, J= 2.6 Hz), 6.70 (1H, dd, J= 8.9, 2.7 Hz), 6.91 - 6.97 (3H, m), 7.17 (1H, d, J= 9.0 Hz), 7.47 (1H, d, J= 2.0 Hz), 8.32 (1H, d, J= 4.8

Hz), 8.40 (1H, s)

Example 591

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{(2-methylpyridin-3-ylmethyl)-[2-(7-oxo-7H-thieno[2,3-c]pyridin-6-yl)ethyl]-amino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

White powder

Melting Point 115 to 117°C

Example 592

Synthesis of 7-{3-[(2,5-dimethyl-2H-pyrazol-3-ylmethyl)-(2-pyridin-3-ylethyl)amino]propoxy}-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione trihydrochloride

Using an appropriate starting material and following the procedure of Example 7 and Example 6, the object compound was synthesized.

White amorphous

^{1}H-NMR (D_2O) δppm:

0.70 (3H, s), 0.97 (3H, t, J=7.0 Hz), 1.30(3H, s), 2.06(3H, s), 2.13-2.30(2H,m),3.29 (3H, s), 3.30-3.37 (2H, m), 3.37-3.48 (2H, m), 3.48-3.68 (3H, m), 3.73 (3H, s), 4.03 (1H, dq, J= 7.0, 7.0 Hz), 4.09 (2H, t, J=5.4 Hz), 4.53 (2H, s), 6.30(1H, s), 6.84(1H, d, J=2.7 Hz), 6.87(1H, dd, J=9.0 and 2.7 Hz), 7.36(1H, d, J=9.0 Hz), 7.95(1H, dd, J=8.0 and 5.9 Hz)), 8.44(1H, d, J=8.0 Hz), 8.64(1H, d, J=5.9 Hz), 8.66(1H, s)

Example 593

Synthesis of 1-ethyl-3,3,5-trimethyl-7-{3-[(4-methyl-thiazol-5-ylmethyl)-(2-pyridin-3-yl-ethyl)amino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 7 and Example 6, the object compound was synthesized.

White powder

Melting Point 175 to 185°C

Example 594

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{(5-methylpyridin-3-ylmethyl)-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-amino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

White powder

Melting Point 128 to 129°C

Example 595

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{(2-methylpyridin-3-ylmethyl)-[2-(4-oxo-4H-thieno[3,2-c]pyridin-5-yl)ethyl]-amino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

White powder

Melting Point 95 to 98°C

Example 596

Synthesis of 1-ethyl-3,3,5-trimethyl-7-{3-[[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-(2-methyl-2H-pyrazol-3-ylmethyl)amino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

White powder

Melting Point 119 to 121°C

Example 597

Synthesis of 7-(3-{(1,5-dimethyl-1H-pyrazol-4-ylmethyl)-[2-(1-oxo-1H-isoquinolin-2-yl)ethyl]amino}propoxy)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 7 and Example 6, the object compound was synthesized.

White amorphous

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (3H, s), 1.01 (3H, t, J= 7.2 Hz), 1.32 (3H, s), 2.22-2.38 (5H, m), 3.20-3.41 (5H, m), 3.41-3.49 (2H, m), 3.72 (3H, s), 4.04-4.17 (4H, m), 4.26-4.38 (2H, m), 4.40-4.47 (2H, m), 6.74 (1H, d, J= 7.4 Hz), 6.88-6.95 (2H, m), 7.42 (1H, d, J= 8.9 Hz), 7.51-7.56 (2H, m), 7.62 (1H, s), 7.66-7.78 (2H, m), 8.24 (1H, d, J= 8.0 Hz)

Example 598

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{(6-methylpyridin-3-ylmethyl)-[2-(1-oxo-1H-isoquinolin-2-yl)ethyl]amino}-propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

White powder

Melting Point 140 to 142°C

Example 599

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{(6-methylpyridin-3-ylmethyl)-[2-(4-oxo-4H-thieno[3,2-c]pyridin-5-yl)ethyl]-amino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

White powder

Melting Point 126 to 129°C

Example 600

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{(6-methylpyridin-3-ylmethyl)-[2-(7-oxo-7H-thieno[2,3-c]pyridin-6-yl)ethyl]-amino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

White powder

Melting Point 120 to 122°C

Example 601

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{(2-methylpyridin-3-ylmethyl)-[2-(1-oxo-1H-isoquinolin-2-yl)ethyl]amino}-propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

White powder

Melting Point 98 to 102°C

Example 602

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]thiazol-2-ylmethyl-amino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

White powder

Melting Point 175 to 176°C

Example 603

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]oxazol-2-ylmethyl-amino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

White powder

Melting Point 130 to 131°C

Example 604

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]thiazol-5-ylmethyl-amino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

White powder

Melting Point 181 to 183°C

Example 605

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]oxazol-5-ylmethyl-amino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

White powder

^{1}H-NMR ($CDCl_3$) δppm:

0.86 (3H, s), 1.15 (3H, t, J= 7.0 Hz), 1.53 (3H, s), 1.83-1.90 (2H,

m), 2.40 (3H, s), 2.65-2.75 (2H, m), 2.83-2.92 (2H, m), 3.40 (3H, s), 3.65-3.72 (1H, m), 3.79 (2H, s), 3.82-3.88 (2H, m) 4.03-4.08 (2H, m), 4.10-4.22 (1H, m), 6.35 (1H, d, J= 7.3 Hz), 6.54 (1H, s), 6.63-6.73 (2H, m), 6.92 (1H, s), 7.09 (1H, d, J= 7.4 Hz), 7.18 (1H, d, J= 8.9 Hz), 7.74 (1H, s)

Example 606

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]thiazol-4-ylmethyl-amino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

White powder

Melting Point 136 to 137°C

Example 607

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]oxazol-4-ylmethyl-amino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

White powder

Melting Point 119 to 120°C

Example 608

Synthesis of 1-ethyl-7-(3-{(2-ethylpyridin-3-ylmethyl)-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}propoxy)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 7 and Example 6, the object compound was synthesized.

White amorphous

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (3H, s), 1.01 (3H, t, J= 7.0 Hz), 1.15-1.31 (3H, m), 1.33 (3H, s), 1.75-2.41 (2H, m), 2.93-3.26 (3H, m), 3.31 (3H, s), 3.54-4.93 (11H, m), 6.58-7.03 (4H, m), 7.39 (1H, d, J= 8.9 Hz), 7.46-7.85 (2H, m), 7.90 (1H, s), 8.42-8.92 (2H, m)

Example 609

Synthesis of 1-ethyl-7-(3-{(2-ethylpyridin-3-ylmethyl)-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}-propoxy)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 7 and Example 6, the object compound was synthesized.

White amorphous

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (3H, s), 1.01 (3H, t, J= 7.0 Hz), 1.15-1.31 (3H, m), 1.32 (3H, s), 1.82-2.00 (2H, m), 2.39 (3H, s), 2.63-2.92 (2H, m), 2.93-3.20 (2H, m), 3.31 (3H, s), 3.51-4.88 (10H, m), 6.38-6.53 (2H, m), 6.54-6.92 (2H, m), 7.39 (1H, d, J= 9.0 Hz), 7.40-7.77 (2H, m), 8.09-8.80 (2H, m)

Example 610

Synthesis of 1-ethyl-3,3,5-trimethyl-7-{3-[[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-(2-propylpyridin-3-ylmethyl)amino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 7 and Example 6, the object compound was synthesized.

White amorphous

^{1}H-NMR (DMSO-D_6) δppm:

0.76 (3H, s), 0.90 (3H, t, J= 6.7 Hz), 1.02 (3H, t, J= 7.0 Hz), 1.33 (3H, s), 1.51-1.72 (2H, m), 1.73-2.00 (2H, m), 2.61-3.12 (4H, m), 3.31 (3H, s), 3.33-4.10 (10H, m), 6.55-7.03 (4H, m), 7.39 (1H, d, J= 9.0 Hz), 7.43-7.68 (2H, m), 7.85-7.95 (1H, m), 8.10-8.78 (2H, m)

Example 611

Synthesis of 1-ethyl-3,3,5-trimethyl-7-{3-[[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-(2-propylpyridin-3-ylmethyl)amino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the

procedure of Example 7 and Example 6, the object compound was synthesized.

White amorphous

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (3H, s), 0.91 (3H, t, J= 7.1 Hz), 1.02 (3H, t, J= 7.0 Hz), 1.33 (3H, s), 1.55-1.76 (2H, m), 2.39 (3H, s), 2.51-2.88 (2H, m), 2.90-3.19 (2H, m), 3.31 (3H, s), 3.55-4.81 (12H, m), 6.42-6.70 (2H, m), 6.78-6.92 (2H, m), 7.39 (1H, d, J= 8.9 Hz), 7.43-7.88 (2H, m), 7.92-8.89 (2H, m)

Example 612

Synthesis of 1-ethyl-3,3,5-trimethyl-7-{3-[(2-pyridin-3-yl-ethyl)thiazol-5-ylmethylamino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 7 and Example 6, the object compound was synthesized.

White powder

Melting Point 163 to 166°C

Example 613

Synthesis of 7-{3-[(2,5-dimethyl-oxazol-4-ylmethyl)-(2-pyridin-3-yl-ethyl)amino]propoxy}-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 7 and Example 6, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

0.74 (3H, s), 0.99 (3H, t, J=7.0 Hz), 1.31 (3H, s), 2.20-2.30(2H,m), 2.36 (3H, s), 2.38 (3H, s), 2.70-3.85 (6H, m), 3.31 (3H, s), 3.66(1H, dq, J= 7.0, 7.0 Hz), 4.05 (1H, dq, J= 7.0, 7.0 Hz), 4.12 (2H, t, J=6.0 Hz), 4.33 (2H, bs), 6.92(1H, dd, J=8.9 and 2.8 Hz), 6.94(1H, d, J=2.8 Hz), 7.42(1H, d, J=8.9 Hz), 7.71(1H, bs), 8.13(1H, bs), 8.61-8.70(1H, m), 8.72(1H, s), 10.60(1H, bs)

Example 614

Synthesis of N-(2-{[[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-

2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]-(2-pyridin-3-yl-ethyl)amino]methyl}phenyl)methanesulfonamide dihydrochloride

Using an appropriate starting material and following the procedure of Example 7 and Example 6, the object compound was synthesized.

White amorphous

^{1}H-NMR (DMSO-d_6) δppm:

0.73 (3H, s), 0.99 (3H, t, J=7.0 Hz), 1.30 (3H, s), 2.2-2.35(2H,m), 3.04 (3H, s), 3.05-3.95 (6H, m), 3.30 (3H, s), 3.65 (1H, dq, J= 7.0, 7.0 Hz), 4.04 (1H, dq, J= 7.0, 7.0 Hz), 4.04-4.20 (2H, m), 4.59 (2H, bs), 6.82-6.95 (2H, m), 7.33-7.50(3H, m), 7.50-7.60(1H, m), 7.60-7.75(1H, m),7.84 (1H, d, J=6.8 Hz), 7.96-8.16 (1H, m), 8.57-8.70 (1H, m), 8.68 (1H, bs)), 10.37(1H, bs)

Example 615

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(4-{(2-methylpyridin-3-ylmethyl)-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-amino}butoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 7 and Example 6, the object compound was synthesized.

White amorphous

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (3H, s), 1.01 (3H, t, J= 7.1 Hz), 1.32 (3H, s), 1.62-2.14 (4H, m), 2.39 (3H, s), 2.50-2.53 (3H, m), 2.73-3.08 (4H, m), 3.14-4.85 (11H, m), 6.70-6.85 (1H, m), 6.86-7.02 (3H, m), 7.40 (1H, d, J= 8.9 Hz), 7.67-7.99 (3H, m), 8.51-9.03 (2H, m)

Example 616

Synthesis of 1-ethyl-3,3,5-trimethyl-7-{4-[[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-(2-methylpyridin-3-ylmethyl)amino]butoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 7 and Example 6, the object compound was

synthesized.

White amorphous

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (3H, s), 1.01 (3H, t, J= 7.0 Hz), 1.32 (3H, s), 1.53-2.15 (4H, m), 2.39 (3H, s), 2.42-2.96 (7H, m), 3.26-4.88 (11H, m), 6.41-6.63 (1H, m), 6.65-6.84 (1H, m), 6.87-6.95 (2H, m), 7.40 (1H, d, J= 8.8 Hz), 7.52-7.89 (2H, m), 8.46-8.88 (2H, m)

Example 617

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(4-{(2-methylpyridin-3-ylmethyl)-[2-(1-oxo-1H-isoquinolin-2-yl)ethyl]amino}-butoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 7 and Example 6, the object compound was synthesized.

White amorphous

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (3H, s), 1.01 (3H, t, J= 7.1 Hz), 1.32 (3H, s), 1.60-2.14 (4H, m), 2.47-3.08 (7H, m), 3.16-4.77 (11H, m), 6.58-6.80 (1H, m), 6.83-7.00 (2H, m), 7.39 (1H, d, J= 8.9 Hz), 7.43-7.62 (2H, m), 7.63-7.99 (3H, m), 8.12-8.30 (1H, m), 8.55-9.02 (2H, m)

Example 618

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(4-{[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]pyridin-4-ylmethylamino}-butoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 7 and Example 6, the object compound was synthesized.

White amorphous

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (3H, s), 1.01 (3H, t, J= 7.1 Hz), 1.32 (3H, s), 1.42-1.91 (4H, m), 3.31 (3H, s), 3.33-4.71 (12H, m), 6.63-6.98 (4H, m), 7.39 (1H, d, J= 8.7 Hz), 7.61-7.70 (1H, m), 7.77-7.94 (3H, m), 8.66-8.82 (2H, m)

Example 619

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(4-{[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]pyridin-4-ylmethyl amino}butoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 7 and Example 6, the object compound was synthesized.

White amorphous

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (3H, s), 1.01 (3H, t, J= 7.1 Hz), 1.31 (3H, s), 1.57-1.99 (4H, m), 2.49 (3H, s), 3.08-4.62 (15H, s), 6.53-6.58 (1H, m), 6.69-6.76 (1H, m), 6.86-6.94 (2H, m), 7.39 (1H, d, J= 8.8 Hz), 7.58-7.65 (1H, m), 7.83-8.13 (2H, m), 8.72-8.89 (2H, m)

Example 620

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(4-{[2-(1-oxo-1H-isoquinolin-2-yl)ethyl]pyridin-4-ylmethylamino}butoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 7 and Example 6, the object compound was synthesized.

White amorphous

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (3H, s), 1.01 (3H, t, J= 7.1 Hz), 1.32 (3H, s), 1.60-1.99 (4H, m), 3.07-4.70 (15H, m), 6.69 (1H, d, J= 7.3 Hz), 6.83-6.98 (2H, m), 7.39 (1H, d, J= 8.8 Hz) 7.48-7.55 (2H, m), 7.65-7.76 (2H, m), 7.82-8.12 (2H, m), 8.20 (1H, d, J=7.9 Hz), 8.70-8.93 (2H, m)

Example 621

Synthesis of 7-(3-{(2-chloro-pyridin-3-ylmethyl)-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}-propoxy)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4] diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 7 and Example 6, the object compound was synthesized.

White amorphous

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (3H, s), 1.01 (3H, t, J= 7.0 Hz), 1.32 (3H, s), 2.08-2.30 (2H, m), 2.39 (3H, s), 3.17-4.85 (15H, m), 6.57 (1H, s), 6.70-6.94 (3H, m), 7.40 (1H, d, J= 9.0 Hz) 7.42-7.74 (2H, m), 8.21-8.57 (2H, m)

Example 622

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{[2-(2-methyl-4-oxo-4H-thieno[3,2-c]pyridin-5-yl)ethyl]pyridin-4-ylmethyl-amino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

^{1}H-NMR ($CDCl_3$) δppm:

0.87 (s, 3H), 1.16 (t, J=7.1 Hz, 3H), 1.53 (s, 3H), 1.81-1.94 (m, 2H), 2.56 (s, 3H), 2.72 (t, J=6.2 Hz, 2H), 2.83-2.90 (m, 2H), 3.38 (s, 3H), 3.67 (s, 2H), 3.66-3.78 (m, 1H), 3.88 (t, J=6.1 Hz, 2H), 4.08-4.23 (m, 3H), 6.48 (d, J=7.1 Hz, 1H), 6.53-6.62 (m, 3H), 6.96 (d, J=7.1 Hz, 1H), 7.07-7.08 (m, 2H), 7.19 (d, J=8.9 Hz, 1H), 8.28-8.32 (m, 2H).

Example 623

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{[2-(3-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]pyridin-4-ylmethyl-amino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (s, 3H), 1.01 (t, J = 7.0 Hz, 3H), 1.32 (s, 3H), 2.08 (br, 2H), 2.22 (s, 3H), 3.20-3.40 (m, 2H), 3.30 (s, 3H), 3.53-3.70 (m, 3H), 3.89-4.13 (m, 5H), 4.24 (br, 2H), 6.67 (br, 1H), 6.70-6.83 (m, 2H), 7.38 (d, J = 9.0 Hz, 1H), 7.62 (br, 2H), 7.89 (br, 2H), 8.71 (br, 2H).

Example 624

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{[2-(4-methyl-7-oxo-7H-furo[2,3-c]pyridin-6-yl)ethyl]pyridin-4-ylmethyl-amino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (s, 3H), 1.01 (t, J = 7.0 Hz, 3H), 1.32 (s, 3H), 2.10 (br, 2H), 2.17 (s, 3H), 3.20-3.39 (m, 2H), 3.30 (s, 3H), 3.61-3.72 (m, 3H), 3.83-4.11 (m, 5H), 4.16 (br, 2H), 6.77 (br, 1H), 6.85 (br, 1H), 6.96 (s, 1H), 7.31 (br, 1H), 7.38 (d, J = 9.0 Hz, 1H), 7.80 (br, 2H), 8.14 (s, 1H), 8.68 (br, 2H).

Example 625

Synthesis of 7-(3-{(2-butylpyridin-3-ylmethyl)-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}propoxy)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 7 and Example 6, the object compound was synthesized.

White amorphous

^{1}H-NMR (DMSO-D_6) δppm:

0.76 (3H, s), 0.86 (3H, t, J= 7.3 Hz), 1.02 (3H, t, J= 7.0 Hz), 1.21-1.40 (5H, m), 1.47-1.67 (2H, m), 1.83-2.06 (2H, m), 2.39 (3H, s), 2.60-3.01 (6H, m), 3.17 (3H, s), 3.22-4.19 (8H, m) 6.35-6.67 (2H, m), 6.69-6.92 (2H, m), 7.39 (1H, d, J= 8.9 Hz) 7.42-7.71 (2H, m), 8.17-8.42 (1H, m), 8.53-8.65 (1H, m)

Example 626

Synthesis of 7-{3-[(2,4-dimethyl-thiazol-5-ylmethyl)-(2-pyridin-3-yl-ethyl)amino]propoxy}-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 7 and Example 6, the object compound was synthesized.

White amorphous

^{1}H-NMR (DMSO-d_6) δppm:

0.74 (3H, s), 0.99 (3H, t, J = 7.0 Hz), 1.31 (3H, s), 2.26(2H,bs), 2.39 (3H, s), 2.59 (3H, s), 3.11-3.61 (6H, m), 3.31 (3H, s), 3.67(1H, t, dq = 7.0, 7.0 Hz), 4.05 (1H, dq, J = 7.0, 7.0 Hz), 4.09-4.17 (2H, m), 4.62 (2H, bs), 6.84-6.95 (2H, m), 7.41(1H, d, J = 8.9 Hz), 7.89(1H, dd, J = 7.8 and 5.6 Hz), 8.35(1H, d, J = 7.8 Hz), 8.76 (1H, d, J = 5.6 Hz), 8.84 (1H, s), 11.2 (1H, bs)

Example 627

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]pyridazin-4-ylmethylamino}-propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

White powder

^{1}H-NMR ($CDCl_3$) δppm:

0.86 (3H, s), 1.16 (3H, t, J= 7.1 Hz), 1.53 (3H, s), 1.87-1.97 (2H, m), 2.73 (2H, t, J= 6.8 Hz), 2.87-2.95 (2H, m), 3.39 (3H, s), 3.66-3.77 (3H, m), 3.85 (2H, t, J= 5.9 Hz), 4.10-4.24 (3H, m), 6.48 (1H, d, J= 7.4 Hz), 6.59 (1H, d, J= 2.7 Hz), 6.65 (1H, dd, J= 2.7 and 9.0 Hz), 6.95 (1H, t, J= 0.8 Hz), 7.09 (1H, d, J= 7.4 Hz), 7.19 (1H, d, J= 9.0 Hz), 7.25-7.28 (1H, m), 7.51 (1H, d, J= 2.1 Hz), 8.89 (1H, dd, J= 1.2 and 5.2 Hz), 9.08 (1H, s)

Example 628

Synthesis of N-[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]-N-(2-pyridin-3-ylethyl)benzenesulfonamide hydrochloride

Using an appropriate starting material and following the procedure of Example 4 and Example 6, the object compound was synthesized.

White amorphous

^{1}H-NMR (DMSO-d_6) δppm:

0.74 (3H, s), 1.01 (3H, t, J = 7.0 Hz), 1.32 (3H, s), 1.85-1.97(2H, m), 3.03(2H, t, J = 7.0 Hz), 3.03-3.62 (4H, m), 3.31 (3H, s), 3.67 (1H, dq, J = 7.0, 7.0 Hz), 3.98 (2H, t, t = 7.0 Hz), 4.06 (1H, dq, J = 7.0, 7.0 Hz), 6.84-6.95 (2H, m), 7.41(1H, d, J = 8.9 Hz), 7.54-7.63(2H, m), 7.63-7.72(1H, m), 7.75-7.84(2H, m), 7.84-7.92(1H, m), 8.34(1H, d, J = 7.4 Hz), 8.74 (1H, d, J = 5.2 Hz), 8.78 (1H, bs)

Example 629

Synthesis of 7-(3-{(2,6-dimethylpyridin-3-ylmethyl)-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}propoxy)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 7 and Example 6, the object compound was synthesized.

White amorphous

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (3H, s), 1.01 (3H, t, J= 7.0 Hz), 1.32 (3H, s), 1.99-3.04 (12H, m), 3.05-4.82 (11H, m), 6.55-7.04 (4H, m), 7.41 (1H, d, J= 8.9 Hz) 7.44-7.82 (2H, m), 7.91 (1H, s), 8.38-8.92 (1H, m)

Example 630

Synthesis of 7-(3-{(2,6-dimethylpyridin-3-ylmethyl)-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}-propoxy)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

White powder

Melting Point 114 to 116°C

Example 631

Synthesis of N-[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]benzenesulfonamide

Using an appropriate starting material and following the procedure of Example 4, the object compound was synthesized.

White powder

Melting Point 179.6 to 182.5°C

Example 632

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]pyridin-4-ylmethyl-amino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (s, 3H), 1.01 (t, J = 7.0 Hz, 3H), 1.32 (s, 3H), 2.00 (br, 2H),

2.16 (s, 3H), 3.21-3.35 (m, 2H), 3.30 (s, 3H), 3.53-3.70 (m, 3H), 3.93 (br, 4H), 4.00-4.19 (m, 3H), 6.70-6.81 (m, 2H), 6.95 (s, 1H), 7.37 (d, J = 9.0 Hz, 1H), 7.45 (br, 1H), 7.78 (br, 2H), 7.93 (br, 1H), 8.67 (br, 2H).

Example 633

Synthesis of N-[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]-N-(2-pyridin-3-ylethyl)benzamide hydrochloride

Benzoyl chloride (0.091 ml, 0.78 mmol) was added to an acetonitrile solution (3 ml) of 1-ethyl-3,3,5-trimethyl-7-[3-(2-pyridin-3-ylethylamino)propoxy]-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione (0.39 g, 0.71 mmol) and triethylamine (0.12 ml, 0.86 mmol) while cooling in an ice-bath, and the mixture was stirred at room temperature overnight. Water was added to the reaction mixture, and extraction with ethyl acetate was conducted. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue thus obtained was purified by medium pressure liquid chromatography (silica gel, ethyl acetate:isopropyl alcohol=100:0-92:8). The purified product was concentrated under reduced pressure and the resultant residue was dissolved in ethyl acetate (10 ml). A 1N-HCl ethanol solution (0.65 ml) was added to the solution, and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate to thereby obtain 0.28 g (yield:54%) of N-[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]-N-(2-pyridin-3-ylethyl)benzamide hydrochloride as a white powder.

Melting Point 179 to 191°C

Example 634

Synthesis of N-[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]-N-[2-(1-oxo-1H-isoquinolin-2-yl)ethyl]benzenesulfonamide

Using an appropriate starting material and following the procedure of Example 4, the object compound was synthesized.

White powder

Melting Point 134 to 137°C

Example 635

Synthesis of pyridine-3-sulfonic acid [3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]-[2-(1-oxo-1H-isoquinolin-2-yl)ethyl]amide

Using an appropriate starting material and following the procedure of Example 4, the object compound was synthesized.

White powder

Melting Point 160 to 164°C

Example 636

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{[2-(4-methyl-7-oxo-7H-thieno[2,3-c]pyridin-6-yl)ethyl]pyridin-4-ylmethyl-amino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (s, 3H), 1.01 (t, J = 7.0 Hz, 3H), 1.32 (s, 3H), 2.05 (br, 2H), 2.24 (s, 3H), 3.30-3.40 (m, 2H), 3.30 (s, 3H), 3.63-3.70 (m, 3H), 3.82 (br, 4H), 3.95-4.10 (m, 1H), 4.25 (br, 2H), 6.72 (br, 1H), 6.80 (br 1H), 7.35-7.43 (m, 3H), 7.85 (br, 2H), 8.07-8.11 (m, 1H), 8.66 (br, 2H).

Example 637

Synthesis of pyridine-3-sulfonic acid [3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amide

Using an appropriate starting material and following the procedure of Example 4, the object compound was synthesized.

White powder

Melting Point 163.3 to 166.3°C

Example 638

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(2-{(2-methylpyridin-3-ylmethyl)-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-amino}ethoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

dihydrochloride

Using an appropriate starting material and following the procedure of Example 7 and Example 6, the object compound was synthesized.

White amorphous

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (3H, s), 1.02 (3H, t, J=7.0 Hz), 1.33 (3H, s), 2.61 (3H, s), 2.77-3.05(4H, m), 3.32(3H, s), 3.48-3.71(3H, m), 3.94-4.16(5H, m), 6.63(1H, d, J=7.3 Hz), 6.83-6.91 (3H, m), 7.39(1H, d, J=8.8 Hz), 7.55(1H, d, J=7.6 Hz), 7.65(1H, t, J=6.2 Hz), 7.84(1H, d, J=2.1 Hz), 8.34-8.38 (1H, m), 8.51(1H, d, J=5.9 Hz)

Example 639

Synthesis of pyridine-3-sulfonic acid [3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4] diazepin-7-yloxy)propyl]-(2-pyridin-3-ylethyl)amide 2 phosphate

Using an appropriate starting material and following the procedure of Example 4 and Example 458, the object compound was synthesized.

White amorhous

^{1}H-NMR (DMSO-d_6) δppm:

0.74 (3H, s), 1.01 (3H, t, J=7.0 Hz), 1.32 (3H, s), 1.89-2.08(2H, m), 2.80-2.98(2H, m), 3.31 (3H, s), 3.31-5.00 (8H, m), 6.84-6.96 (2H, m), 7.30(1H, dd, J=8.0 and 4.8 Hz), 7.40(1H, d, J=8.7Hz), 7.54-7.74(2H, m), 8.18-8.27(1H, m), 8.42(1H, dd, J=4.8 and 1.5 Hz), 8.44 (1H, d, J=1.8 Hz), 8.83(1H, dd, J=4.8 Hz , J=1.5 Hz), 8.99 (1H, d, J=1.8 Hz)

Example 640

Synthesis of 2,4-dimethyl-thiazole-5-sulfonic acid [3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo [b][1,4]diazepin-7-yloxy)propyl]-(2-pyridin-3-yl-ethyl)amide hydrochloride

Using an appropriate starting material and following the procedure of Example 4 and Example 6, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (3H, s), 1.01 (3H, t, J=7.0 Hz), 1.32 (3H, s), 1.89-2.25(2H, m),

2.49 (3H, s), 2.62 (3H, s), 3.08 (2H, t, J=7.0 Hz), 3.32 (3H, s), 3.32-3.90 (3H, m), 3.54 (2H, t, J=7.0 Hz), 4.01 (2H, t, J=7.0 Hz), 4.01-4.20 (1H, m), 6.84-6.96 (2H, m), 7.41(1H, d, J=8.9Hz), 7.90(1H, dd, J=8.0 and 5.4 Hz), 8.37 (1H, d, J=8.0 Hz), 8.75(1H, d, J=5.4 Hz), 8.82 (1H, s)

Example 641

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{[2-(7-oxo-7H-thieno[2,3-c]pyridin-6-yl)ethyl]pyridin-3-ylmethylamino}-propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.85 (s, 3H), 1.14 (t, J=7.1 Hz, 3H), 1.52 (s, 3H), 1.81-1.93 (m, 2H), 2.72 (t, J=6.8 Hz, 2H), 2.89 (t, J=6.1 Hz, 2H), 3.38 (s, 3H), 3.68 (s, 2H), 3.60-3.75 (m, 1H), 3.86 (t, J=6.0 Hz, 2H), 4.05-4.21 (m, 3H), 6.55 (d, J=7.1 Hz, 1H), 6.60-6.68 (m, 2H), 6.96-7.03 (m, 1H), 7.07 (d, J=7.1 Hz, 1H), 7.12-7.18 (m, 2H), 7.42-7.50 (m, 1H), 7.66-7.70 (m, 1H), 8.35-8.37 (m, 1H), 8.47 (s, 1H).

Example 642

Synthesis of 1-ethyl-7-(3-{[2-(2-ethyl-4-oxo-4H-thieno[3,2-c]pyridin-5-yl)ethyl]pyridin-3-ylmethylamino}propoxy)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (s, 3H), 1.01 (t, J = 7.0 Hz, 3H), 1.28 (t, J = 7.5 Hz, 3H), 1.32 (s, 3H), 2.25 (br, 2H), 2.87 (q, J = 7.5 Hz, 2H), 3.20-3.35 (m, 2H), 3.32 (s, 3H), 3.51-3.69 (m, 3H), 3.97-4.15 (m, 5H), 4.28 (br, 2H), 6.90 (br, 3H), 7.22 (s, 1H), 7.42 (d, J = 9.0 Hz, 1H), 7.50-7.68 (m, 2H), 8.18 (br, 1H), 8.73 (br, 1H), 8.80 (br, 1H).

Example 643

Synthesis of 1-ethyl-7-(3-{[2-(7-methoxy-2-oxo-3,4-dihydro-2H-quinolin-1-yl)ethyl]pyridin-3-ylmethylamino}propoxy)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

dihydrochloride

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (s, 3H), 1.02 (t, J = 7.0 Hz, 3H), 1.32 (s, 3H), 2.31 (br, 2H), 2.51-2.60 (m, 2H), 2.77-2.82 (m, 2H), 3.28 (br, 2H), 3.32 (s, 3H), 3.50-3.70 (m, 3H), 3.77 (s, 3H), 4.01-4.14 (m, 3H), 4.43 (br, 2H), 4.68 (br, 2H), 6.60 (dd, J = 2.0, 8.2 Hz, 1H), 6.79 (br, 1H), 6.91 (dd, J = 2.8, 9.0 Hz, 1H), 6.94 (d, J = 2.8 Hz, 1H), 7.14 (d, J = 8.2 Hz, 1H), 7.41 (d, J = 9.0 Hz, 1H), 7.90 (br, 1H), 8.67 (br, 1H), 8.87 (br, 1H), 9.12 (br, 1H).

Example 644

Synthesis of 2,4-dimethyl-thiazole-5-sulfonic acid [3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]-[2-(1-oxo-1H-isoquinolin-2-yl)ethyl]amide

Using an appropriate starting material and following the procedure of Example 4, the object compound was synthesized.

White powder

Melting Point 76 to 84°C

Example 645

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{[2-(4-oxo-2-trifluoromethyl-4H-furo[3,2-c]pyridin-5-yl)ethyl]pyridin-4-ylmethylamino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (s, 3H), 1.02 (t, J = 7.0 Hz, 3H), 1.32 (t, J = 7.5 Hz, 3H), 2.45-2.60 (m, 2H), 3.20-3.35 (m, 2H), 3.30 (s, 3H), 3.59-3.70 (m, 3H), 3.81 (br, 4H), 3.98-4.06 (m, 1H), 4.13 (br, 2H), 6.63-6.80 (m, 3H), 7.36 (d, J = 9.0 Hz, 1H), 7.61-7.87 (m, 4H), 8.65 (br, 2H).

Example 646

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{(2-methylpyridin-3-ylmethyl)-[2-(4-oxo-2-trifluoromethyl-4H-furo[3,2-c]

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pyridin-5-yl)ethyl]amino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (s, 3H), 1.02 (t, J = 7.0 Hz, 3H), 1.32 (s, 3H), 1.98 (br, 2H), 2.74 (br, 5H), 3.20-3.35 (m, 2H), 3.31 (s, 3H), 3.55-3.69 (m, 3H), 3.99-4.10 (m, 5H), 6.70-6.90 (m, 3H), 7.39 (d, J = 9.0 Hz, 1H), 7.76 (br, 3H), 8.26 (br, 1H), 8.59 (br, 1H).

Example 647

Synthesis of 7-(3-{(2,4-dimethylpyridin-3-ylmethyl)-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}propoxy)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

0.76 (s, 3H), 1.02 (t, J = 7.0 Hz, 3H), 1.33 (s, 3H), 1.99 (br, 2H), 2.43 (br, 3H), 2.62 (br, 3H), 2.73 (br, 4H), 3.33 (s, 3H), 3.61-3.70 (m, 3H), 3.90-4.10 (m, 5H), 6.59 (br, 1H), 6.82-6.92 (m, 3H), 7.40 (d, J = 9.0 Hz, 1H), 7.49 (br, 2H), 7.87 (br, 1H), 8.40 (br, 1H).

Example 648

Synthesis of 1-ethyl-3,3,5-trimethyl-7-{3-[[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-(2-trifluoromethylpyridin-3-ylmethyl)amino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.86 (s, 3H), 1.15 (t, J=7.1 Hz, 3H), 1.53 (s, 3H), 1.85-1.94 (m, 2H), 2.78 (t, J=7.2 Hz, 2H), 2.89 (t, J=6.2 Hz, 2H), 3.38 (s, 3H), 3.63-3.76 (m, 1H), 3.87-3.93 (m, 4H), 4.03-4.22 (m, 3H), 6.41-6.44 (m, 1H), 6.61 (d, J=2.7 Hz, 1H), 6.67 (dd, J=9.0 and 2.7 Hz, 1H), 6.94-6.95 (m, 1H), 7.01 - 7.08 (m, 2H), 7.19 (d, J=9.0 Hz, 1H), 7.50-7.51 (m, 1H), 7.79-7.81 (m, 1H), 8.46 (d, J=3.6 Hz, 1H).

Example 649

Synthesis of 1-ethyl-3,3,5-trimethyl-7-{3-[[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-(2-trifluoromethyl pyridin-3-ylmethyl)amino]propoxy}-1,5-dihydrobenzo[b][1,4] diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.86 (s, 3H), 1.15 (t, J=7.1 Hz, 3H), 1.53 (s, 3H), 1.87-1.95 (m, 2H), 2.43 (s, 3H), 2.78 (t, J=7.2 Hz, 2H), 2.88 (t, J=6.2 Hz, 2H), 3.38 (s, 3H), 3.63-3.76 (m, 1H), 3.86 (s, 2H), 3.92 (t, J=6.0 Hz, 2H), 4.05-4.22 (m, 3H), 6.34-6.37 (m, 1H), 6.53 (s, 1H), 6.63 (d, J=2.7 Hz, 1H), 6.68 (dd, J=9.0 and 2.7 Hz, 1H), 6.99 (d, J=7.4 Hz, 1H), 7.01-7.09 (m, 1H), 7.19 (d, J=9.0 Hz, 1H), 7.80-7.84 (m, 1H), 8.45 (d, J=3.6 Hz, 1H).

Example 650

Synthesis of 1-Ethyl-3,3,5-trimethyl-7-(3-{[3-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)propyl]pyridin-4-ylmethylamino} propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride dihydrochloride

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

0.76 (s, 3H), 1.02 (t, J = 7.0 Hz, 3H), 1.32 (s, 3H), 2.22 (br, 4H), 2.39 (s, 3H), 3.10 (br, 2H), 3.21 (br, 2H), 3.31 (s, 3H), 3.45-3.70 (m, 1H), 4.01-4.10 (m, 5H), 4.58 (br, 2H), 6.56 (s, 1H), 6.79 (d, J = 7.4 Hz, 1H), 6.87-6.92 (m, 2H), 7.40 (d, J = 9.0 Hz, 1H), 7.57 (d, J = 7.4 Hz, 1H), 8.08 (br, 2H), 8.82 (br, 2H).

Example 651

Synthesis of pyrazine-2-carboxylic acid [3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4] diazepin-7-yloxy)propyl]-(2-pyridin-3-ylethyl)amide hydrochloride

Using an appropriate starting material and following the procedure of Example 45, the object compound was synthesized.

^{1}H-NMR (DMSO-D_6) δppm:

0.75 (3H, s), 1.01 (3H, t, J=7.0 Hz), 1.32 (3H, s), 1.89-2.25(2H, m), 3.00-3.23 (2H, m), 3.29 and 3.32 (3H, s), 3.32-3.78 (4H, m), 3.78-3.95(2H, m), 3.95-4.29 (2H, m), 6.67-6.80 (1H, m), 6.92-7.[illegible], m), 7.36 and 7.42(1H, d, J=9.5Hz), 7.80 and 7.95(1H, dd, J=7.7 and 5.6 Hz), 8.14 and 8.48(1H, d, J=8.0 Hz), 8.52-9.02(5H, m)

Example 652

Synthesis of 1-ethyl-3,3,5-trimethyl-7-{3-[[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-(2,4,6-trimethylpyridin-3-ylmethyl)amino]propoxy}-1,5-dihydro-enzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

0.76 (s, 3H), 1.02 (t, J = 7.0 Hz, 3H), 1.33 (s, 3H), 2.00 (br, 2H), 2.36 (br, 3H), 2.43-2.62 (m, 6H), 2.76 (br, 4H), 3.33 (s, 3H), 3.55-3.68 (m, 3H), 3.95 (br, 2H), 4.03-4.11 (m, 3H), 6.59 (br, 1H), 6.80-6.94 (m, 3H), 7.27 (br, 1H), 7.39-7.47 (m, 2H), 7.89 (s, 1H).

Example 653

Synthesis of N-[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]-N-(2-pyridin-3-ylethyl)nicotinamide

Using an appropriate starting material and following the procedure of Example 459, the object compound was synthesized.

White powder

Melting Point 135.5 to 138.1°C

Example 654

Synthesis of N-[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]-N-pyridin-4-ylmethylnicotinamide 2.5 phosphate

Using an appropriate starting material and following the procedure of Example 633 and Example 458, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

0.75(3H, s), 1.00 (3H, t, J=7.0 Hz), 1.32 (3H, s), 1.82-2.27(2H, m), 3.29 (3H, s), 3.36-3.52 (2H, m), 3.52-4.25(4H, m), 4.57 and 4.78 (2H,

s), 6.53-7.09 (2H, m), 7.09-7.56(4H, m), 7.69-8.05 (1H, m), 8.37-8.88 (4H, m)

Example 655

Synthesis of thiazole-4-carboxylic acid [3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]-(2-pyridin-3-ylethyl)amide hydrochloride

Using an appropriate starting material and following the procedure of Example 45, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

0.74 (3H, s), 1.00 (3H, t, J=7.0 Hz), 1.32 (3H, s), 1.89-2.25(2H, m), 2.87-3.21 (2H, m), 3.31 (3H, s), 3.31-4.27 (8H, m), 6.74-6.94 (1H, m), 6.95-7.05 (1H, m), 7.28-7.47 (1H, m), 7.65-7.94 (1H, m), 8.01 (1H, bs), 8.06-8.50 (1H, m), 8.50-8.94 (2H, m), 9.05-9.22 (1H, m)

Example 656

Synthesis of N-[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]-2-pyridin-3-yl-N-pyridin-4-ylmethylacetamide 1.5 methanesulfonate

Benzotriazol-1-yloxytris(dimethylamino) phosphonium hexafluorophosphate (BOP) (0.3 g, 0.68 mmol) was added to a dichloromethane solution (6 ml) of 1-ethyl-3,3,5-trimethyl-7-{3-[(pyridin-4-ylmethyl)amino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione (0.39 g, 0.73 mmol), 3-pyridylacetic acid hydrochloride (0.14 g, 0.8 mmol), and triethylamine (0.31 ml, 2.2 mmol) while cooling in an ice-bath, and the mixture was stirred at room temperature overnight. Water was added to the reaction mixture, and extraction with dichloromethane was conducted. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue thus obtained was purified by medium pressure liquid chromatography (NH-silica gel, ethyl acetate:isopropyl alcohol=100:0→91:9). The purified product was concentrated under reduced pressure and the resultant residue was dissolved in ethanol (10 ml). Methanesulfonic acid (0.047 ml, 0.72 mmol) was added to the solution, and concentrated under reduced pressure. The resultant residue was washed with diethylether by decantation to thereby obtain 0.17 g (yield:35%) of N-[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-

2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]-2-pyridin-3-yl-N-pyridin-4-ylmethylacetamide 1.5 methanesulfonate as a pale yellow white amorphous solid.

^{1}H-NMR (DMSO-D_6) δppm:

0.73 (3H, s), 1.00 (3H, t, J=7.3 Hz), 1.32 (3H, s), 1.85-2.25(2H, m), 2.35 (4.5H, s), 3.29 and 3.30 (3H, s), 3.30-3.97 (2H, m), 3.97-4.27 (6H, m), 4.79 and 4.99 (2H, s), 6.82-7.04 (2H, m), 7.33-7.48 (1H, m), 7.54-7.95 (3H, m), 8.10-8.23 (1H, m), 8.57-8.90(4H, m)

Example 657

Synthesis of oxazole-4-carboxylic acid [3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]-(2-pyridin-3-ylethyl)amide hydrochloride

Using an appropriate starting material and following the procedure of Example 45, the object compound was synthesized.

^{1}H-NMR (DMSO-D_6) δppm:

0.74 (3H, s), 1.00 (3H, t, J=7.3 Hz), 1.32 (3H, s), 1.98-2.25(2H, m), 3.03-3.21 (2H, m), 3.31 (3H, s), 3.40-4.22 (8H, m), 6.74-7.05 (2H, m), 7.31-7.47 (1H, m), 7.75-8.03 (1H, m), 8.32 (1H, d, J=7.3 Hz), 8.37-8.60 (2H, m), 8.60-8.97 (2H, m)

Example 658

Synthesis of thiophene-3-carboxylic acid [3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]-(2-pyridin-3-ylethyl)amide hydrochloride

Using an appropriate starting material and following the procedure of Example 633, the object compound was synthesized.

^{1}H-NMR (DMSO-D_6) δppm:

0.74 (3H, s), 1.00 (3H, t, J=7.2 Hz), 1.32 (3H, s), 1.88-2.25(2H, m), 3.09 (2H, bs), 3.31 (3H, s), 3.32-4.30 (8H, m), 6.64-7.18 (3H, m), 7.39 (1H, d, J=9.3 Hz), 7.55 (1H, dd, J=4.9 and 2.9 Hz), 7.62 (1H, bs), 7.67-8.22 (1H, m), 8.22-.18 (3H, m)

Example 659

Synthesis of furan-2-carboxylic acid [3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]-(2-pyridin-3-ylethyl)amide hydrochloride

Using an appropriate starting material and following the

procedure of Example 633, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

0.74 (3H, s), 1.01 (3H, t, J=7.0 Hz), 1.32 (3H, s), 1.92-2.12 (2H, m), 3.01-3.21 (2H, m), 3.31 (3H, s), 3.30-3.90 (5H, m), 4.00-4.15 (3H, m), 6.56-6.62 (1H, m), 6.85-7.00 (3H, m), 7.36-7.45 (1H, m), 7.78 (1H, s), 7.85-8.00 (1H, m), 8.38 (1H, bs), 8.74 (1H, d, J=5.3 Hz), 8.82 (1H, bs)

Example 660

Synthesis of 1,3,3,5-tetramethyl-7-{3-[(pyridin-4-ylmethyl) amino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 77, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.87 (3H, s), 1.53 (3H, s), 1.92-2.10 (2H, m), 2.84 (2H, t, J=6.8 Hz), 3.39 (3H, s), 3.41 (3H, s), 3.85 (2H, s), 4.08 (2H, t, J=6.2), 6.71 (1H, d, J=2.7 Hz), 6.80 (1H, dd, J=2.7 and 9.0 Hz), 7.14 (1H, d, J=9.0), 7.20-7.34 (2H, m), 8.45-8.65 (2H, m).

Example 661

Synthesis of 1-ethyl-7-{2-hydroxy-3-[2-(1-oxo-1H-isoquinolin-2-yl)ethylamino]propoxy}-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.84 (3H, s), 1.14 (3H, t, J=7.0 Hz), 1.52 (3H, s), 2.75-3.04 (2H, m), 3.11 (2H, t, J=6.1 Hz), 3.78 (3H, s), 3.59-3.79 (1H, m), 3.89-4.29 (6H, m), 6.52 (1H, d, J=7.3 Hz), 6.68-6.86 (2H, m), 7.11 (1H, d, J=7.3 Hz), 7.18 (1H, d, J=8.7 Hz), 7.43-7.57 (2H, m), 7.57-7.74 (1H, m), 8.42 (1H, d, J=8.2 Hz).

Example 662

Synthesis of 1-ethyl-3,3,5-trimethyl-7-{3-[(pyridin-3-ylmethyl)amino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 77, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.86 (3H, s), 1.14 (3H, t, J=7.1 Hz), 1.52 (3H, s), 1.96-2.06 (2H, m), 2.85 (2H, t, J=6.8 Hz), 3.39 (3H, s), 3.65-3.74 (1H, m), 3.85 (2H, s), 4.07 (2H, t, J=6.1 Hz), 4.10-4.21 (1H, m), 6.71 (1H, d, J=2.8 Hz), 6.80 (1H, dd, J=9.0 and 2.8 Hz), 7.19 (1H, d, J=9.0 Hz), 7.22-7.29 (1H, m), 7.65-7.68 (1H, m), 8.50 (1H, d, J=1.6 Hz), 8.58-8.61 (1H, m)

Example 663

Synthesis of 1-ethyl-3,3,5-trimethyl-7-{3-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethylamino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 18, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.85 (3H, s), 1.14 (3H, t, J=7.1 Hz), 1.52 (3H, s), 1.92-2.00 (2H, m), 2.41 (3H, s), 2.88 (2H, t, J=6.8 Hz), 3.03 (2H, t, J=6.2 Hz) 3.39 (3H, s), 3.62-3.74 (1H, m), 4.02 (2H, t, J=6.1 Hz), 4.14 (2H, t, J=6.2 Hz), 4.16-4.22 (1H, m), 6.42 (1H, d, J=9.0 Hz), 6.54 (1H, s), 6.70 (1H, d, J=2.7 Hz), 6.72-6.82 (1H, m), 7.13-7.20 (2H, m)

Example 664

Synthesis of 1-ethyl-3,3,5-trimethyl-7-{3-[(pyridin-2-ylmethyl)amino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 77, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.86 (3H, s), 1.14 (3H, t, J=7.1 Hz), 1.52 (3H, s), 2.03-2.09 (2H, m), 2.91 (2H, t, J=6.7 Hz), 3.48 (3H, s), 3.64-3.76 (1H, m), 3.97 (2H, s), 4.10 (2H, t, J=6.2 Hz), 4.14-4.23 (1H, m), 6.73 (1H, d, J=2.7 Hz), 6.82 (1H, dd, J=9.0 and 2.7 Hz), 7.16-7.21 (2H, m), 7.27-7.32 (1H, m), 7.85 (1H, td, J=7.7, 1.8 Hz), 8.58-8.56 (1H, m)

Example 665

Synthesis of 1-ethyl-3,3,5-trimethyl-7-[3-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethylamino]propoxy}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 18, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.86 (3H, s), 1.14 (3H, t, J= 7.1 Hz), 1.52 (3H, s), 1.91-2.00 (2H, m), 2.85 (2H, t, J= 6.7 Hz), 3.03 (2H, t, J= 6.2 Hz), 3.39 (3H, s),3.66-3.76 (1H, m), 4.02 (2H, t, J= 6.1 Hz), 4.09-4.24 (3H, m), 6.48 (1H, d, J= 7.4 Hz), 6.69 (1H, d, J= 2.8 Hz), 6.76 (1H, dd, J= 9.0, 2.8 Hz), 6.97 (1H, d, J=2.0 Hz), 7.16-7.24 (2H, m), 7.48 (1H, d, J=2.1 Hz)

Example 666

Synthesis of 1-ethyl-3,3,5-trimethyl-7-{3-[(2-methylpyridin-3-ylmethyl)amino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 77, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.86 (3H, s), 1.14 (3H, t, J = 7.0 Hz), 1.53 (3H, s), 1.98-2.07 (2H, m), 2.57 (3H, s), 2.89 (2H, t, J= 6.8 Hz), 3.39 (3H, s),3.62-3.73 (1H, m), 3.82 (2H,s), 4.07-4.21 (3H, m), 6.71 (1H, d, J= 2.8 Hz), 6.80 (1H, dd, J=9.0 and 2.8 Hz), 7.10 (1H, dd, J = 7.7 and 4.9 Hz), 7.20 (1H, d, J = 9.0 Hz), 7.59-7.62 (1H, m), 8.38-8.41 (1H, m)

Example 667

Synthesis of 1-ethyl-3,3,5-trimethyl-7-{3-[(6-methylpyridin-3-ylmethyl)amino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 77, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.86 (3H, s), 1.14 (3H, t, J=7.1 Hz), 1.52 (3H, s), 1.95-2.07 (2H, m), 2.54 (3H, s), 2.84 (2H, t, J=6.8 Hz), 3.39 (3H, s),3.64-3.76 (1H, m), 3.80 (2H,s), 4.04-4.20 (3H, m), 6.71 (1H, d, J=2.8 Hz), 6.79 (1H, dd, J=9.0 and 2.8 Hz), 7.11 (1H, d, J=7.9 Hz), 7.19 (1H, d, J=9.0 Hz), 7.56 (1H, dd, J=7.9 and 2.3 Hz), 8.44-8.45 (1H, m)

Example 668

Synthesis of 1-ethyl-7-[3-(4-methoxybenzylamino)propoxy]

-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 77, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.86(3H, s), 1.14 (3H, t, J=7.0 Hz), 1.52 (3H, s), 2.00 (2H, quin, J=6.5 Hz), 2.83(2H, t, J=6.5 H), 3.39 (3H, s), 3.70 (1H, dq, J=7.0, 7.0 Hz), 3.76 (2H, s), 3.80 (3H, s), 4.07(2H, t, J=6.5 Hz), 4.18 (1H, dq, J=7.0, 7.0 Hz), 6.71 (1H, d, J=2.7 Hz), 6.80 (1H, dd, J=2.7 and 9.0 Hz), 6.86 (2H, d, J=8.5 Hz), 7.19 (1H, d, J=9.0 Hz), 7.24 (2H, d, J=8.5 Hz)

Example 669

Synthesis of 1-ethyl-3,3,5-trimethyl-7-{3-[(5-methylpyridin-3-ylmethyl)amino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 77, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.86 (3H, s), 1.14 (3H, t, J=7.1 Hz), 1.50 (3H, s), 1.98-2.05 (2H, m), 2.32 (3H, s), 2.85 (2H, t, J=6.8 Hz), 3.39 (3H, s),3.62-3.72 (1H, m), 3.81 (2H,s), 4.05-4.17 (3H, m), 6.71 (1H, s), 6.80 (1H, dd, J=9.0 and 2.8 Hz), 7.19 (1H, d, J=9.0 Hz), 7.48 (1H, s), 8.34-8.38 (2H, m)

Example 670

Synthesis of 1-ethyl-7-{3-[(2-ethylpyridin-3-ylmethyl)amino]propoxy}-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 77, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.86 (3H, s), 1.14 (3H, t, J = 7.1 Hz), 1.29 (3H, t, J = 7.5 Hz), 1.52 (3H, s), 1.99-2.05 (2H, m), 2.82-2.91 (4H, m), 3.39 (3H, s),3.62-3.75 (1H, m), 3.84 (2H,s), 4.09 (2H, t, J=6.2 Hz) 4.10-4.23 (1H, m), 6.71 (1H, d, J = 2.8 Hz), 6.80 (1H, dd, J = 9.0 and 2.8 Hz), 7.09 (1H, dd, J = 7.6 and 4.9 Hz), 7.20 (1H, d, J = 9.0 Hz), 7.63 (1H, d, J = 7.7 Hz), 8.43-8.46 (1H, m)

Example 671

Synthesis of 1-ethyl-3,3,5-trimethyl-7-{3-[(2-propylpyridin-3-ylmethyl)amino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 77, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.86 (3H, s), 0.99 (3H, t, J=7.4 Hz), 1.14 (3H, t, J=7.1 Hz), 1.52 (3H, s), 1.69-1.81 (2H, m), 1.99-2.07 (2H, m), 2.77-2.90 (4H, m), 3.39 (3H, s), 3.60-3.73 (1H, m), 3.84 (2H,s), 4.06-4.23 (3H, m), 6.72 (1H, s), 6.79 (1H, dd, J=9.0 and 2.8 Hz), 7.06-7.09 (1H, m), 7.20 (1H, d, J=8.0 Hz), 7.63 (1H, d, J=7.7 Hz), 8.42-8.45 (1H, m)

Example 672

Synthesis of 1-ethyl-3,3,5-trimethyl-7-{4-[(2-methylpyridin-3-ylmethyl)amino]butoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 77, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.86 (3H, s), 1.14 (3H, t, J=7.1 Hz), 1.54 (3H, s), 1.67-1.75 (2H, m), 1.85-1.92 (2H, m), 2.58 (3H, s), 2.76 (2H, t, J=7.0 Hz), 3.39 (3H, s), 3.60-3.77 (1H, m), 3.80 (2H,s), 3.99 (2H, t, J=6.3 Hz), 4.11-4.22 (1H, m), 6.74 (1H, s), 6.79 (1H, dd, J=8.9 and 2.8 Hz), 7.10 (1H, dd, J=7.6 and 4.9 Hz), 7.19 (1H, d, J=9.0 Hz), 7.61 (1H, d, J=6.1 Hz), 8.38-8.41 (1H, m)

Example 673

Synthesis of 1-ethyl-3,3,5-trimethyl-7-{4-[(pyridin-4-ylmethyl)amino]butoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 77, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.86 (3H, s), 1.14 (3H, t, J=7.1 Hz), 1.52 (3H, s), 1.64-1.78 (2H, m), 1.83-1.95 (2H, m), 2.72 (2H, t, J=7.1 Hz), 3.39 (3H, s), 3.63-3.73 (1H, m), 3.84 (2H,s), 3.99 (2H, t, J=6.3 Hz), 4.09-4.21 (1H, m), 6.71 (1H, s), 6.79 (1H, dd, J=9.0 and 2.8 Hz), 7.19 (1H, d, J=9.0 Hz), 7.26-7.29 (2H, m), 8.55 (2H, dd, J=4.4 and 1.6 Hz)

Example 674

Synthesis of 1-ethyl-3,3,5-trimethyl-7-{3-[(pyridazin-4-ylmethyl)amino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 77, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.86 (3H, s), 1.15 (3H, t, J=7.1 Hz), 1.52 (3H, s), 1.97-2.06 (2H, m), 2.85 (2H, t, J=6.7 Hz), 3.40 (3H, s), 3.65-3.75 (1H, m), 3.90 (2H, s), 4.09 (2H, t, J=6.0 Hz), 4.10-4.22 (1H, m), 6.71 (1H, d, J=2.8 Hz), 6.80 (1H, dd, J=9.0 and 2.8 Hz), 7.21 (1H, d, J=9.0 Hz), 7.46-7.49 (1H, m), 9.11 (1H, dd, J=5.2 and 1.2 Hz), 9.21 (1H, s)

Example 675

Synthesis of 7-{3-[(2,6-dimethylpyridin-3-ylmethyl)amino]propoxy}-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 77, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.86 (3H, s), 1.14 (3H, t, J=7.1 Hz), 1.52 (3H, s), 1.97-2.05 (2H, m), 2.50 (3H, s), 2.54 (3H, s), 2.87 (2H, t, J=6.7 Hz), 3.39 (3H, s), 3.60-3.77 (1H, m), 3.78 (2H, s), 4.06-4.24 (3H, m), 6.71 (1H, s), 6.80 (1H, dd, J=9.0 and 2.8 Hz), 6.95 (1H, d, J=7.3 Hz), 7.20 (1H, d, J=9.0 Hz), 7.48 (1H, d, J=7.7 Hz),

Example 676

Synthesis of 1-ethyl-3,3,5-trimethyl-7-{2-[(2-methylpyridin-3-ylmethyl)amino]ethoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 77, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.85 (3H, s), 1.14 (3H, t, J=7.1 Hz), 1.52 (3H, s), 2.59 (3H, s), 3.02-3.10 (2H, m), 3.39 (3H, s), 3.65-3.76 (1H, m), 3.89 (2H, s), 4.09-4.21 (3H, m), 6.73-6.75 (1H, m), 6.80-6.85 (1H, m), 7.10-7.14 (1H, m), 7.19-7.23 (1H, m), 7.65 (1H, dd, J=7.7 and 1.5 Hz), 8.40-8.42 (1H, m)

Example 677

Synthesis of N-[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]-N-[2-(1-oxo-1H-isoquinolin-2-yl)ethyl]nicotinamide

Using an appropriate starting material and following the procedure of Example 459, the object compound was synthesized.

White amorphous

^{1}H-NMR ($CDCl_3$) δppm:

0.82 (3H, s), 1.13 (3H, t, J= 7.0 Hz), 1.51 (3H, s), 1.88-2.45 (2H, m), 3.37 (3H, s), 3.42-3.60 (2H, m), 3.60-3.90 (3H, m), 3.95 (2H, t, J= 6.2 Hz), 4.01-4.27 (1H, m), 4.40 (2H, t, J= 6.2 Hz), 6.40-6.67 (2H, m), 667- 7.43(4H, m), 7.43-7.61 (2H, m), 7.61-7.76 (2H, m), 8.13-8.78 (3H, m)

Example 678

Synthesis of N-[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]-2-methyl-N-(2-pyridin-3-ylethyl)benzamide hydrochloride

Using an appropriate starting material and following the procedure of Example 633, the object compound was synthesized.

White powder

Melting Point 155.3 to 159.3°C (dec.)

Example 679

Synthesis of N-[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]-2-methoxy-N-(2-pyridin-3-ylethyl)isonicotinamide

Using an appropriate starting material and following the procedure of Example 459, the object compound was synthesized.

White powder

Melting Point 112.8 to 113.9°C

Example 680

Synthesis of cyclohexanecarboxylic acid [3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]-(2-pyridin-3-ylethyl)amide hydrochloride

Using an appropriate starting material and following the procedure of Example 633, the object compound was synthesized.

White powder

Melting Point 153.4 to 157.5°C (dec.)

Example 681

Synthesis of N-[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)-propyl]-N-(2-pyridin-3-yl-ethyl)-acetamide hydrochloride

Using an appropriate starting material and following the procedure of Example 633, the object compound was synthesized.

White amorphous

^{1}H-NMR (DMSO-d_6) δppm:

0.73 and 0.74(3H, s), 1.01(3H, t, J=7.0 Hz), 1.32 (3H, s), 1.85-2.12 (2H, m), 1.93 and 1.95(3H, s), 2.92-3.11 (2H, m), 3.12-3.95 (5H, m), 3.32 (3H, s), 3.95-4.16(3H, m), 6.88-7.00 (2H, m), 7.40 (1H, dd, J=8.8 and 2.7 Hz), 7.89 (1H, dt, J=8.1 and 5.5Hz), 8.36 (1H, d, J=8.1Hz,), 8.74 (1H, d, J=5.5 Hz), 8.77-8.86(1H, m)

Example 682

Synthesis of 7-(4-amino-butoxy)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 2, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.86 (3H, s), 1.14 (3H, t, J= 7.1 Hz), 1.52 (3H, s), 1.60-1.70 (2H, m), 1.82-1.90 (2H, m), 2.80 (2H, t, J= 7.0 Hz), 3.40 (3H, s), 3.64-3.76 (1H, m), 4.00 (2H, t, J= 6.3 Hz), 4.12-4.24 (1H, m), 6.72 (1H, d, J= 2.7 Hz), 6.81 (1H, dd, J= 9.0 and 2.7 Hz), 7.20 (1H, d, J= 9.0 Hz)

Example 683

Synthesis of 7-(2-amino-ethoxy)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 2, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

0.86 (3H, s), 1.15 (3H, t, J= 7.1 Hz), 1.53 (3H, s), 3.13 (2H, t, J= 5.1 Hz), 3.40 (3H, s), 3.47-3.76 (1H, m), 4.01 (2H, t, J= 5.1 Hz), 4.11-4.24 (1H, m), 6.75 (1H, d, J= 2.8 Hz), 6.83 (1H, dd, J= 9.0 and 2.8 Hz), 7.21 (1H, d, J= 9.0 Hz)

Example 684

Synthesis of 1,5-dimethyl-7-{3-[[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-(2-methylpyridin-3-ylmethyl)amino]propoxy}spiro[benzo[b][1,4]diazepine-3,1'-cyclobutane]-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

1.64 (br, 4H), 2.28 (br, 2H), 2.42 (s, 3H), 2.49 (s, 3H), 2.75 (br, 2H), 2.84-2.88 (m, 4H), 3.39 (s, 3H), 3.40 (s, 3H), 3.64 (br, 2H), 3.89 (br, 2H), 4.00 (br, 2H), 6.33-6.35 (m, 1H), 6.51 (br, 1H), 6.56-6.69 (m, 2H), 6.89-6.92 (m, 2H), 7.47 (br, 1H), 8.32 (br, 2H).

Example 685

Synthesis of 7-[3-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)propoxy]-1,5-dimethylspiro[benzo[b][1,4]diazepine-3,1'-cyclobutane]-2,4-dione

Using an appropriate starting material and following the procedure of Example 1, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

1.57-1.67 (m, 4H), 2.11-2.23 (m, 2H), 2.78-2.90 (m, 2H), 3.35 (s, 3H), 3.37 (s, 3H), 3.93 (t, J=6.7 Hz, 2H), 4.05 (t, J=5.9 Hz, 2H), 6.61 (d, J=2.8 Hz, 1H), 6.71 (dd, J=9.0 and 2.8 Hz, 1H), 7.12 (d, J=9.0 Hz, 1H), 7.71-7.75 (m, 2H), 7.83-7.86 (m, 2H).

Example 686

Synthesis of 7-(3-Aminopropoxy)-1,5-dimethylspiro[benzo[b][1,4]diazepine-3,1'-cyclobutane]-2,4-dione

Using an appropriate starting material and following the procedure of Example 2, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

1.63-1.68 (m, 4H), 1.96-2.01 (m, 2H), 2.78-2.83 (m, 2H), 2.93 (t, J=6.7 Hz, 2H), 3.38 (s, 3H), 3.42 (s, 3H), 4.07 (t, J=6.2 Hz, 2H), 6.74 (d, J=2.7 Hz, 1H), 6.80 (dd, J=8.9 and 2.7 Hz, 1H), 7.16 (d, J=8.9 Hz, 1H).

Example 687

Synthesis of

1,5-Dimethyl-7-{3-[(2-methylpyridin-3-ylmethyl)amino]propoxy}spiro[benzo[b][1,4]diazepine-3,1'-cyclobutane]-2,4-dione

Using an appropriate starting material and following the procedure of Example 77, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

1.62-1.68 (m, 4H), 2.00-2.05 (m, 2H), 2.57 (s, 3H), 2.82-2.91 (m, 4H), 3.39 (s, 3H), 3.41 (s, 3H), 3.82 (s, 2H), 4.08 (t, J=6.1 Hz, 2H), 6.73 (d, J=2.7 Hz, 1H), 6.79 (dd, J=8.9 and 2.7 Hz, 1H), 7.10 (dd, J=7.6 and 4.9 Hz, 1H), 7.16 (d, J=8.9 Hz, 1H), 7.62 (dd, J=7.6 and 1.4 Hz, 1H), 8.40 (dd, J=4.9 and 1.4 Hz, 1H).

Example 688

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{[2-(1-oxo-1H-isoquinolin-2-yl)ethyl]thiazol-2-ylmethylamino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 6, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm: 0.75 (s, 3H), 1.01 (t, J = 7.0 Hz, 3H), 1.32 (s, 3H), 2.20 (br, 2H), 3.30 (s, 3H), 3.21-3.58 (m, 4H), 3.61-3.71 (m, 1H), 4.00-4.11 (m, 3H), 4.42 (br, 2H), 4.81 (br, 2H), 6.69 (d, J = 7.0 Hz, 1H), 6.82-6.89 (m, 2H), 7.38 (d, J = 9.0 Hz, 1H), 7.50-7.54 (m, 2H), 7.66-7.75 (m, 2H), 7.89 (br, 2H), 8.21 (d, J = 8.0 Hz, 1H).

Example 689

Synthesis of

1-ethyl-7-(3-{(3-fluorobenzyl)-[2-(1-oxo-1H-isoquinolin-2-yl)ethyl]amino}propoxy)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione hydrochloride

Using an appropriate starting material and following the procedure of Example 6, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (s, 3H), 1.01 (t, J = 7.0 Hz, 3H), 1.32 (s, 3H), 2.29 (br, 2H), 3.31 (s, 3H), 3.50 (br, 4H), 3.61-3.68 (m, 1H), 4.02-4.18 (m, 3H), 4.48-4.60 (m, 4H), 6.72 (d, J = 7.2 Hz, 1H), 6.85-6.90 (m, 2H), 7.30-7.42 (m, 2H), 7.46-7.81 (m, 7H), 8.23 (d, J = 8.0 Hz, 1H).

Example 690

Synthesis of

1-ethyl-7-(3-{(3-methoxybenzyl)-[2-(1-oxo-1H-isoquinolin-2-yl)ethyl]amino}propoxy)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione hydrochloride

Using an appropriate starting material and following the procedure of Example 6, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (s, 3H), 1.01 (t, J = 7.0 Hz, 3H), 1.32 (s, 3H), 2.27 (br, 2H), 3.21-3.30 (m, 5H), 3.42 (s, 3H), 3.51 (br, 2H), 3.61-3.72 (m, 1H), 4.02-4.18 (m, 3H), 4.38-4.61 (m, 4H), 6.73 (d, J = 7.2 Hz, 1H), 6.86-6.90 (m, 2H), 7.01 (d, J = 8.8 Hz, 1H), 7.18 (d, J = 7.6 Hz, 1H), 7.31-7.42 (m, 3H), 7.51-7.56 (m, 2H), 7.68-7.77 (m, 2H), 8.21 (d, J = 8.0 Hz, 1H).

Example 691

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{[2-(1-oxo-1H-isoquinolin-2-yl)ethyl]thiophen-2-ylmethylamino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione hydrochloride

Using an appropriate starting material and following the procedure of Example 6, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (s, 3H), 1.01 (t, J = 7.0 Hz, 3H), 1.32 (s, 3H), 2.29 (br, 2H), 3.21-3.29 (m, 5H), 3.49 (br, 4H), 3.62-3.70 (m, 1H), 4.01-4.29 (m, 3H), 4.48 (br, 2H), 6.72 (d, J = 7.1 Hz, 1H), 6.86-6.93 (m, 2H), 7.15 (br, 1H), 7.40 (d, J = 8.9 Hz, 1H), 7.50-7.55 (m, 3H), 7.67-7.74 (m, 3H), 8.21 (d, J = 8.0 Hz, 1H).

Example 692

Synthesis of 7-(3-{bis-[2-(1-oxo-1H-isoquinolin-2-yl)ethyl]amino}propoxy)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione hydrochloride

Using an appropriate starting material and following the procedure of Example 6, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

0.74 (s, 3H), 1.00 (t, J = 7.0 Hz, 3H), 1.32 (s, 3H), 2.28 (br, 2H), 3.29 (s, 3H), 3.61 (br, 2H), 3.61-3.71(m, 5H), 3.95-4.09 (m, 1H), 4.17 (br, 2H), 4.45 (br, 4H), 6.71-6.74 (m, 2H), 6.91-6.97 (m, 2H), 7.40 (d, J = 9.0 Hz, 1H), 7.49-7.57 (m, 4H), 7.67-7.74 (m, 4H), 8.15 (d,

J = 8.2 Hz, 2H).

Example 693

Synthesis of 1-ethyl-7-(3-{[2-(7-methoxy-2-oxo-3,4-dihydro-2H-quinolin-1-yl)ethyl]pyridin-4-ylmethylamino}propoxy)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 6, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

0.74 (s, 3H), 1.00 (t, J = 7.0 Hz, 3H), 1.32 (s, 3H), 2.25 (br, 4H), 3.01-3.31 (m, 4H), 3.31 (s, 3H), 3.61-3.70 (m, 1H), 4.00-4.12 (m, 5H), 4.61 (br, 2H), 6.65 (d, J = 7.4 Hz, 1H), 6.86-6.91 (m, 2H), 7.39 (d, J = 8.9 Hz, 1H), 7.47-7.53 (m, 2H), 7.65-7.74 (m, 2H), 8.08 (br, 2H), 8.21 (d, J = 8.0 Hz, 1H), 8.80 (br, 2H).

Example 694

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{[2-(2-oxo-2H-quinolin-1-yl)ethyl]pyridin-4-ylmethylamino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 6, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

0.74 (s, 3H), 1.00 (t, J = 7.0 Hz, 3H), 1.32 (s, 3H), 2.28 (br, 2H), 3.21-3.49 (m, 5H), 3.60-3.70 (m, 3H), 4.01-4.19 (m, 3H), 4.78 (br, 4H), 6.64 (d, J = 7.4 Hz, 1H), 6.88 (br, 2H), 7.30 (br, 1H), 7.39 (d, J = 8.9 Hz, 1H), 7.55-8.20 (m, 6H), 8.82 (br, 2H).

Example 695

Synthesis of 1-ethyl-7-{3-[(2-(6-methoxy-2-oxo-2H-quinolin-1-yl)ethyl)pyridin-4-ylmethylamino]propoxy}-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 6, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

0.74 (s, 3H), 1.00 (t, J = 7.0 Hz, 3H), 1.32 (s, 3H), 2.17 (br, 2H), 3.01-3.35 (m, 5H), 3.53-3.70 (m, 3H), 3.82 (s, 3H), 4.01-4.12 (m, 3H), 4.67 (br, 4H), 6.63 (d, J = 7.4 Hz, 1H), 6.83 - 6.89 (m, 2H), 7.21

(d, J = 9.2 Hz, 1H), 7.32 (s, 1H), 7.39 (d, J = 9.0 Hz, 1H), 7.70 (br, 1H), 7.91 (d, J = 9.5 Hz, 1H), 8.00 (br, 2H), 8.82 (br, 2H).

Example 696

Synthesis of 1-ethyl-7-(3-{[2-(6-methoxyquinolin-2-yloxy) ethyl]pyridin-4-ylmethylamino}propoxy)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione trihydrochloride

Using an appropriate starting material and following the procedure of Example 6, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

0.74 (s, 3H), 1.00 (t, J = 7.0 Hz, 3H), 1.32 (s, 3H), 2.09 (br, 2H), 3.01 (br, 2H), 3.31 (s, 3H), 3.70-3.90 (m, 4H), 3.98-4.18 (m, 5H), 4.33 (br, 2H), 4.80 (br, 2H), 6.50 (d, J = 9.6 Hz, 1H), 6.79-6.90 (m, 2H), 7.21-7.25 (m, 1H), 7.30-7.39 (m, 2H), 7.85 (d, J = 9.6 Hz, 1H), 8.20 (d, J = 8.9 Hz, 1H), 8.21 (br, 2H), 8.88 (br, 2H).

Example 697

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{[2-(2-oxo-3,4-dihydro-2H-quinolin-1-yl)ethyl]pyridin-4-ylmethylamino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 6, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

0.74 (s, 3H), 1.00 (t, J = 7.0 Hz, 3H), 1.32 (s, 3H), 2.10 (br, 2H), 2.51-2.60 (m, 2H), 2.85 (br, 4H), 3.31 (s, 3H), 3.10-3.35 (m, 2H), 3.52-3.70 (m, 3H), 4.01-4.11 (m, 3H), 4.22 (br, 2H), 6.85-6.89 (m, 2H), 7.00-7.02 (m, 1H), 7.13 (br, 1H), 7.19-7.24 (m, 2H), 7.40 (d, J = 8.8 Hz, 1H), 7.82 (br, 2H), 8.73 (br, 2H).

Example 698

Synthesis of 1-ethyl-3,3,5-trimethyl-7-{3-[(2-(4-oxo-4H-thieno[3,2-c]pyridin-5-yl)ethyl)pyridin-4-ylmethylamino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 6, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

0.74 (s, 3H), 1.00 (t, J = 7.0 Hz, 3H), 1.32 (s, 3H), 2.08 (br, 2H), 3.05 (br, 2H), 3.31 (s, 3H), 3.53-3.70 (m, 1H), 3.95-4.09 (m, 5H),

4.31 (br, 4H), 6.71-6.83 (m, 2H), 6.95 (br, 1H), 7.39 (d, J = 8.9 Hz, 1H), 7.45-7.47 (m, 1H), 7.57-7.64 (m, 2H), 7.88 (br, 2H), 8.72 (br, 2H).

Example 699

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{[2-(7-oxo-7H-thieno[2,3-c]pyridin-6-yl)ethyl]pyridin-4-ylmethylamino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 6, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

0.74 (s, 3H), 1.00 (t, J = 7.0 Hz, 3H), 1.32 (s, 3H), 2.32 (br, 2H), 3.33 (s, 3H), 3.26-3.37 (m, 2H), 3.43 (br, 2H), 3.62-3.70 (m, 1H), 4.00-4.13 (m, 3H), 4.53 (br, 2H), 4.82 (br, 2H), 6.82-6.89 (m, 2H), 6.92 - 6.93 (m, 1H), 7.38-7.42 (m, 2H), 7.69 (d, J = 7.2 Hz, 1H), 8.09 (d, J = 5.2 Hz, 1H), 8.44 (br, 2H), 9.00 (br, 2H).

Example 700

Synthesis of 1-ethyl-7-(3-{[2-(8-methoxy-2-oxo-2H-quinolin-1-yl)ethyl]pyridin-4-ylmethylamino}propoxy)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 6, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

0.74 (s, 3H), 1.01 (t, J = 7.0 Hz, 3H), 1.32 (s, 3H), 2.33 (br, 2H), 3.32 (s, 3H), 3.25-3.38 (m, 2H), 3.53-3.69 (m, 3H), 3.86 (s, 3H), 4.03-4.10 (m, 1H), 4.14 (br, 2H), 4.65 (br, 2H), 4.81 (br, 2H), 6.64 (d, J = 9.4 Hz, 1H), 6.89-6.95 (m, 2H), 7.21-7.33 (m, 3H), 7.41 (d, J = 8.9 Hz, 1H), 7.92 (d, J = 9.4 Hz, 1H), 8.14 (br, 2H), 8.68 (br, 2H).

Example 701

Synthesis of 1-ethyl-7-(3-{[2-(8-methoxyquinolin-2-yloxy)ethyl]pyridin-4-ylmethylamino}propoxy)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione trihydrochloride

Using an appropriate starting material and following the procedure of Example 6, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

0.74 (s, 3H), 1.00 (t, J = 7.0 Hz, 3H), 1.32 (s, 3H), 2.26 (br, 2H), 3.15-3.21 (m, 2H), 3.31 (s, 3H), 3.58-3.65 (m, 1H), 3.90 (s, 3H), 3.98-4.12 (m, 5H), 4.51-4.80 (m, 4H), 6.52 (d, J = 9.6 Hz, 1H), 6.83-6.89 (m, 2H), 7.08-7.11 (m, 1H), 7.19-7.21 (m, 1H), 7.32-7.48 (m, 2H), 7.89 (d, J = 9.6 Hz, 1H), 8.00 (br, 2H), 8.80 (br, 2H).

Example 702

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]pyridin-4-ylmethylamino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 6, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

0.74 (s, 3H), 1.01 (t, J = 7.0 Hz, 3H), 1.32 (s, 3H), 2.16 (br, 2H), 3.09 (br, 2H), 3.31 (s, 3H), 3.60-3.75 (m, 3H), 3.91-4.08 (m, 3H), 4.38 (br, 4H), 6.77-6.87 (m, 3H), 6.94 (br, 1H), 7.39 (d, J = 9.0 Hz, 1H), 7.70 (br, 1H), 7.90 (br, 1H), 8.11 (br, 2H), 8.84 (br, 2H).

Example 703

Synthesis of 1-ethyl-7-(3-{[2-(6-methoxy-2-oxo-3,4-dihydro-2H-quinolin-1-yl)ethyl]pyridin-4-ylmethylamino}propoxy)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 6, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

0.74 (s, 3H), 1.01 (t, J = 7.0 Hz, 3H), 1.32 (s, 3H), 2.16 (br, 2H), 2.48-2.54 (m, 2H), 2.77 (br, 2H), 3.31 (s, 3H), 3.25-3.34 (m, 2H), 3.53-3.69 (m, 3H), 3.76 (s, 3H), 3.98-4.10 (m, 3H), 4.33 (br, 2H), 4.74 (br, 2H), 6.60 (d, J = 8.3 Hz, 1H), 6.74 (br, 1H), 6.82-6.91 (m, 2H), 7.13 (d, J = 8.3 Hz, 1H), 7.40 (d, J = 9.0 Hz, 1H), 7.98 (br, 2H), 8.80 (br, 2H).

Example 704

Synthesis of 1-ethyl-7-(3-{[2-(7-methoxy-2-oxo-3,4-dihydro-2H-quinolin-1-yl)ethyl]pyridin-4-ylmethylamino}propoxy)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the

procedure of Example 6, the object compound was synthesized.

^{1}H-NMR (DMSO-d_6) δppm:

0.74 (s, 3H), 1.01 (t, J = 7.0 Hz, 3H), 1.32 (s, 3H), 2.22 (br, 2H), 2.48-2.53 (m, 2H), 2.83 (br, 2H), 3.10-3.25 (m, 2H), 3.31 (s, 3H), 3.53-3.63 (m, 3H), 3.73 (s, 3H), 4.00-4.10 (m, 3H), 4.32 (br, 2H), 4.61 (br, 2H), 6.74-6.77 (m, 1H), 6.84 6.91 (m, 3H), 7.16 (br, 1H), 7.40 (d, J = 8.9 Hz, 1H), 8.00 (br, 2H), 8.83 (br, 2H).

Example 704A

Synthesis of 1,3,3-trimethyl-8-(3-{[2-(1-oxo-1H-isoquinolin-2-yl)ethyl]pyridin-4-ylmethylamino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 8, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

1.05 (3H, br), 1.52 (3H, br), 1.88 - 1.93 (2H, m), 2.71 (2H, t, J = 6.7 Hz), 2.88 (2H, t, J = 6.0 Hz), 3.41 (3H, s), 3.67 (2H, s), 3.84 (2H, t, J = 5.9 Hz), 4.10 (2H, t, J = 6.0 Hz), 6.41 (1H, d, J = 7.3 Hz), 6.52 (1H, dd, J = 8.8 and 2.6 Hz), 6.61 (1H, d, J = 2.6 Hz), 6.87 (1H, d, J = 8.8 Hz), 6.97 (1H, d, J = 7.3 Hz), 7.08 (2H, d, J = 5.7 Hz), 7.49-7.53 (2H, m), 7.64 - 7.69 (1H, m), 7.78 (1H, br), 8.26 (2H, d, J = 5.7 Hz), 8.38 (1H, d, J = 7.3 Hz).

Example 704B

Synthesis of 1,3,3-trimethyl-8-{3-[2-(1-oxo-1H-isoquinolin-2-yl)ethylamino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

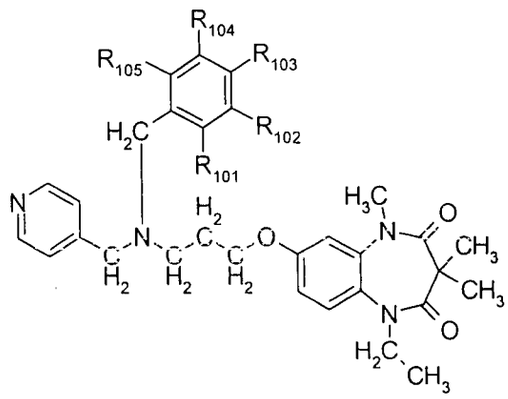
Using an appropriate starting material and following the procedure of Example 18, the object compound was synthesized.

^{1}H-NMR ($CDCl_3$) δppm:

1.05 (3H, br), 1.55 (3H, br), 1.93 - 1.99 (2H, m), 2.86 (2H, t, J = 6.7 Hz), 3.06 (2H, t, J = 6.2 Hz), 3.43 (3H, s), 4.01 (2H, t, J = 6.2 Hz), 4.09 - 4.15 (3H, m), 6.46 (1H, d, J = 7.4 Hz), 6.66 - 6.72 (2H, m), 6.87 (1H, d, J = 8.6 Hz), 7.11 (1H, d, J = 7.3 Hz), 7.46 - 7.51 (2H, m), 7.61 - 7.67 (1H, m), 7.87 (1H, br), 8.41 (1H, d, J = 8.0 Hz).

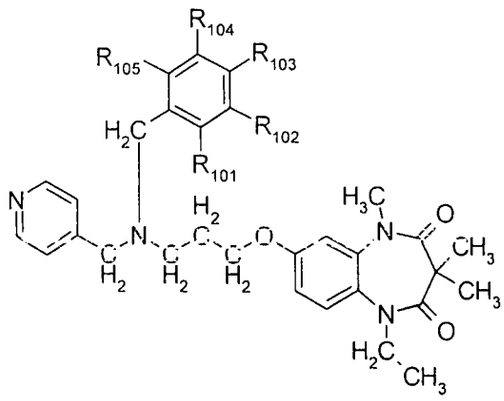
Using appropriate starting materials and following the procedures of the above-mentioned Examples, the compounds shown in

Table 34



Example No.	R101	R102	R103	R104	R105	MS(M+1)
Example 705	-H	-H	-H	-H	-H	501
Example 706	-H	-H	$-C_6H_5$	-H	-H	577
Example 707	-H	-H	$-OCH_3$	-H	-H	531
Example 708	-H	$-OCH_3$	-H	-H	-H	531
Example 709	-H	-H	$-NHCOCH_3$	-H	-H	558
Example 710	-Cl	-H	-H	-H	-H	535
Example 711	-H	-Cl	-H	-H	-H	535
Example 712	-H	-H	-Cl	-H	-H	535
Example 713	$-OCH_3$	-H	-H	-H	-H	531
Example 714	-H	$-C_6H_5$	-H	-H	-H	577
Example 715	-H	-H	-2-THIENYL	-H	-H	583
Example 716	-H	-H	-3-PYRIDYL	-H	-H	578
Example 717	-H	-3-PYRIDYL	-H	-H	-H	578
Example 718	-3-PYRIDYL	-H	-H	-H	-H	578

Table 35



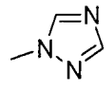
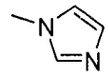
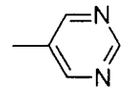
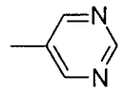
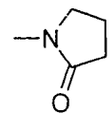
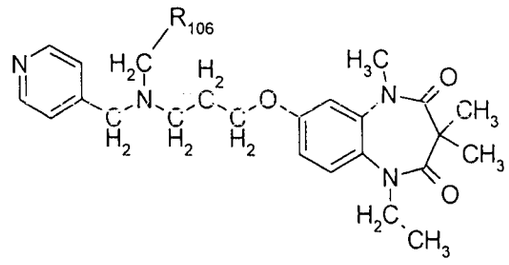
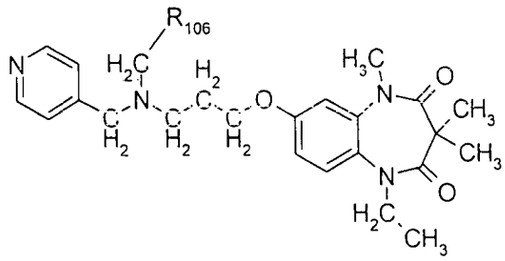
Example No.	R101	R102	R103	R104	R105	MS(M+1)
Example 719	-H	-H		-H	-H	568
Example 720	-H	-H		-H	-H	567
Example 712	-H		-H	-H	-H	567
Example 722	-H	-H		-H	-H	579
Example 723	-H		-H	-H	-H	579
Example 724	-H	-H		-H	-H	584

Table 36



Example No.	R106	MS(M+1)
Example 725	-3-FURYL	491
Example 726	-2-PYRIDYL	502
Example 727	-3-PYRIDYL	502
Example 728	-4-PYRIDYL	502
Example 729	-2-THIENYL	507
Example 730	-3-THIENYL	507
Example 731	$-CH=CHC_6H_5$(trans)	527
Example 732	-2-FURYL	491
Example 733	$-CH_2C_6H_5$	515
Example 734	$-CH(CH_3)C_6H_5$	529
Example 735	$-(CH_2)_2C_6H_5$	529
Example 736	-2-BENZTHIAZOLYL	558

Table 37



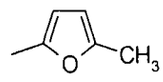
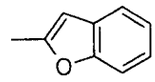
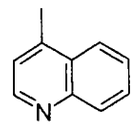
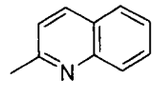
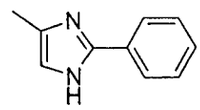
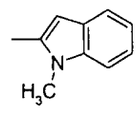
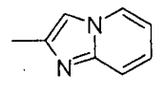
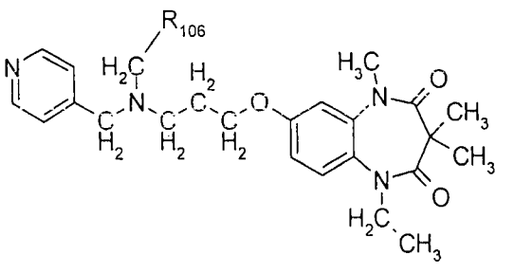
Example No.	R106	MS(M+1)
Example 737		491
Example 738		505
Example 739		521
Example 740		541
Example 741		552
Example 742		552
Example 743		567
Example 744		554
Example 745		541

Table 38



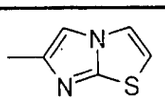
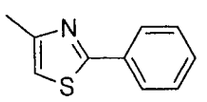
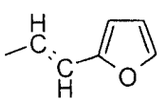
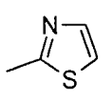
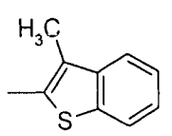
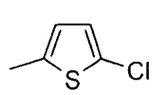
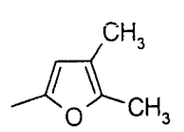
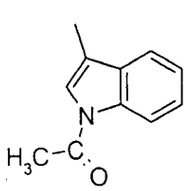
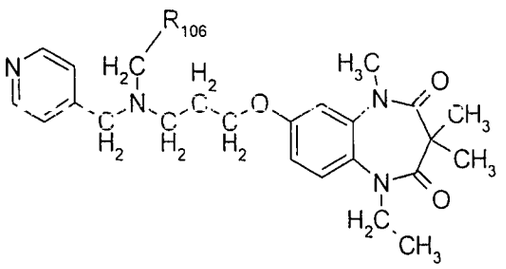
Example No.	R106	MS(M+1)
Example 746		547
Example 747		584
Example 748		517
Example 749		508
Example 750		571
Example 751		541
Example 753		519
Example 753		582

Table 39



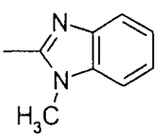
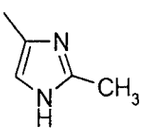
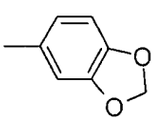
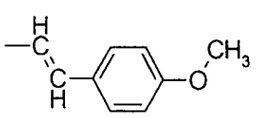
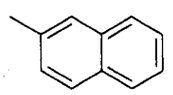
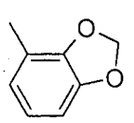
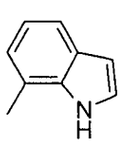
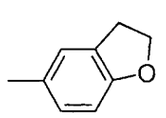
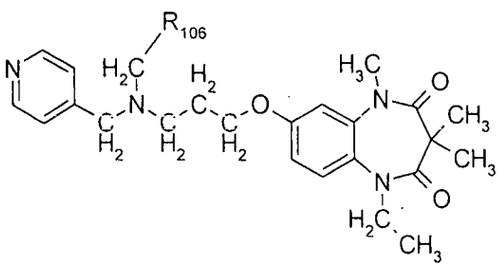
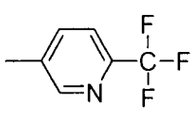
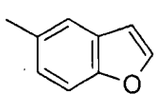
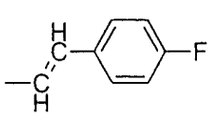
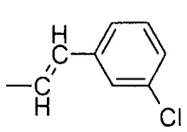
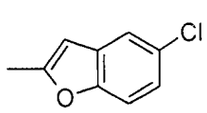
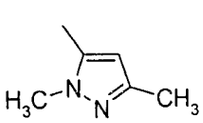
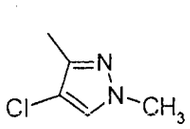
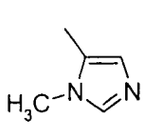
Example No.	R106	MS(M+1)
Example 754		555
Example 755		505
Example 756		545
Example 757		557
Example 758		551
Example 759		545
Example 760		540
Example 761		543

Table 40



Example No.	R106	MS(M+1)
Example 762		570
Example 763		541
Example 764		545
Example 765		561
Example 766		575
Example 767		519
Example 768		539
Example 769		505

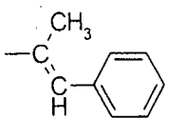
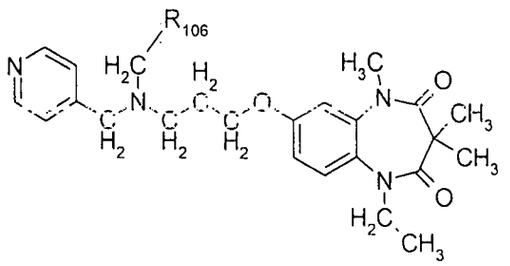
Example 770		541

Table 41



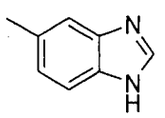
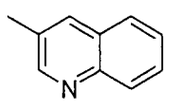
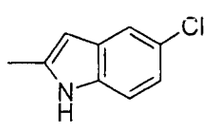
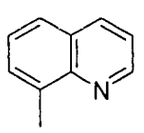
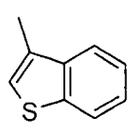
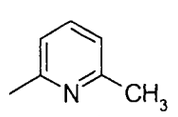
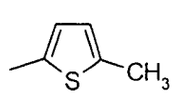
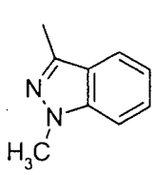
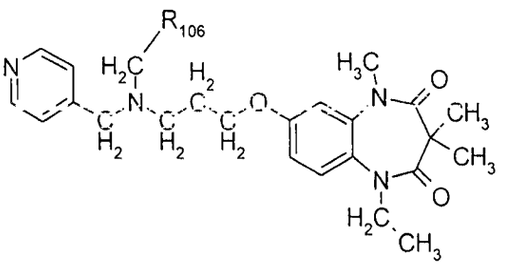
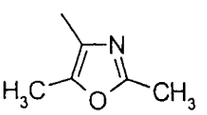
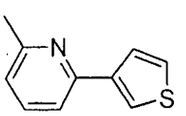
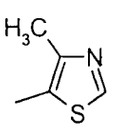
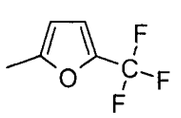
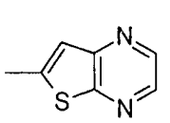
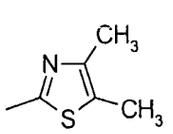
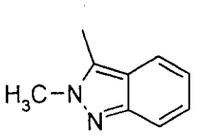
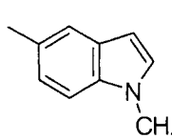
Example No.	R106	MS(M+1)
Example 771		541
Example 772		552
Example 773		574
Example 774		552
Example 775		557
Example 776		516
Example 777		521
Example 778		555

Table 42



Example No.	R106	MS(M+1)
Example 779		520
Example 780		584
Example 781		522
Example 782		559
Example 783		559
Example 784		536
Example 785		555
Example 786		554

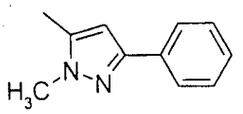
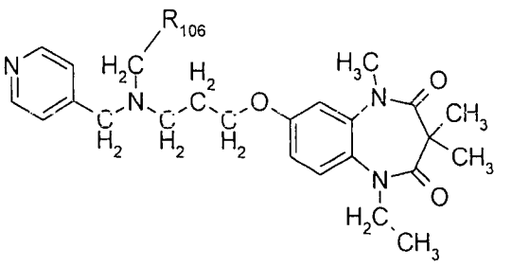
Example 787		581

Table 43



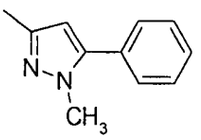
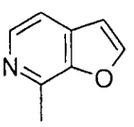
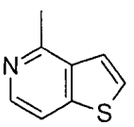
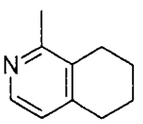
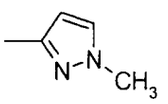
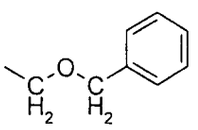
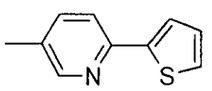
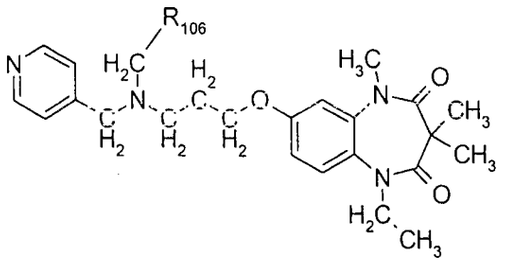
Example No.	R106	MS(M+1)
Example 788		581
Example 789		542
Example 790		558
Example 791		556
Example 792		505
Example 793		545
Example 794		584

Table 44



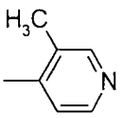
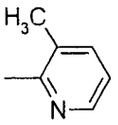
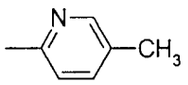
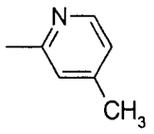
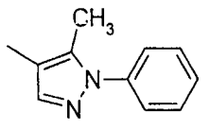
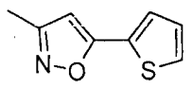
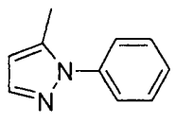
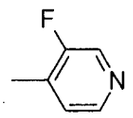
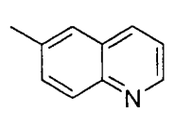
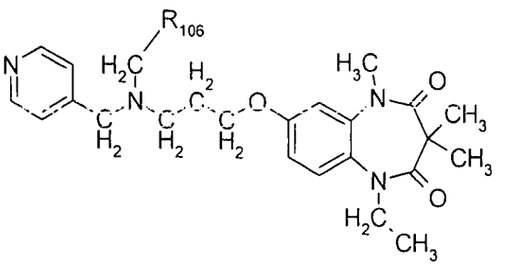
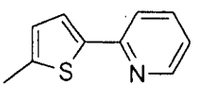
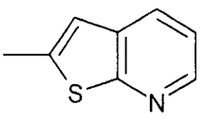
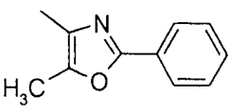
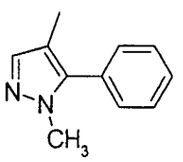
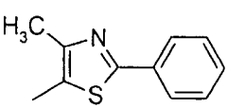
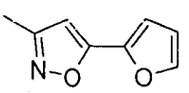
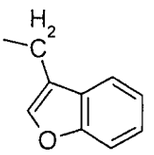
Example No.	R106	MS(M+1)
Example 795		516
Example 796		516
Example 797		516
Example 798		516
Example 799		581
Example 800		574
Example 801		567
Example 802		520
Example 803		552

Table 45



Example No.	R106	MS(M+1)
Example 804		584
Example 805		558
Example 806		582
Example 807		581
Example 808		598
Example 809		558
Example 810		555

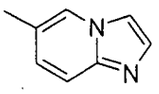
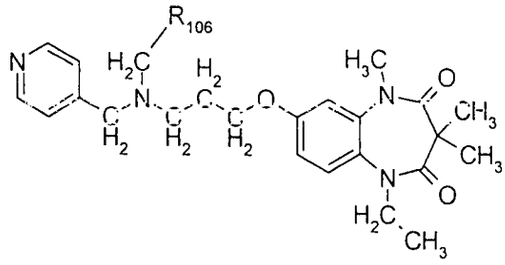
Example 811		541

Table 46



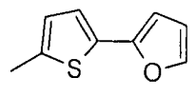
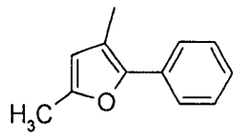
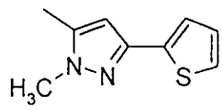
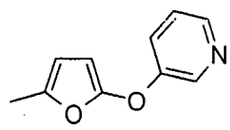
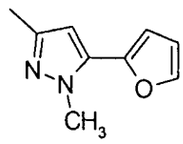
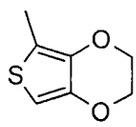
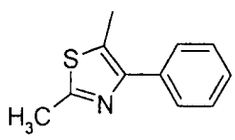
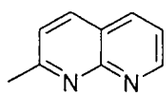
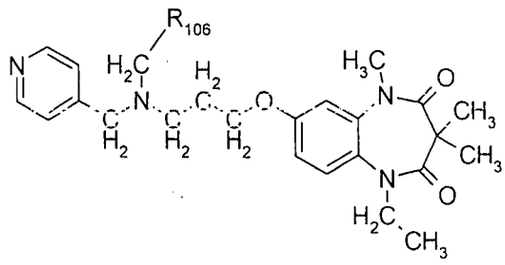
Example No.	R106	MS(M+1)
Example 812		573
Example 813		581
Example 814		587
Example 815		584
Example 816		571
Example 817		565
Example 818		598
Example 819		553

Table 47



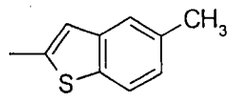
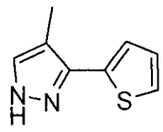
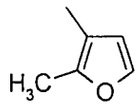
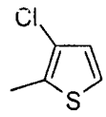
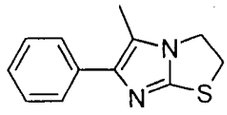
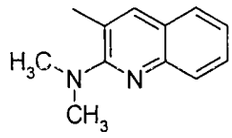
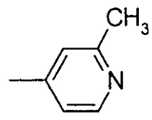
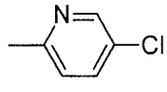
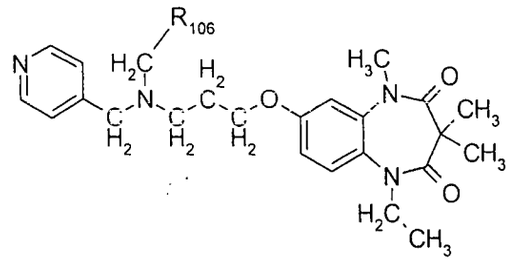
Example No.	R106	MS(M+1)
Example 820		571
Example 821		573
Example 822		505
Example 823		541
Example 824		625
Example 825		595
Example 826		516
Example 827		536

Table 48



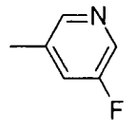
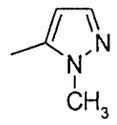
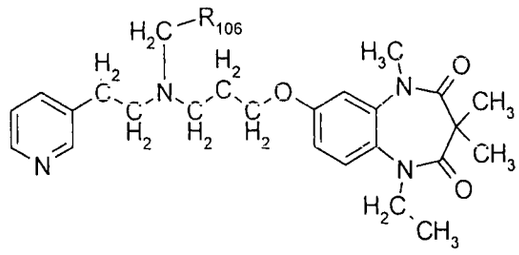
Example No.	R106	MS(M+1)
Example 828		520
Example 829		505

Table 49



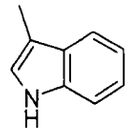
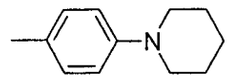
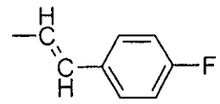
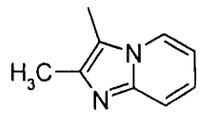
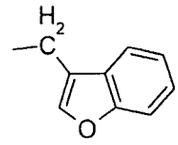
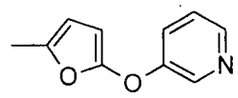
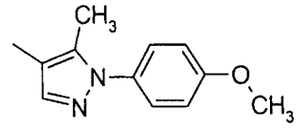
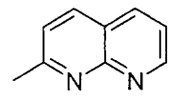
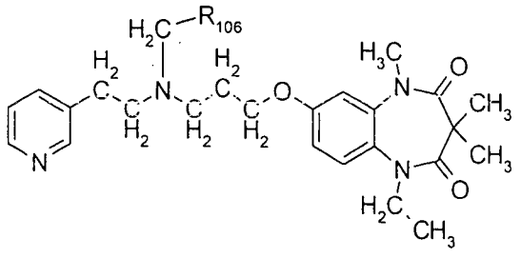
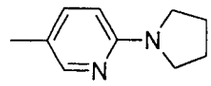
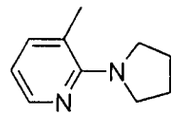
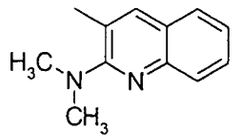
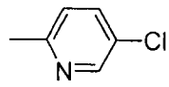
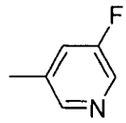
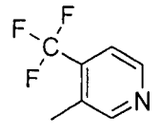
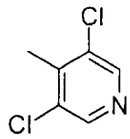
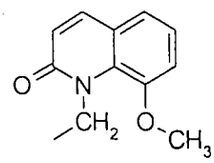
Example No.	R106	MS(M+1)
Example 830		554
Example 831		598
Example 832		559
Example 833		569
Example 834		569
Example 835		598
Example 836		625
Example 837		567

Table 50



Example No.	R106	MS(M+1)
Example 838		585
Example 839		585
Example 840		609
Example 841		550
Example 842		534
Example 843		584
Example 844		584

Example 845		626

284

Hz, 1H), 8.28 (br, 2H), 8.94 (br, 2H).

Example 546

Synthesis of N-(2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)-N-methyl-2-thiophen-2-ylacetamide dihydrochloride

Using an appropriate starting material and following the procedure of Example 487, the object compound was synthesized.

White solid

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (s, 3H), 1.00 (t, J = 7.0 Hz, 3H), 1.32 (s, 3H), 2.26 (br, 2H), 3.08 (s, 3H), 3.22 (br, 2H), 3.31 (s, 3H), 3.45-3.63 (m, 3H), 3.67-3.86 (m, 2H), 3.97 (s, 2H), 3.98-4.10 (m, 3H), 4.62 (br, 2H), 6.87-6.97 (m, 4H), 7.36-7.39 (m, 2H), 8.20 (br, 2H), 8.90 (br, 2H).

Example 547

Synthesis of N-(2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)-N-methyl-2-thiophen-3-ylacetamide dihydrochloride

Using an appropriate starting material and following the procedure of Example 487, the object compound was synthesized.

White solid

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (s, 3H), 1.00 (t, J = 7.0 Hz, 3H), 1.32 (s, 3H), 2.25 (br, 2H), 3.05 (s, 3H), 3.22 (br, 2H), 3.31 (s, 3H), 3.49-3.80 (m, 7H), 3.95-4.10 (m, 3H), 4.62 (br, 2H), 6.86-6.92 (m, 2H), 6.99-7.01 (m, 1H), 7.25 (br, 1H), 7.40 (d, J = 9.0 Hz, 1H), 7.44-7.46 (m, 1H), 8.21 (br, 2H), 8.91 (br, 2H).

Example 548

Synthesis of thiazole-4-carboxylic acid (2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)methyl amide trihydrochloride

Using an appropriate starting material and following the procedure of Example 487, the object compound was synthesized.

White solid

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (s, 3H), 1.00 (t, J = 7.0 Hz, 3H), 1.32 (s, 3H), 2.31 (br, 2H), 3.17 (s, 3H), 3.23-3.40 (m, 2H), 3.31 (s, 3H), 3.61-3.80 (m, 3H), 3.95-4.11 (m, 5H), 4.66 (br, 2H), 6.89-6.92 (m, 2H), 7.40 (d, J = 9.0 Hz, 1H), 8.23-8.32 (m, 3H), 8.96 (br, 2H), 9.15-9.17 (m, 1H).

Example 549

Synthesis of isoxazole-5-carboxylic acid (2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)methyl amide trichloride

Using an appropriate starting material and following the procedure of Example 487, the object compound was synthesized.

White solid

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (s, 3H), 1.00 (t, J = 7.0 Hz, 3H), 1.32 (s, 3H), 2.29 (br, 2H), 3.17 (s, 3H), 3.25 (br, 2H), 3.31 (s, 3H), 3.55-3.77 (m, 3H), 3.81-4.10 (m, 5H), 4.69 (br, 2H), 6.87-6.93 (m, 2H), 7.04 (d, J = 1.8 Hz, 1H), 7.40 (d, J = 9.0 Hz, 1H), 8.30 (br, 2H), 8.75-8.76 (m, 1H), 8.95 (br, 2H).

Example 550

Synthesis of 5-methyl-isoxazole-3-carboxylic acid (2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethyl-amino}ethyl)methylamide trihydrochloride

Using an appropriate starting material and following the procedure of Example 487, the object compound was synthesized.

White solid

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (s, 3H), 1.00 (t, J = 7.0 Hz, 3H), 1.32 (s, 3H), 2.27 (br, 2H), 2.46 (s, 3H), 3.11 (s, 3H), 3.21-3.47 (m, 2H), 3.32 (s, 3H), 3.50-3.95 (m, 5H), 4.00-4.13 (m, 3H), 4.67 (br, 2H), 6.50 (s, 1H), 6.87-6.93 (m, 2H), 7.40 (d, J = 9.0 Hz, 1H), 8.24 (br, 2H), 8.93 (br, 2H).

Example 551

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{[2-(4-oxo-4H-

furo[3,2-c]pyridin-5-yl)ethyl]pyridin-3-ylmethylamino}-propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

White powder

Melting Point 118 to 119°C

Example 552

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]pyridin-3-ylmethylamino}-propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 6, the object compound was synthesized.

White amorphous

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (3H, s), 1.01 (3H, t, J= 7.1 Hz), 1.32 (3H, s), 2.20-2.43 (2H, m), 3.08-3.40 (5H, m), 3.43-4.68 (10H, m), 6.82-6.94 (4H m), 7.41 (1H, d, J= 8.9 Hz), 7.70-7.75 (2H, m), 7.92 (1H, d, J= 1.9 Hz), 8.36-8.48 (1H, m), 8.74-8.80 (1H, m), 8.94-9.02 (1H, m)

Example 553

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]pyridin-3-ylmethyl-amino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

White powder

^{1}H-NMR ($CDCl_3$) δppm:

0.86 (3H, s), 1.16 (3H, t, J= 7.1 Hz), 1.53 (3H, s), 1.88-1.93 (2H, m), 2.41 (3H, s), 2.70 (2H, t, J= 6.8 Hz), 2.86 (2H, t, J= 6.2 Hz), 3.39 (3H, s), 3.68-3.75 (3H, m), 3.86 (2H, t, J= 6.1 Hz), 4.07 (2H, t, J= 6.1 Hz) 4.14-4.21 (1H, m), 6.36 (1H, d, J= 7.3 Hz), 6.52 (1H, s), 6.62 (1H, s), 6.67 (1H, dd, J= 9.0, 2.8 Hz), 7.00 (1H, d, J= 7.4 Hz), 7.07 (1H, dd, J= 7.7, 4.9 Hz), 7.17 (1H, d, J= 9.0 Hz), 7.50 (1H, d, J= 7.8 Hz), 8.42 (1H, d, J= 4.8 Hz), 8.48 (1H, s)

Example 554

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{[2-(2-oxo-2H-quinolin-1-yl)ethyl]pyridin-3-ylmethylamino}-propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 7 and Example 6, the object compound was synthesized.

White amorphous

^{1}H-NMR (DMSO-d_6) δppm:

0.74 (3H, s), 1.00 (3H, t, J= 7.0 Hz), 1.32 (3H, s), 2.18-2.39 (2H, m), 3.04-3.79 (7H, m), 3.99-4.28 (3H, m), 4.42-4.94 (5H, m), 6.66 (1H, d, J= 9.5 Hz), 6.78-6.97 (2H, m), 7.32 (1H, t, J= 7.4 Hz), 7.40 (1H, d, J= 8.9 Hz), 7.63 (1H, t, J= 7.2 Hz), 7.70-7.84 (3H, m), 8.00 (1H, d, J= 9.5 Hz), 8.39-8.52 (1H, m), 8.73-8.82 (1H, m), 8.99 (1H, s)

Example 555

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{[2-(2-oxo-3,4-dihydro-2H-quinolin-1-yl)ethyl]pyridin-3-ylmethylamino}-propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 7 and Example 6, the object compound was synthesized.

White amorphous

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (3H, s), 1.00 (3H, t, J= 7.1 Hz), 1.32 (3H, s), 2.15-2.40 (2H, m), 2.57 (2H, t, J= 8.2 Hz), 2.89 (2H, t, J= 7.7 Hz), 3.08-3.96 (8H, m), 3.99-4.22 (3H, m), 4.29-4.51 (2H, m), 4.51-4.80 (2H, m), 6.86-6.94 (2H, m), 7.00-7.06 (1H, m), 7.20-7.32 (3H, m), 7.41 (1H, d, J= 8.9 Hz), 7.72-7.85 (1H, m), 8.46-8.60 (1H, m), 8.79-8.84 (1H, m), 9.04 (1H, s)

Example 556

Synthesis of 7-(3-{[2-(7-bromo-1-oxo-1H-isoquinolin-2-yl)ethyl]pyridin-4-ylmethylamino}propoxy)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

pale yellow powder

Melting Point 146 to 147°C

Example 557

Synthesis of 1-ethyl-7-(3-{(2-hydroxy-pyridin-4-ylmethyl)-[2-(7-oxo-7H-furo[2,3-c]pyridin-6-yl)ethyl]amino}propoxy)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

White powder

Melting Point 160.5 to 161.5°C

Example 558

Synthesis of 1-ethyl-3,3,5-trimethyl-7-{3-[(2-methylpyridin-4-ylmethyl)-(2-pyridin-3-yl-ethyl)amino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione trihydrochloride

Using an appropriate starting material and following the procedure of Example 7 and Example 6, the object compound was synthesized.

White amorphous

^{1}H-NMR (DMSO-d_6) δppm:

0.74 (3H, s), 1.00 (3H, t, J=7.0 Hz), 1.31 (3H, s), 1.68-2.48(2H,m), 2.64 (3H, s), 2.70-4.25 (6H, m), 3.30 (3H, s), 3.43 (2H, t, J=7.0 Hz), 3.66(1H, dq, J= 7.0 , 7.0Hz), 4.05 (1H, dq, J= 7.0, 7.0 Hz), 4.23-4.99 (2H, bs), 6.80-7.00(2H, m), 7.40(1H, d, J=9.0 Hz), 7.48-8.23(3H, m), 8.32(1H, bs), 8.50-9.00(1H, m), 8.74(1H, d, J=5.7 Hz), 8.80(1H, s), 12.00(1H, bs)

Example 559

Synthesis of N-(2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)-N-methyl-4-trifluoromethyl-benzamide dihydrochloride

Using an appropriate starting material and following the procedure of Example 487, the object compound was synthesized.

colorless amorphous

^{1}H-NMR (DMSO-d_6) δppm:

0.74 (s, 3H), 1.00 (t, J = 7.0 Hz, 3H), 1.32 (s, 3H), 2.30 (br, 2H), 2.91 (s, 3H), 3.11-3.30 (m, 2H), 3.29 (s, 3H), 3.59-3.69 (m, 3H), 4.02 (br, 2H), 4.01-4.15 (m, 3H), 4.63 (br, 2H), 6.82-6.90 (m, 2H), 7.39 (d, J = 8.9 Hz, 1H), 7.55-8.02 (m, 6H), 8.81 (br, 2H).

Example 560

Synthesis of 3-cyano-N-(2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)-N-methylbenzamide dihydrochloride

Using an appropriate starting material and following the procedure of Example 487, the object compound was synthesized.

colorless amorphous

^{1}H-NMR (DMSO-d_6) δppm:

0.74 (s, 3H), 1.00 (t, J = 7.0 Hz, 3H), 1.32 (s, 3H), 2.32 (br, 2H), 2.92 (s, 3H), 3.15-3.28 (m, 2H), 3.29 (s, 3H), 3.55-3.70 (m, 3H), 3.87 (br, 2H), 4.00-4.12 (m, 3H), 4.58 (br, 2H), 6.86-6.90 (m, 2H), 7.39 (d, J = 8.9 Hz, 1H), 7.63-7.68 (m, 1H), 7.73-8.14 (m, 5H), 8.84 (br, 2H).

Example 561

Synthesis of 1H-indazole-3-carboxylic acid (2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl) methylamide trihydrochloride

Using an appropriate starting material and following the procedure of Example 487, the object compound was synthesized.

colorless amorphous

^{1}H-NMR (DMSO-d_6) δppm:

0.73 (s, 3H), 0.99 (t, J=7.0 Hz, 3H), 1.31 (s, 3H), 2.32 (br, 2H), 3.06 (br, 3H), 3.28 (br, 3H), 3.43 (br, 2H), 3.61-3.69 (m, 3H), 4.01-4.11 (m, 5H), 4.67 (br, 2H), 6.84-6.89 (m, 2H), 7.20-7.24 (m, 1H), 7.33-7.36 (m, 1H), 7.40-7.44 (m, 1H), 7.61-7.63 (m, 1H), 8.04 (br, 3H), 8.83 (br, 2H), 13.7 (br, 1H).

Example 562

Synthesis of 1H-pyrrole-3-carboxylic acid (2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]

diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)
methylamide dihydrochloride

Using an appropriate starting material and following the procedure of Example 487, the object compound was synthesized.

colorless amorphous

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (s, 3H), 1.00 (t, J = 7.0 Hz, 3H), 1.32 (s, 3H), 2.26 (br, 2H), 3.10-3.25 (m, 5H), 3.31 (s, 3H), 3.57-3.69 (m, 3H), 3.87 (br, 2H), 4.02-4.08 (m, 3H), 4.60 (br, 2H), 6.15 (s, 1H), 6.63 (br, 1H), 6.83-6.94 (m, 3H), 7.39 (d, J = 8.9 Hz, 1H), 7.99 (br, 2H), 8.81 (br, 2H).

Example 563

Synthesis of N-(2-{[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)-N-methylnicotinamide trihydrochloride

Using an appropriate starting material and following the procedure of Example 487, the object compound was synthesized.

colorless amorphous

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (s, 3H), 1.00 (t, J = 7.0 Hz, 3H), 1.32 (s, 3H), 2.33 (br, 2H), 2.98 (s, 3H), 3.30 (s, 3H), 3.43 (br, 2H), 3.53-3.70 (m, 3H), 3.93-4.20 (m, 5H), 4.84 (br, 2H), 6.87-6.92 (m, 2H), 7.40 (d, J = 8.9 Hz, 1H), 7.78 (br, 1H), 8.28 (br, 3H), 8.80 (br, 1H), 8.94 (br, 3H).

Example 564

Synthesis of 1-ethyl-7-(3-{(2-hydroxypyridin-4-ylmethyl)-[2-(1-oxo-1H-isoquinolin-2-yl)ethyl]amino}propoxy)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

White powder

Melting Point 155 to 156°C

Example 565

Synthesis of

1,3,3,5-Tetramethyl-7-(3-{[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]pyridin-4-ylmethylamino}propoxy)-1,5-dihydrobenzo[b][1,4]

diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 7 and Example 6, the object compound was synthesized.

colorless solid

Melting Point 149 to 153°C

^{1}H-NMR (DMSO-d_6) δppm:

0.76 (3H, s), 1.32 (3H, s), 1.73-2.42 (2H, m), 3.30 (3H, s), 3.32 (3H, s), 2.80-3.50 (4H, m), 3.83-4.81 (6H, m), 6.65-6.90 (3H, m), 6.94 (1H, d, J=1.6 Hz), 7.35 (1H, d, J=8.9 Hz), 7.71 (1H, d, J=7.5 Hz), 7.91 (1H, d, J=2.1 Hz), 7.95-8.35 (2H, m), 8.60-9.03 (2H, m).

Example 566

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]pyrimidin-5-ylmethyl-amino}-propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

White powder

Melting Point 154°C

Example 567

Synthesis of 1-Ethyl-3,3,5-trimethyl-7-{3-[[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-(2-methylpyridin-3-ylmethyl) amino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

White powder

Melting Point 128 to 129°C

Example 568

Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{[2-(4-oxo-4H-thieno[3,2-c]pyridin-5-yl)ethyl]pyridin-3-ylmethylamino}-propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Using an appropriate starting material and following the procedure of Example 7, the object compound was synthesized.

Ivory white powder

Melting Point 114°C

Example 569

Synthesis of 1-ethyl-3,3,5-trimethyl-7-{3-[[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-(3-methylpyridin-4-ylmethyl)amino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 7 and Example 6, the object compound was synthesized.

White amorphous

^{1}H-NMR (DMSO-d_6) δppm:

0.75 (3H, s), 1.02 (3H, t, J= 7.0 Hz), 1.32 (3H, s), 1.78-2.08 (2H, m), 2.27-2.46 (5H, m), 2.60-3.07 (3H, m), 3.31 (3H, s), 3.62-3.77 (2H, m), 3.79-5.39 (8H, m), 6.39-6.58 (1H, m), 6.58-6.74 (1H, m), 6.80-6.90 (2H, m), 7.39 (1H, d, J= 9.0 Hz), 7.45-7.59 (1H, m),7.61-7.95 (1H, m), 8.30-8.61 (1H, m), 8.64-8.81 (1H, m)

Example 570

Synthesis of 1-ethyl-3,3,5-trimethyl-7-{3-[[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-(2-methylpyridin-4-ylmethyl)amino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Using an appropriate starting material and following the procedure of Example 7 and Example 6, the object compound was synthesized.

White amorphous

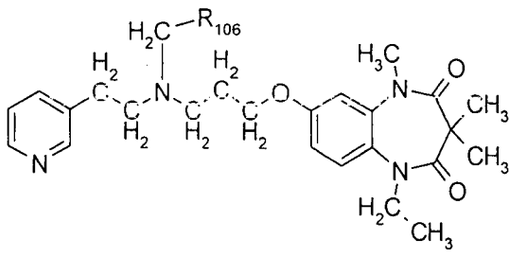
^{1}H-NMR (DMSO-d_6) δppm:

0.75 (3H, s), 1.01 (3H, t, J= 7.0 Hz), 1.33 (3H, s), 2.03-2.38 (2H, m), 2.39 (3H, s), 2.55-2.78 (3H, m), 3.00-3.54 (5H, m), 3.62-3.71 (1H, m), 3.89-4.18 (5H, m), 4.26-4.64 (4H, m), 6.55 (1H, s), 6.67-6.76 (1H, m), 6.77-6.93 (2H, m), 7.39 (1H, d, J= 9.0 Hz), 7.58-7.64 (1H, m) 7.79-8.25 (2H, m), 8.60-8.78 (1H, m)

Example 571

Synthesis of 7-(3-{(5-chloro-pyridin-2-ylmethyl)-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-amino}-propoxy)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

Table 51



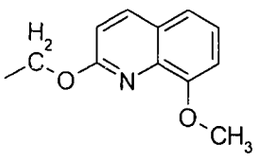
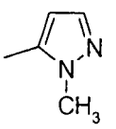
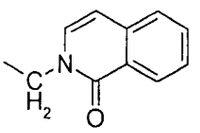
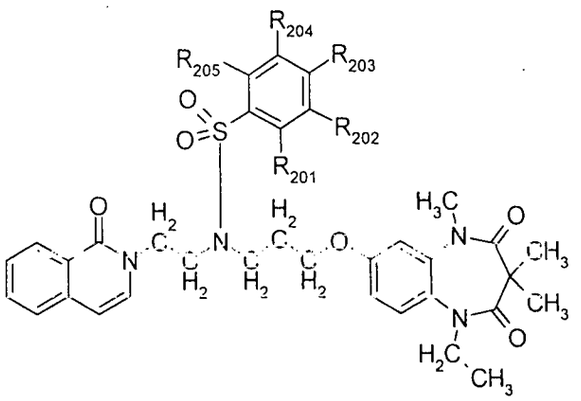
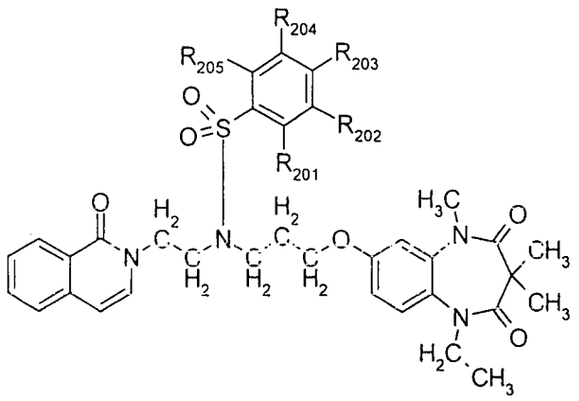
Example No.	R106	MS(M+1)
Example 846		626
Example 847		519
Example 848		596

Table 52



Example No.	R201	R202	R203	R204	R205	MS(M+1)
Example 849	-H	-H	$-OCH_3$	-H	-H	661
Example 850	-H	-H	-Cl	-H	-H	665
Example 851	-H	-H	-H	-H	$-CH_3$	645
Example 852	-H	-H	-F	-H	-H	649
Example 853	-H	-H	-H	-H	-Cl	665
Example 854	-H	-H	-H	-H	$-CO_2CH_3$	689
Example 855	-CN	-H	-H	-H	-H	656
Example 856	-H	$-OCH_3$	-H	-H	-H	661
Example 857	-H	-F	-H	-H	-H	649
Example 858	-H	-H	-H	-H	-F	649
Example 859	-H	$-CH_3$	-H	-H	-H	645
Example 860	-H	-Cl	-H	-H	-H	665
Example 861	-H	-H	-H	-H	-H	631
Example 862	-H	-H	$-NHCOCH_3$	-H	-H	688
Example 863	-H	-H	$-CH_3$	-H	-H	645
Example 864	-H	$-CO_2H$	-H	-H	-H	675
Example 865	-H	-CN	-H	-H	-H	656
Example 866	-H	-H	-CN	-H	-H	656

Table 53



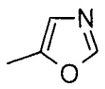
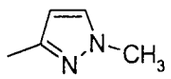
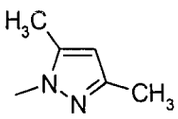
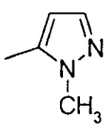
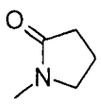
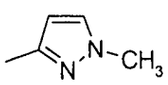
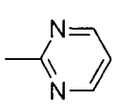
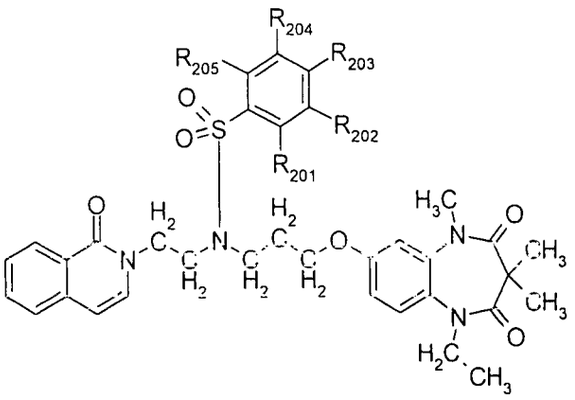
Example No.	R201	R202	R203	R204	R205	MS(M+1)
Example 867	-H	-H		-H	-H	698
Example 868	-H	-H		-H	-H	711
Example 869	-H	-H		-H	-H	725
Example 870	-H		-H	-H	-H	711
Example 871	-H	-H		-H	-H	714
Example 872	-H		-H	-H	-H	711
Example 873	-H		-H	-H	-H	709

Table 54



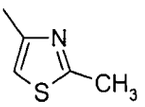
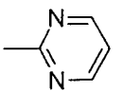
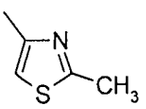
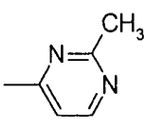
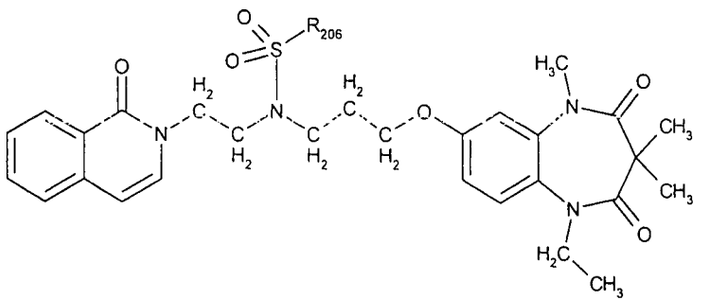
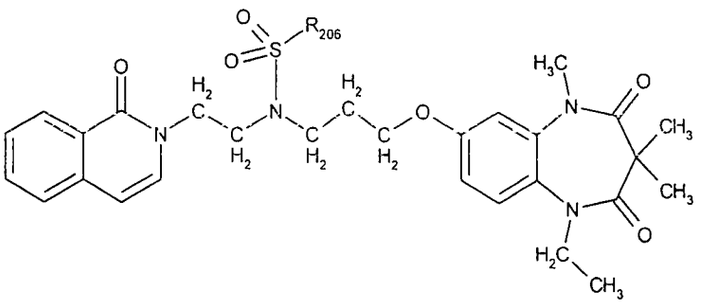
Example No.	R201	R202	R203	R204	R205	MS(M+1)
Example 874	-H		-H	-H	-H	728
Example 875	-H	-H		-H	-H	709
Example 876	-H	-H		-H	-H	728
Example 877	-H		-H	-H	-H	723

Table 55



Example No.	R206	MS(M+1)
Example 878	-2-THIENYL	637
Example 879	$-CH_2C_6H_5$	645
Example 880	-3-THIENYL	637
Example 881	-2-FURYL	621

Table 56



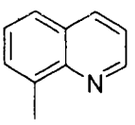
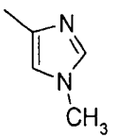
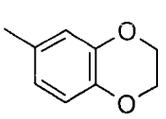
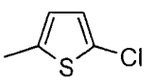
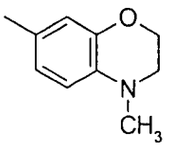
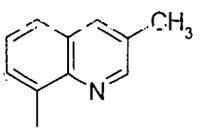
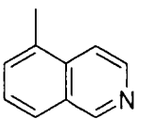
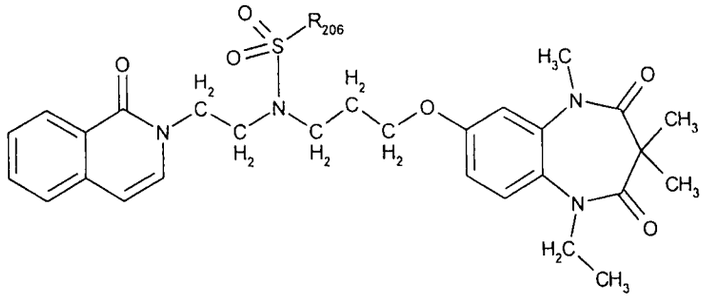
Example No.	R206	MS(M+1)
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Example 883		635
Example 884		689
Example 885		671
Example 886		702
Example 887		696
Example 888		682

Table 57



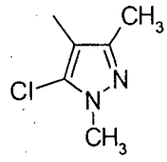
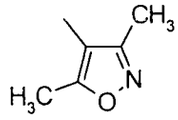
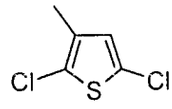
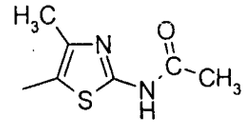
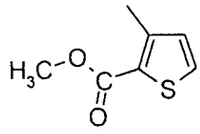
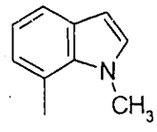
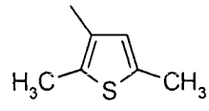
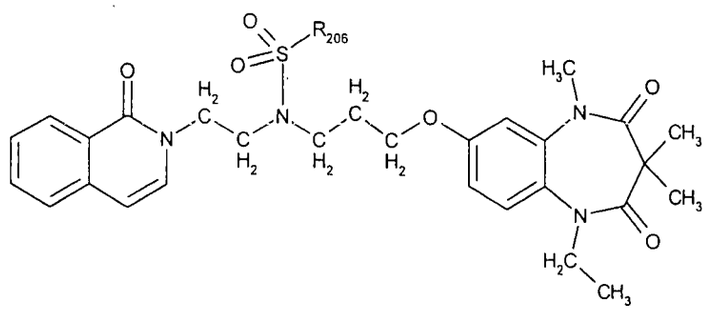
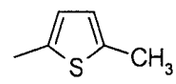
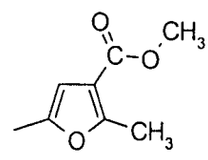
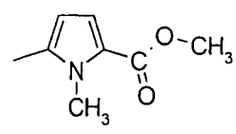
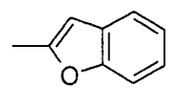
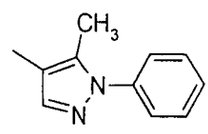
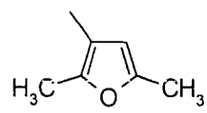
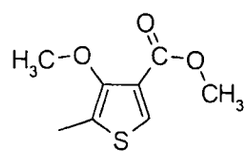
Example No.	R206	MS(M+1)
Example 889		683
Example 890		650
Example 891		705
Example 892		709
Example 893		695
Example 894		684
Example 895		665

Table 58



Example No.	R206	MS(M+1)
Example 896		651
Example 897		693
Example 898		692
Example 899		671
Example 900		711
Example 901		649
Example 902		725

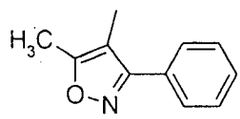
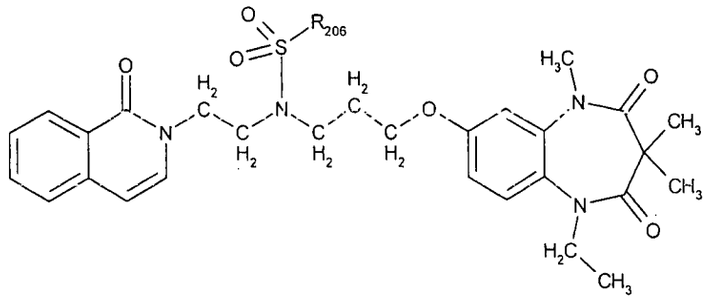
Example 903		712

Table 59



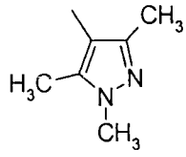
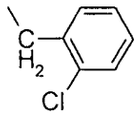
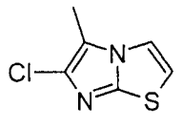
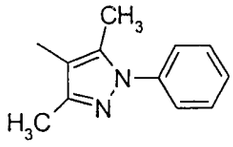
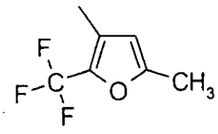
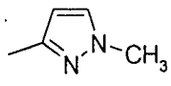
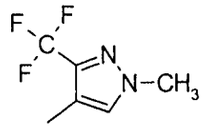
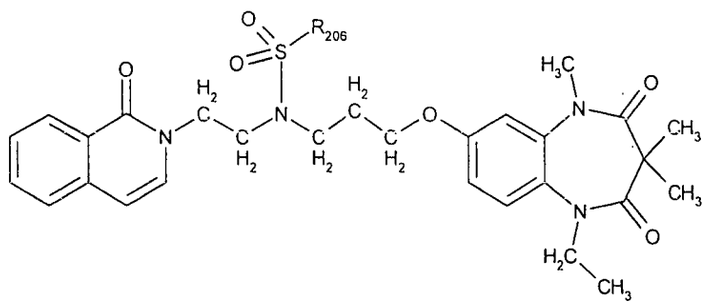
Example No.	R206	MS(M+1)
Example 904		663
Example 905		679
Example 906		711
Example 907		725
Example 908		703
Example 909		635
Example 910		703

Table 60



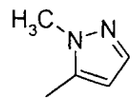
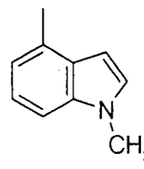
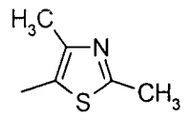
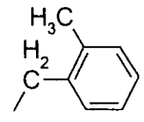
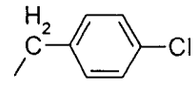
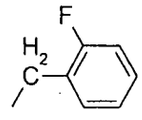
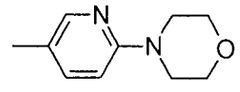
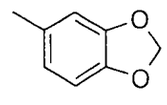
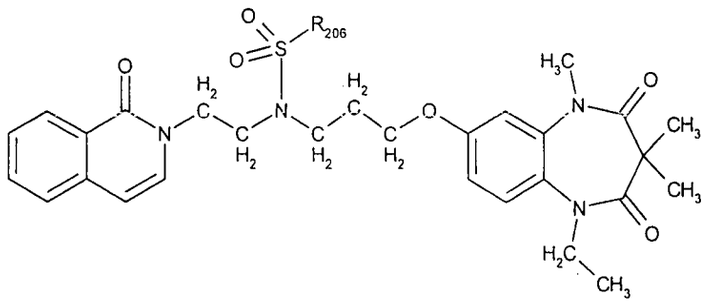
Example No.	R206	MS(M+1)
Example 911		635
Example 912		684
Example 913		666
Example 914		659
Example 915		679
Example 916		663
Example 917		717
Example 918		675

Table 61



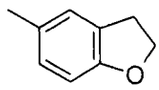
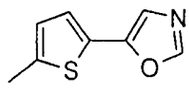
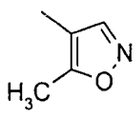
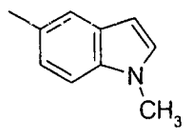
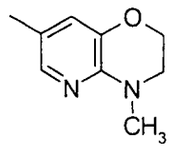
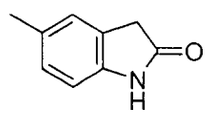
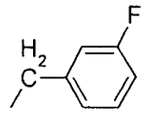
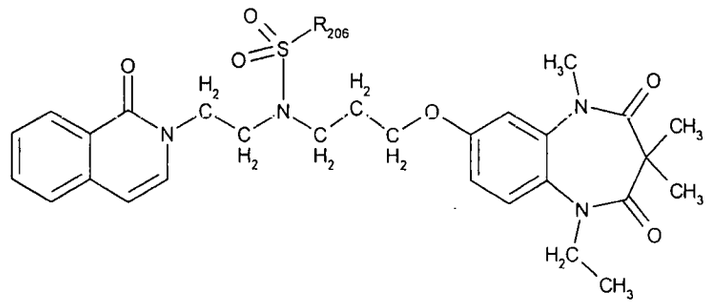
Example No.	R206	MS(M+1)
Example 919		673
Example 920		704
Example 921		636
Example 922		684
Example 923		703
Example 924		686
Example 925		663

Table 62



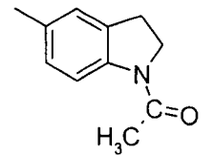
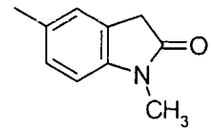
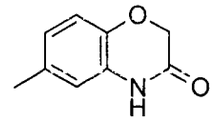
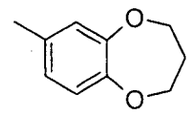
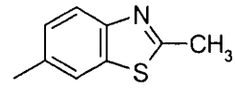
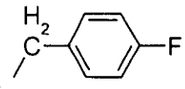
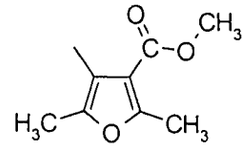
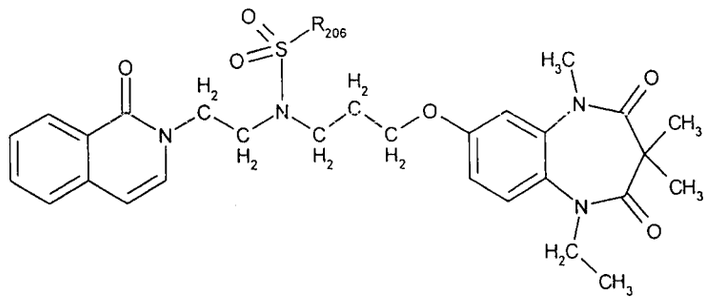
Example No.	R206	MS(M+1)
Example 926		714
Example 927		700
Example 928		702
Example 929		703
Example 930		702
Example 931		663
Example 932		707

Table 63



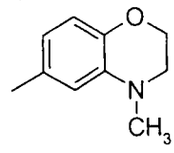
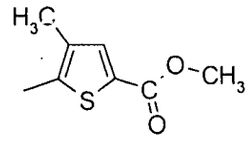
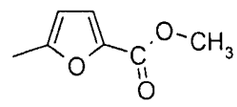
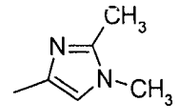
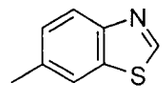
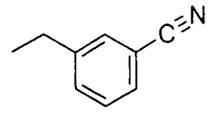
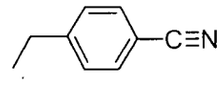
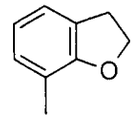
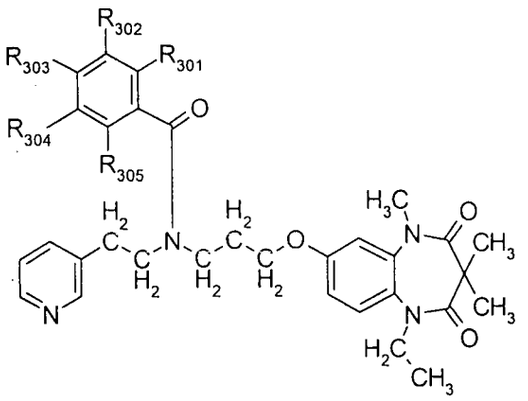
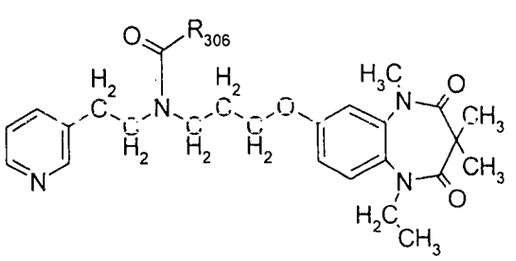
Example No.	R206	MS(M+1)
Example 933		702
Example 934		709
Example 935		679
Example 936		649
Example 937		688
Example 938		670
Example 939		670
Example 940		673

Table 64



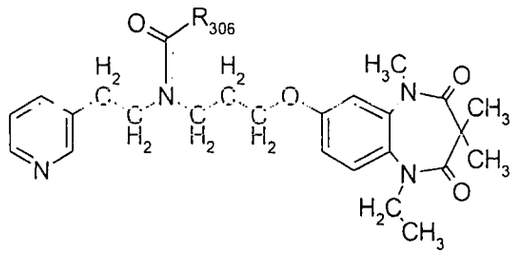
Example No.	R301	R302	R303	R304	R305	MS(M+1)
Example 941	-H	-H	-H	-H	-H	529
Example 942	-H	-H	$-CH_3$	-H	-H	543
Example 943	-H	-H	-Cl	-H	-H	563
Example 944	-H	-H	-F	-H	-H	547
Example 945	-H	-H	$-OCH_3$	-H	-H	559
Example 946	$-OCH_3$	-H	-H	-H	-H	559
Example 947	-Cl	-H	-H	-H	-H	563
Example 948	$-CH_3$	-H	-H	-H	-H	543
Example 949	-F	-H	-H	-H	-H	547
Example 950	-H	$-OCH_3$	-H	-H	-H	559
Example 951	-H	-Cl	-H	-H	-H	563
Example 952	-H	$-CH_3$	-H	-H	-H	543
Example 953	-H	-F	-H	-H	-H	547

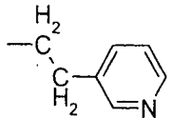
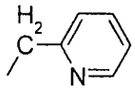
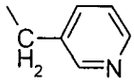
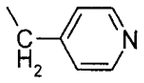
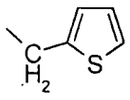
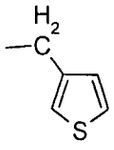
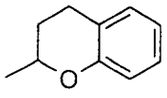
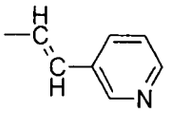
Table 65



Example No.	R306	MS(M+1)
Example 954	$-CH_2OC_6H_5$	559
Example 955	$-(CH_2)_2C_6H_5$	557
Example 956	$-CH=CHC_6H_5$(trans)	555
Example 957	-2-PYRIDYL	530
Example 958	-3-PYRIDYL	530
Example 959	-4-PYRIDYL	530
Example 960	-2-FURYL	519
Example 961	-2-THIENYL	535
Example 962	-3-FURYL	519
Example 963	-3-THIENYL	535
Example 964	-2-BENZTHIAZOLYL	586

Table 66



Example No.	R306	MS(M+1)
Example 965		558
Example 966		544
Example 967		544
Example 968		544
Example 969		549
Example 970		549
Example 971		585
Example 972		556

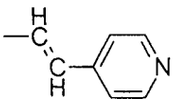
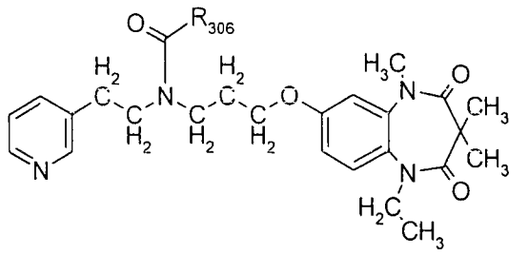
Example 973		556

Table 67



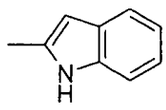
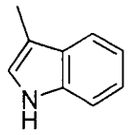
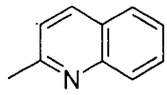
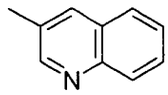
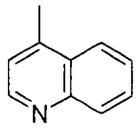
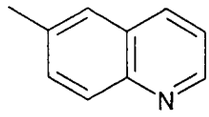
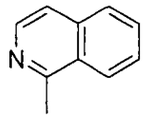
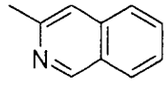
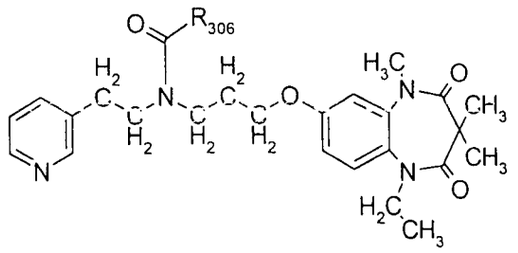
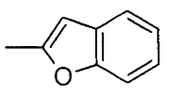
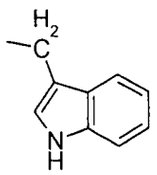
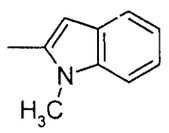
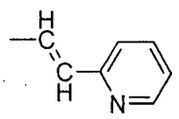
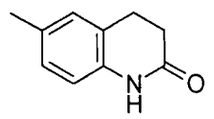
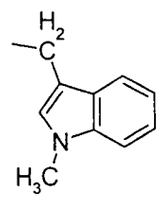
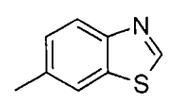
Example No.	R306	MS(M+1)
Example 974		568
Example 975		568
Example 976		580
Example 977		580
Example 978		580
Example 979		580
Example 980		580
Example 981		580

Table 68



Example No.	R306	MS(M+1)
Example 982		569
Example 983		582
Example 984		582
Example 985		556
Example 986		598
Example 987		596
Example 988		586

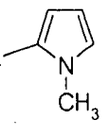
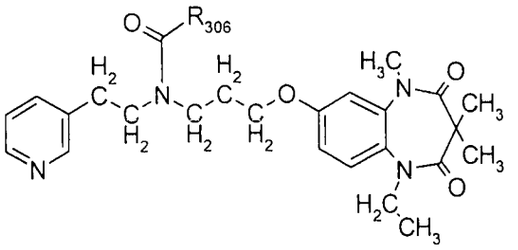
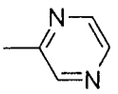
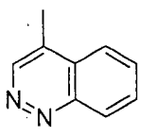
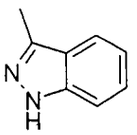
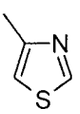
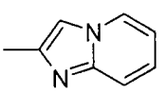
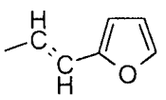
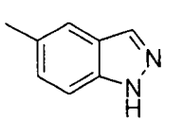
Example 989		532

Table 69



Example No.	R306	MS(M+1)
Example 990		531
Example 991		581
Example 992		569
Example 993		536
Example 994		569
Example 995		545
Example 996		569

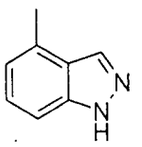
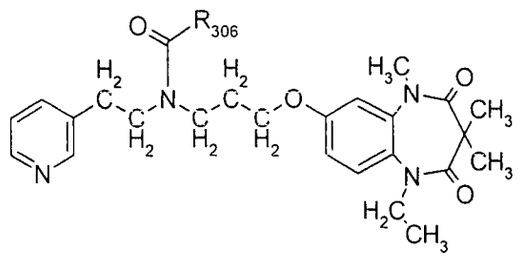
Example 997		569

Table 70



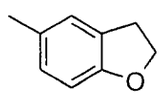
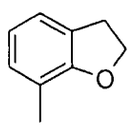
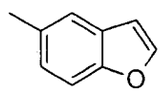
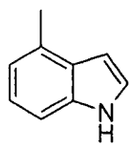
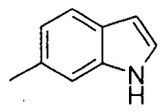
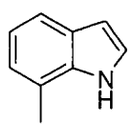
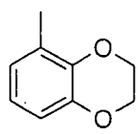
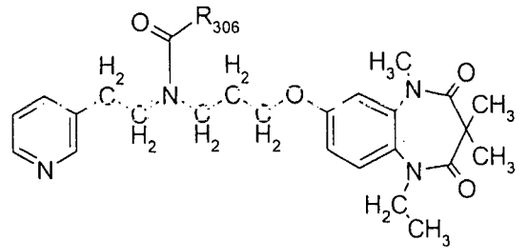
Example No.	R306	MS(M+1)
Example 998		571
Example 999		571
Example 1000		569
Example 1001		568
Example 1002		568
Example 1003		568
Example 1004		587

Table 71



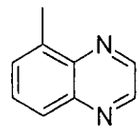
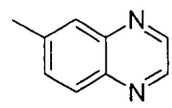
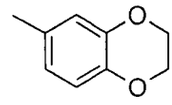
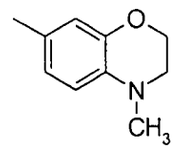
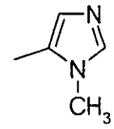
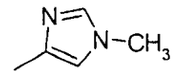
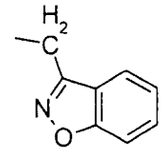
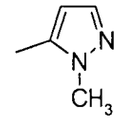
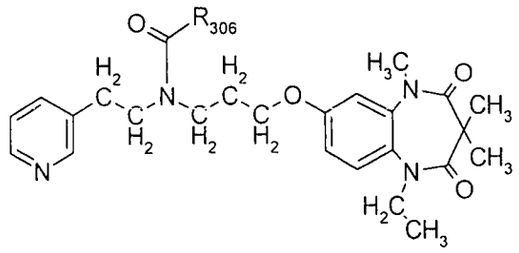
Example No.	R306	MS(M+1)
Example 1005		581
Example 1006		581
Example 1007		587
Example 1008		600
Example 1009		533
Example 1010		533
Example 1011		584
Example 1012		533

Table 72



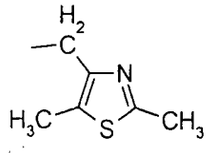
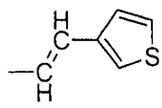
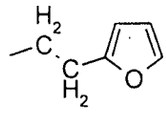
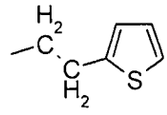
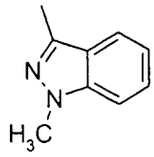
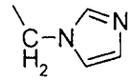
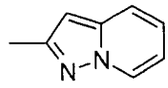
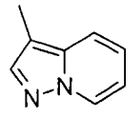
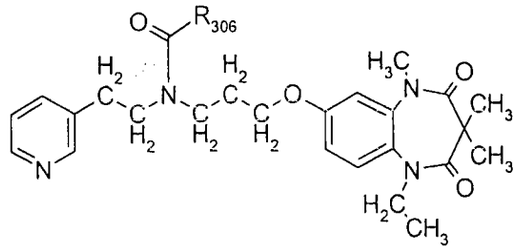
Example No.	R306	MS(M+1)
Example 1013		578
Example 1014		561
Example 1015		547
Example 1016		563
Example 1017		583
Example 1018		533
Example 1019		569
Example 1020		569

Table 73



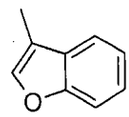
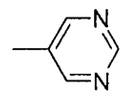
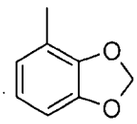
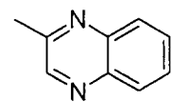
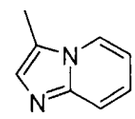
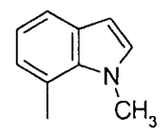
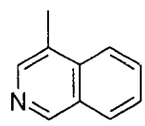
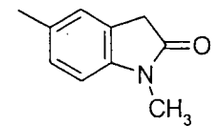
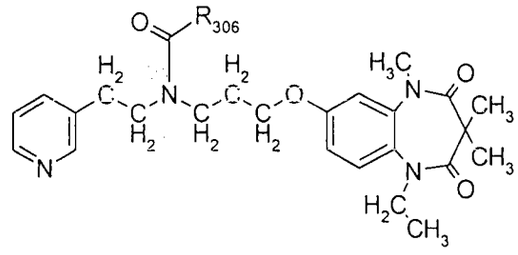
Example No.	R306	MS(M+1)
Example 1021		569
Example 1022		531
Example 1023		573
Example 1024		581
Example 1025		569
Example 1026		582
Example 1027		580
Example 1028		598

Table 74



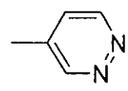
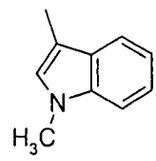
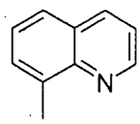
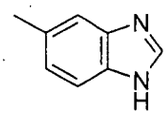
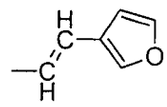
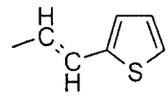
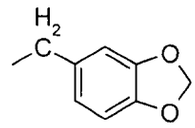
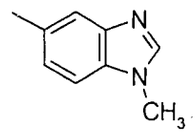
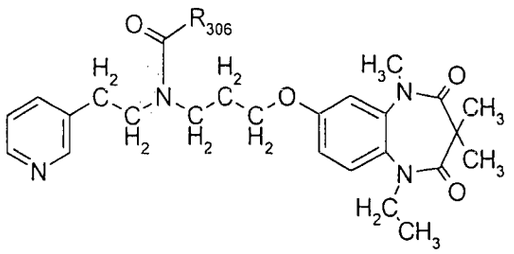
Example No.	R306	MS(M+1)
Example 1029		531
Example 1030		582
Example 1031		580
Example 1032		569
Example 1033		545
Example 1034		561
Example 1035		587
Example 1036		583

Table 75



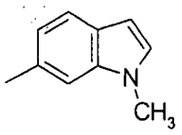
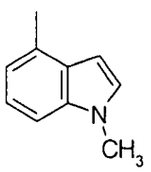
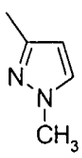
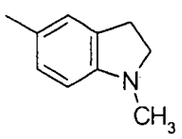
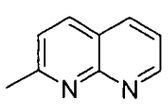
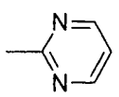
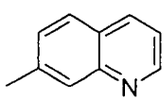
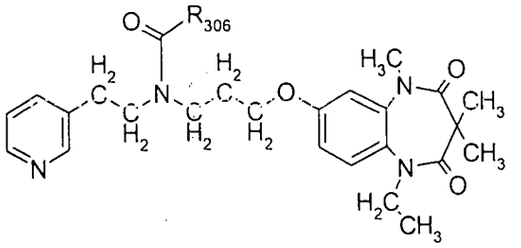
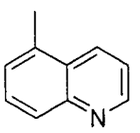
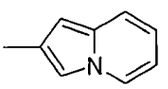
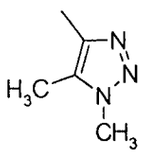
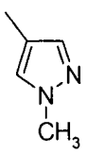
Example No.	R306	MS(M+1)
Example 1037		582
Example 1038		582
Example 1039		533
Example 1040		584
Example 1041		581
Example 1042		531
Example 1043		580

Table 76



Example No.	R306	MS(M+1)
Example 1044		580
Example 1045		568
Example 1046		548
Example 1047		533

Pharmacological Test 1

(1) Production of human Kv1.5-expressing CHO-K1 cell lines

CHO-K1 cell lines stably expressing human Kv1.5 channels were prepared in the following manner.

Full-length human Kv1.5 cDNA was cloned from a human heart cDNA library (produced by Stratagene). The obtained human Kv1.5 sequence corresponds to the sequence described in FASEB J. 5, 331-337 (1991).

The obtained human Kv1.5 cDNA was inserted into a plasmid encoding a CMV promoter and a G418 resistance marker to produce a Kv1.5 expression vector. The human Kv1.5 expression vector was transfected

into CHO-K1 cells by the lipofectamine method. After culturing the cells in an F-12 medium (produced by Invitrogen Corp.) containing 10% FBS (produced by Invitrogen Corp.) for 3 or 4 days, the medium was replaced with a FBS-containing F-12 medium that included 1,000 μg/ml of G418 (produced by Invitrogen Corp.), and single colonies were isolated. The amount of Kv1.5 channel expression in the single colonies was quantified at the mRNA level by RT-PCR and then quantified at the protein level by western blotting. Finally, the expressed current was analyzed by patch clamp method. Cell lines expressing a current of 200 pA or more per cell were selected as channel-expressing cell lines for activity measurement by patch clamp method.

(2) Production of CHO cell line expressing human GIRK1/4

CHO cell lines stably expressing human GIRK1/4 channels were prepared in the following manner.

Full-length human GIRK1 cDNA was cloned from HuH cell- and HeLa cell-derived cDNA libraries. Full-length GIRK4 cDNA was amplified from a human heart cDNA library (produced by Clontech Laboratories, Inc.) by PCR using synthetic primers shown in Table 1, and cloned into the Eco-RI restriction enzyme site of pCR-Blunt (produced by Invitrogen Corporation) or into the HincII site of pUC118 (produced by Takara Bio, Inc.).

Table 77

Primer	Sequence	
hGIRK1-S	5'-ATGTCTGCACTCCGAAGGAAATTTG-3'	SEQ ID No.1
hGIRK1-A	5'-TTATGTGAAGCGATCAGAGTTC-3'	SEQ ID No.2
hGIRK1-F2	5'-GCAGGGTACCCCTTCGTATTATGTCTGCACTCC-3'	SEQ ID No.3
hGIRK1-A3	5'-GGTGTCTGCCGAGATTTGA-3'	SEQ ID No.4
hGIRK1-A4	5'-CCGAGTGTAGGCGATCACCC-3'	SEQ ID No.5
hGIRK4-S	5'-ATGGCTGGCGATTCTAGGAATGCC-3'	SEQ ID No.6
hGIRK4-A	5'-TCTCACCGAGCCCCTGGCCTCCC-3'	SEQ ID No.7
hGIRK4-S2	5'-AACCAGGACATGGAGATTGG-3'	SEQ ID No.8
hGIRK4-A2	5'-GAGAACAGGAAAGCGGACAC-3'	SEQ ID No.9

The obtained human GIRK1 and GIRK4 cDNA sequences correspond to known sequences (NCBI database: GIRK1 (NM_002239) and

GIRK4 (NM_000890) respectively). The obtained GIRK1 and GIRK4 cDNA sequences were cloned into the Eco-RI restriction enzyme site of pCR-Blunt (available from Invitrogen Corporation) or into the HincII site of pUC118 (available from Takara Bio, Inc.). A GIRK4 expression vector was constructed by insertion into the BamHI-XhoI site of pcDNA5/FRT. A GIRK1 expression vector was constructed by insertion into the KpnI-XhoI site of pcDNA3.1(+) or pCAG_neo. FLP-IN-CHO cells (produced by Invitrogen Corporation) were transfected with human GIRK1 and GIRK4 expression vectors by using Lipofectamine 2000 (produced by Invitrogen Corporation) according to the protocol enclosed with the reagent or using an electronic induction method ("Nucleofector Kit-T", produced by Amaxa). First, the cells transfected with the GIRK4 expression vector were cultured in a 10% serum-containing F12 medium (produced by Sigma) supplemented with 600 μg/ml of hygromycin in an incubator with 5% carbon dioxide at 37°C. Then the cells expressing GIRK4 were transfected with the GIRK1 expression vector and were cultured in 10% serum-containing F12 medium supplemented with 350 μg/ml of G418 and 600 μg/ml of hygromycin in an incubator with 5% carbon dioxide at 37°C to select GIRK1/4 expressing cell lines. Cell populations whose growth was observed after about 2 weeks were isolated using cloning rings, and the obtained single colonies were proliferated. RNA was extracted from single colonies, and single-stranded cDNA was synthesized by a cDNA synthesis kit (produced by Invitrogen Corporation), and the amount of expression was quantified at the mRNA level by real-time PCR (Applied Biosystems, Ltd.). Finally, the expressed current was analyzed by patch clamp method described below. The cell lines expressing a current of 500 pA or more per cell were selected as channel-expressing cell lines for activity measurement by patch clamping method.

(3) Measurement of ion channel current by patch clamp method (human Kv1.5-expressing CHO-K1 cell line)

An experiment was carried out using a patch clamp setup at room temperature (20 to 26°C). A perfusion chamber having a diameter of 20 mm (flow rate: about 5 ml/min) was mounted on the stage of a

phase-contrast inverted microscope (produced by Nikon Corporation) placed on a vibration isolated table. A poly-L-lysine (produced by Sigma)-coated coverslip (diameter: 15 mm, produced by Matsunami Glass Ind., Ltd.) on which human Kv1.5-expressing cells were cultured was placed in the perfusion chamber.

Depolarizing stimulation pulses were applied and ionic current was recorded by using a patch clamp amplifier (EPC-7 or EPC-7 PLUS, produced by HEKA) and a personal computer (manufactured by IBM Corp.) in which software for data acquisition and analysis of ion channel current (PULSE 8.77, produced by HEKA) was installed. The current was measured in the whole-cell configuration of the patch-clamp technique. The tip (resistance: 2 to 4 MΩ) of a borosilicate glass pipette (produced by Sutter Instrument Co.) was gently placed on the cell membrane by using a three-dimensional mechanical micromanipulator (produced by Shoshin EM Corporation). Weak suction resulted in giga seal formation (the pipette resistance increased to more than 1 GΩ). Subsequently, stronger suction was applied to break the cell membrane. The capacitative current derived from the cell membrane was corrected using a patch clamp amplifier. Subsequently, the series resistance (Rs) between the pipette and the interior of the cell was measured and corrected.

The composition of the extracellular solution used is shown below. Unless otherwise specified, these components were obtained from Wako Pure Chemical Industries, Ltd.

NaCl	140 mM,
KCl	40 mM,
$CaCl_2$	1.8 mM,
$MgCl_2$	1 mM,
NaH_2PO_4	0.33 mM,
HEPES	5 mM
Glucose	5.5 mM (pH = 7.4)

Each test compound was prepared as a 1000-fold concentrated stock solution that was dissolved in DMSO and then diluted in the extracellular solution.

The composition of the electrode internal solution used is

shown below. Unless otherwise specified, these components were obtained from Wako Pure Chemical Industries, Ltd.

KOH	100 mM,
KCl	40 mM,
Aspartic acid	70 mM,
$MgCl_2$	1 mM,
MgATP	5 mM,
K_2 creatine phosphate	5 mM,
HEPES	5 mM
EGTA	5 mM (pH = 7.2)

(4) Measurement of ion channel current by patch clamp method (human GIRK1/4-expressing CHO-K1 cell line)

An experiment was carried out using a patch clamp setup at room temperature (20 to 26°C). A perfusion chamber having a diameter of 20 mm (flow rate: about 5 ml/min) was mounted on the stage of a phase-contrast inverted microscope (produced by Nikon Corporation) placed on a vibration isolation table. A poly-L-lysine (produced by Sigma)-coated coverslip (diameter: 15 mm, produced by Matsunami Glass Ind., Ltd.) on which human GIRK1/4-expressing cells were cultured was placed in the perfusion chamber.

Hyperpolarizing stimulation pulses were applied and ionic current was recorded using a patch clamp amplifier (EPC-7 or EPC-7 PLUS, manufactured by HEKA) and a personal computer (manufactured by IBM Corp.) in which software for data acquisition and analysis of ion channel current (PULSE 8.77, manufactured by HEKA) was installed. The current was measured in the whole-cell configuration of the patch-clamp technique. The tip (resistance: 2 to 4 MΩ) of a borosilicate glass pipette (produced by Sutter Instrument Co.) was gently placed on the cell membrane by using a three-dimensional mechanical micromanipulator (produced by Shoshin EM Corporation). Weak suction resulted in giga seal formation (the pipette resistance increased to more than 1 GΩ). Subsequently, stronger suction was applied to break the cell membrane. The capacitative current derived from the cell membrane was corrected using a patch clamp amplifier.

Subsequently, the series resistance (Rs) between the pipette and the interior of the cell was measured and corrected.

The composition of the extracellular solution used is shown below. Unless otherwise specified, these components were obtained from Wako Pure Chemical Industries, Ltd.

NaCl	140 mM,
KCl	4 mM,
$CaCl_2$	1.8 mM,
$MgCl_2$	1 mM,
NaH_2PO_4	0.33 mM,
HEPES	5 mM
Glucose	5.5 mM (pH = 7.4)

Each test compound was prepared as a 1000-fold concentrated stock solution that was dissolved in DMSO and then diluted in the extracellular solution.

The composition of the electrode internal solution used is shown below. Unless otherwise specified, these components were obtained from Wako Pure Chemical Industries, Ltd.

KOH	100 mM,
KCl	40 mM,
Aspartic acid	70 mM,
$MgCl_2$	1 mM,
MgATP	5 mM,
K_2 creatine phosphate	5 mM,
HEPES	5 mM
EGTA	5 mM (pH = 7.2)

(5) Measurement of human Kv1.5 current

While the membrane potential was holded at -80 mV, depolarizing pulses (-80 mV for 0.05 seconds → +40 mV for 0.2 seconds → -40 mV for 0.2 seconds → -80 mV for 0.05 seconds) were applied at a stimulation frequency of 1 Hz to measure Kv1.5 channel current. More specifically, first, while perfusing an extracellular solution containing 0.1% DMSO and holding the membrane potential at -80 mV, depolarizing pulses were applied. The current obtained during the

pulse application was recorded as a current in the absence of the test compounds. Subsequently, while perfusing an extracellular solution containing 0.1 μM of a test compound and holding the membrane potential at -80 mV, depolarizing pulses were applied. After the inhibitory effect of the test compound had been stabilized, the current was recorded. The same procedure was repeated using an extracellular solution containing 1 μM of the test compound and then using an extracellular solution containing 10 μM of the test compound. The current obtained using the solution containing the test compound at each concentration was recorded.

The data was analyzed by using the step end current recorded during the +40 mV depolarizing stimulation. The "step end current" refers to the average current flowing for a period of 195 to 199 milliseconds from the start of the +40 mV depolarizing pulse stimulation.

Using the step end current in the presence of the test compound and the step end current in the absence of the test compound, the relative current in the solution containing the test compound at each concentration was calculated according to the following formula:

Relative current =

(Step end current in the presence of the test compound) / (Step end current in the absence of the test compound)

(6) Measurement of human GIRK1/4 current

While the membrane potential was holded at -80 mV, hyperpolarizing pulses (-80 mV for 0.05 seconds → -120 mV for 0.2 seconds → -80 mV for 0.05 seconds) were applied at a stimulation frequency of 1 Hz to measure GIRK1/4 channel current. More specifically, first, while perfusing an extracellular solution containing 0.1% DMSO and maintaining the membrane potential at -80 mV, hyperpolarizing pulses were applied. The current obtained during the pulse application was recorded as the current in the absence of the test compounds. Subsequently, while perfusing an extracellular solution containing 0.1 μM of a test compound and maintaining the membrane potential at -80 mV, hyperpolarizing pulses were applied.

After the inhibitory effect of the test compound had been stabilized, the current was recorded. The same procedure was repeated using an extracellular solution containing 1 μM of the test compound and then using an extracellular solution containing 10 μM of the test compound. The current obtained using the solution containing the test compound at each concentration were recorded.

The data was analyzed by using the step end current recorded during the -120 mV depolarizing stimulation. The "step end current" refers to the average current flowing for a period of 195 to 199 milliseconds from the start of the -120 mV depolarizing pulse stimulation.

Using the step end current in the presence of the test compound and the step end current in the absence of the test compound, the relative current in the solution containing the test compound at each concentration was calculated according to the following formula:

Relative current =

(Step end current in the presence of the test compound) / (Step end current in the absence of the test compound)

(7) Calculation of inhibitory activity on Kv1.5 channel ionic current and GIRK1/4 channel current

The concentration for 50% inhibition of Kv1.5 channel current or GIRK1/4 channel current (IC_{50} value) was calculated according to the following nonlinear regression equation:

[0423]

Relative current = $1/(1+ [\text{Concentration of the compound}]/IC_{50})^{nH}$

wherein nH is the Hill coefficient.

[0424]

Table 78 shows the test results.

[0425]

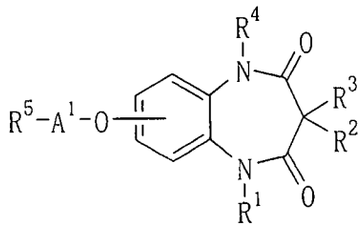
Table 78

Test Compound	KDR IC$_{50}$ (μM)	GIRK1/4 IC$_{50}$(μM)
Compound of Example 8	0.40	0.93
Compound of Example 10	0.58	3.6
Compound of Example 14	0.58	0.72
Compound of Example 19	0.54	1.4
Compound of Example 23	0.18	0.25
Compound of Example 31	1.30	2.90
Compound of Example 45	0.69	2.15
Compound of Example 50	0.25	0.46
Compound of Example 51	0.21	1.5
Compound of Example 54	0.28	0.97
Compound of Example 63	0.24	0.92
Compound of Example 68	0.38	5.1
Compound of Example 85	0.15	0.15
Compound of Example125	0.19	0.091
Compound of Example132	0.27	0.27
Compound of Example 200	0.29	0.59
Compound of Example 229	0.16	0.69
Compound of Example 242	0.18	0.22
Compound of Example 330	0.16	0.49
Compound of Example 395	0.19	0.33
Compound of Example 398	0.22	0.49
Compound of Example 417	0.18	0.98
Compound of Example 464	0.44	3.20
Compound of Example 551	0.39	5.20
Compound of Example 568	0.42	0.05
Compound of Example 573	0.33	1.50
Compound of Example 575	0.44	0.50
Compound of Example 590	0.46	2.40
Compound of Example 595	0.50	0.79
Compound of Example 611	0.31	0.37
Compound of Example 628	0.98	2.50
Compound of Example 629	0.76	0.17

Compound of Example 633	1.10	8.40
Compound of Example 634	0.36	0.49

CLAIMS

1. A benzodiazepine compound represented by General Formula (1)



(1)

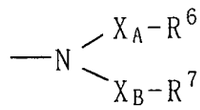
or a salt thereof,

wherein R^1, R^2, R^3, and R^4 are each independently hydrogen or lower alkyl;

R^2 and R^3 may be linked to form lower alkylene;

A^1 is lower alkylene optionally substituted with one or more hydroxy; and

R^5 is group represented by



wherein R^6 and R^7 are each independently hydrogen or organic group; X_A and X_B are each independently bond, lower alkylene, lower alkenylene, -CO-, $-SO_2-$, $-SO_2$-lower alkylene, -CO-lower alkylene, -CO-lower alkenylene, lower alkylene-N(lower alkyl)-CO-lower alkylene, lower alkylene-N(lower alkyl)-, lower alkylene-N(lower alkyl)-CO- or lower alkylene-O-.

2. A benzodiazepine compound represented by General Formula (1) or a salt thereof according to claim 1, wherein R^6 and R^7 are each independently hydrogen, lower alkyl, cyclo lower alkyl, aryl or heterocyclic group.

3. A benzodiazepine compound represented by General Formula (1) or a salt thereof according to claim 2, wherein R^6 and R^7 are each independently hydrogen, lower alkyl, cyclo lower alkyl, aryl or saturated or unsaturated monocyclic or polycyclic heterocyclic group containing at least one hetero atom selected from among oxygen, sulfur and nitrogen.

4. A benzodiazepine compound represented by General Formula (1) or a salt thereof according to claim 3, wherein R^6 and R^7 are each independently hydrogen, lower alkyl, cyclo lower alkyl, phenyl, naphthyl, furyl, thienyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, pyrrolyl, triazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, imidazo[2,1-b]thiazolyl, thieno[2,3-b]pyrazinyl, 2,3-dihydroimidazo[2,1-b]thiazolyl, benzothiazolyl, indolyl, imidazo[1,2-a]pyridyl, benzothienyl, benzimidazolyl, 2,3-dihydrobenzo[b]furyl, benzofuryl, indazolyl, furo[2,3-c]pyridyl, furo[3,2-c]pyridyl, thieno[2,3-c]pyridyl, thieno[3,2-c]pyridyl, thieno[2,3-b]pyridyl, benzo[1,3]dioxolyl, benzisoxazolyl, pyrazolo[2,3-a]pyridyl, indolizinyl, 2,3-dihydroindolyl, isoquinolyl, 1,2,3,4-tetrahydro-1H-isoquinolyl, carbostyril, 3,4-dihydrocarbostyril, quinolyl, chromanyl, 5,6,7,8-tetrahydroisoquinolyl, 3,4-dihydro-1H-isoquinolyl, naphthyridinyl, 1,4-benzodioxanyl, cinnolinyl, quinoxalinyl, or 2,3-dihydrobenz-1,4-oxazinyl, each of which is optionally substituted.

5. A benzodiazepine compound represented by General Formula (1) or a salt thereof according to claim 4, wherein R^6 and R^7 are each one of the following (1) to (52):

(1) hydrogen,

(2) lower alkyl,

(3) cyclo lower alkyl,

(4) phenyl optionally substituted with one or more substituents selected from the group consisting of the following (4-1) to (4-25):

(4-1) cyano,

(4-2) hydroxy,

(4-3) halogen,

(4-4) lower alkyl optionally substituted with one or more substituents selected from the group consisting of halogen, imidazolyl and morpholinyl,

(4-5) lower alkoxy optionally substituted with one or more substituents selected from the group consisting of amino and lower alkyl amino,

(4-6) pyridyl,

(4-7) thienyl,

(4-8) piperazinyl optionally substituted with one or more lower alkyl,

(4-9) phenyl,

(4-10) pyrazolyl optionally substituted with one or more lower alkyl,

(4-11) pyrimidinyl optionally substituted with one or more lower alkyl,

(4-12) piperidyl optionally substituted with one or more lower alkyl,

(4-13) furyl,

(4-14) carboxy,

(4-15) lower alkoxycarbonyl,

(4-16) amino optionally substituted with one or more substituents selected from the group consisting of lower alkanoyl and lower alkylsulfonyl,

(4-17) lower alkylthio,

(4-18) triazolyl,

(4-19) imidazolyl,

(4-20) pyrrolidinyl optionally substituted with one or more oxo,

(4-21) lower alkylsulfonyl,

(4-22) lower alkylenedioxy optionally substituted with one or more halogen,

(4-23) nitro,

(4-24) oxazolyl, and

(4-25) thiazolyl optionally substituted with one or more lower alkyl,

(5) naphthyl,

(6) furyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl optionally substituted with halogen, carboxy, sulfo, pyridyloxy, lower alkoxycarbonyl and phenyl,

(7) thienyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower alkylenedioxy, carboxy, halogen, pyridyl, lower alkoxy, lower alkoxycarbonyl, oxazolyl and furyl,

(8) imidazolyl optionally substituted with one or more substituents selected from the group consisting of phenyl, lower alkyl and halogen,

(9) pyrazolyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl optionally substituted with halogen, halogen, phenyl optionally substituted with lower alkoxy, furyl and thienyl,

(10) oxazolyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl and phenyl,

(11) isoxazolyl optionally substituted with one or more substituents selected from the group consisting of phenyl, lower alkyl, thienyl and furyl,

(12) thiazolyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl optionally substituted with lower alkoxy, phenyl and lower alkanoylamino,

(13) pyrrolyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl and lower alkoxycarbonyl,

(14) triazolyl optionally substituted with one or more lower alkyl,

(15) pyridyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl optionally substituted with halogen, oxo, hydroxy, lower alkoxy, halogen, pyrrolidinyl, morpholinyl and thienyl,

(16) pyrimidinyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl and phenyl,

(17) pyridazinyl,

(18) pyrazinyl,

(19) imidazo[2,1-b]thiazolyl optionally substituted with one or more halogen,

(20) thieno[2,3-b]pyrazinyl,

(21) 2,3-dihydroimidazo[2,1-b]thiazolyl optionally substituted with one or more phenyl,

(22) benzothiazolyl optionally substituted with one or more lower alkyl,

(23) indolyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower alkanoyl and halogen,

(24) imidazo[1,2-a]pyridyl optionally substituted with one or more

lower alkyl,

(25) benzothienyl optionally substituted with one or more lower alkyl,

(26) benzimidazolyl optionally substituted with one or more lower alkyl,

(27) 2,3-dihydrobenzo[b]furyl,

(28) benzofuryl optionally substituted with one or more halogen,

(29) indazolyl optionally substituted with one or more lower alkyl,

(30) furo[2,3-c]pyridyl optionally substituted with one or more substituents selected from the group consisting of oxo and lower alkyl,

(31) furo[3,2-c]pyridyl optionally substituted with one or more substituents selected from the group consisting of oxo, lower alkyl optionally substituted with halogen, halogen, furyl, pyridyl and phenyl optionally substituted with one or more substituents selected from the group consisting of amino and lower alkoxy,

(32) thieno[2,3-c]pyridyl optionally substituted with one or more substituents selected from the group consisting of oxo group and lower alkyl,

(33) thieno[3,2-c]pyridyl optionally substituted with one or more substituents selected from the group consisting of oxo and lower alkyl,

(34) thieno[2,3-b]pyridyl,

(35) benzo[1,3]dioxolyl optionally substituted with one or more halogen,

(36) benzisoxazolyl,

(37) pyrazolo[2,3-a]pyridyl,

(38) indolizinyl,

(39) 2,3-dihydroindolyl optionally substituted with one or more substituents selected from the group consisting of oxo, lower alkyl and lower alkanoyl,

(40) isoquinolyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl, halogen and oxo,

(41) 1,2,3,4-tetrahydro-1H-isoquinolyl optionally substituted with one or more oxo,

(42) carbostyril optionally substituted with one or more lower alkoxy,

(43) 3,4-dihydrocarbostyril optionally substituted with one or more lower alkoxy,

(44) quinolyl optionally substituted with one or more substituents selected from the group consisting of amino optionally substituted with one or two lower alkyl, lower alkoxy, lower alkyl and oxo,

(45) chromanyl optionally substituted with one or more lower alkyl,

(46) 5,6,7,8-tetrahydroisoquinolyl optionally substituted with one or more oxo,

(47) 3,4-dihydro-1H-isoquinolyl optionally substituted with one or more oxo,

(48) naphthyridinyl,

(49) 1,4-benzodioxanyl,

(50) cinnolinyl,

(51) quinoxalinyl, or

(52) 2,3-dihydrobenz-1,4-oxazinyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl and oxo.

6. A benzodiazepine compound represented by General Formula (1) or a salt thereof according to claim 5, wherein R^6 and R^7 are each one of the following (4a), (6a), (7a), (15a), (30a), (31a), (32a), (33a), (40a) and (44a):

(4a) phenyl optionally substituted with one or more substituents selected from the group consisting of the following (4a-1), (4a-4) and (4a-6):

(4a-1) cyano,

(4a-4) lower alkyl optionally substituted with one or more halogen, and

(4a-6) pyridyl,

(6a) furyl,

(7a) thienyl,

(15a) pyridyl optionally substituted with one or more lower alkyl,

(30a) furo[2,3-c]pyridyl optionally substituted with one or more oxo,

(31a) furo[3,2-c]pyridyl optionally substituted with one or more substituents selected from the group consisting of oxo and lower alkyl,

(32a) thieno[2,3-c]pyridyl optionally substituted with one or more oxo,

(33a) thieno[3,2-c]pyridyl optionally substituted with one or more

oxo,

(40a) isoquinolyl optionally substituted with one or more oxo, and

(44a) quinolyl optionally substituted with one or more oxo.

7. A benzodiazepine compound represented by General Formula (1) or a salt thereof according to claim 5, which is selected from the group consisting of the following compounds:

1-ethyl-3,3,5-trimethyl-7-{3-[(2-pyridin-3-ylethyl)pyridin-4-ylmethylamino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione trihydrochloride,

3,3,5-trimethyl-1-propyl-7-{3-[(2-pyridin-3-ylethyl)pyridin-4-ylmethylamino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione trihydrochloride,

1,5-diethyl-3,3-dimethyl-7-{3-[(2-pyridin-3-ylethyl)pyridin-4-ylmethylamino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione trihydrochloride,

1,3,3,5-tetramethyl-7-{3-[(2-pyridin-3-ylethyl)pyridin-4-ylmethylamino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione trihydrochloride,

1-ethyl-3,3,5-trimethyl-7-(3-{[2-(1-oxo-1H-isoquinolin-2-yl)ethyl]pyridin-4-ylmethylamino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride,

1-ethyl-3,3,5-trimethyl-7-(3-{[2-(7-oxo-7H-furo[2,3-c]pyridin-6-yl)ethyl]pyridin-4-ylmethylamino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride,

N-methyl-N-(2-{pyridin-4-ylmethyl-[3-(1,3,3,5-tetramethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]amino}ethyl)benzamide dihydrochloride,

1,3,3,5-tetramethyl-7-{3-[(2-methylbenzyl)-(2-pyridin-3-ylethyl)amino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride,

1,3,3,5-tetramethyl-7-{3-[(2-pyridin-3-ylethyl)-(quinolin-4-ylmethyl)amino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione trihydrochloride,

1-ethyl-3,3,5-trimethyl-7-{3-[(3-methylpyridin-4-ylmethyl)-(2-pyridin-3-ylethyl)amino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2

,4-dione trihydrochloride,
1-ethyl-3,3,5-trimethyl-7-(3-{[2-(2-oxo-2H-quinolin-1-yl)ethyl]pyridin-4-ylmethylamino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride,
1-ethyl-3,3,5-trimethyl-7-(3-{[2-(7-oxo-7H-thieno[2,3-c]pyridin-6-yl)ethyl]pyridin-4-ylmethylamino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride,
4-({[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]-[2-(1-oxo-1H-isoquinolin-2-yl)ethyl]amino}methyl)benzonitrile,
1-ethyl-3,3,5-trimethyl-7-(3-{[2-(1-oxo-1H-isoquinolin-2-yl)ethyl]thiophen-3-ylmethylamino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione,
1-ethyl-7-(3-{furan-2-ylmethyl-[2-(1-oxo-1H-isoquinolin-2-yl)ethyl]amino}propoxy)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione,
7-{3-[benzyl-(2-pyridin-3-ylethyl)amino]propoxy}-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione,
3-{[[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]-(2-pyridin-3-ylethyl)amino]methyl}benzonitrile,
1-ethyl-3,3,5-trimethyl-7-{3-[(2-pyridin-3-ylbenzyl)-(2-pyridin-3-ylethyl)amino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione,
4-({[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]-[2-(7-oxo-7H-furo[2,3-c]pyridin-6-yl)ethyl]amino}methyl)benzonitrile,
1-ethyl-3,3,5-trimethyl-7-{3-[[2-(7-oxo-7H-furo[2,3-c]pyridin-6-yl)ethyl]-(4-trifluoromethylbenzyl)amino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione,
1-ethyl-3,3,5-trimethyl-7-(3-{(2-methylbenzyl)-[2-(7-oxo-7H-furo[2,3-c]pyridin-6-yl)ethyl]amino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione,
1-ethyl-3,3,5-trimethyl-7-(3-{[2-(7-oxo-7H-furo[2,3-c]pyridin-6-yl)ethyl]thiophen-2-ylmethylamino}propoxy)-1,5-dihydrobenzo[b]

[1,4]diazepine-2,4-dione,
1-ethyl-3,3,5-trimethyl-7-(3-{[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]pyridin-4-ylmethylamino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride,
1-ethyl-3,3,5-trimethyl-7-(3-{[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]pyridin-3-ylmethylamino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione,
1-ethyl-3,3,5-trimethyl-7-(3-{[2-(4-oxo-4H-thieno[3,2-c]pyridin-5-yl)ethyl]pyridin-3-ylmethylamino}propoxy)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione,
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1-ethyl-3,3,5-trimethyl-7-{3-[[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-(2-propylpyridin-3-ylmethyl)amino]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride,
N-[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]-N-(2-pyridin-3-ylethyl)benzenesulfonamide hydrochloride,
7-(3-{(2,6-dimethylpyridin-3-ylmethyl)-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}propoxy)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride,
N-[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yloxy)propyl]-N-(2-pyridin-3-ylethyl)benzamide hydrochloride, and
N-[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-

benzo[b][1,4]diazepin-7-yloxy)propyl]-N-[2-(1-oxo-1H-isoquinolin-2-yl)ethyl]benzenesulfonamide.

8. A pharmaceutical composition comprising a benzodiazepine compound represented by Formula (1) or a salt thereof according to claim 1, and a pharmacologically acceptable carrier.

9. A pharmaceutical composition according to claim 8 for preventing and/or treating arrhythmia.

10. A benzodiazepine compound represented by Formula (1) or a salt thereof according to claim 1 for use in the pharmaceutical composition.

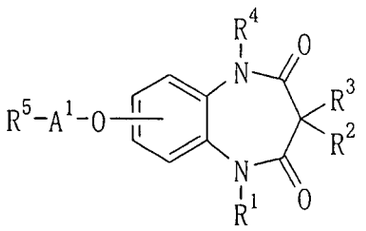
11. Use of a benzodiazepine compound represented by Formula (1) or a salt thereof according to claim 1 as a pharmaceutical composition.

12. Use of a benzodiazepine compound represented by Formula (1) or a salt thereof according to claim 1 for the production of a pharmaceutical composition.

13. A method of preventing and/or treating arrhythmia, comprising administering to a patient a benzodiazepine compound represented by Formula (1) or a salt thereof according to claim 1.

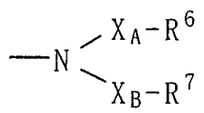
ABSTRACT

The present invention provides a novel benzodiazepine compound that blocks the I_{Kur} current or the Kv1.5 channel potently and more selectively than other K^+ channels. The benzodiazepine compound of the invention is represented by General Formula (1)



(1)

wherein R^1, R^2, R^3, and R^4 are each independently hydrogen or lower alkyl; R^2 and R^3 may be linked to form lower alkylene;
A^1 is lower alkylene optionally substituted with one or more hydroxy; and
R^5 is group represented by



wherein R^6 and R^7 are each independently hydrogen or organic group; Y_A and Y_B are each independently bond, lower alkylene, etc.

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<120> BENZODIAZEPINE COMPOUND AND PHARMACEUTICAL COMPOSITION

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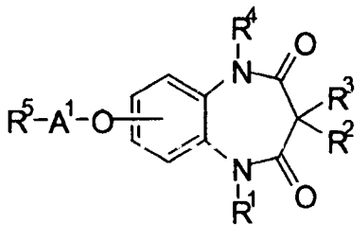
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COMPUESTO DE BENZODIAZEPINA Y COMPOSICIÓN FARMACÉUTICA

RESUMEN

La presente invención provee un nuevo compuesto de benzodiazepina que bloquea la corriente I_{Kur} o el canal Kv1.5 en forma potente y más selectiva que otros canales de K^+. El compuesto de benzodiazepina de la invención está representado por la Fórmula general (1)

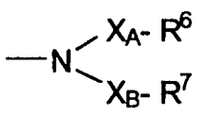


(1)

en donde R^1, R^2, R^3 y R^4 son cada uno independientemente hidrógeno o alquilo inferior; R^2 y R^3 pueden estar unidos para formar alquileno inferior;

A^1 es alquileno inferior opcionalmente substituido con uno o más hidroxi; y

R^5 es un grupo representado por:



en donde R^6 y R^7 son cada uno independientemente hidrógeno o un grupo orgánico;

X_A y X_B son cada uno independientemente un enlace, alquileno inferior, etc.

La presente invención se refiere a un compuesto de benzodiazepina y a una composición farmacéutica.

La fibrilación atrial (denominada a continuación "AF") es el tipo de arritmia observado con mayor frecuencia en los exámenes clínicos. Aunque no es una arritmia letal, la AF causa embolia cerebral cardiogénica y por lo tanto se la reconoce como una arritmia que afecta mucho los pronósticos vitales y la calidad de vida. Es conocido que la aparición de la AF aumenta con la edad y que ataques repetidos de AF llevan a una AF crónica (seria) (The Journal of American Medical Association, 285, 2370-2375 (2001) y Circulation, 114, 119-123 (2006)).

Para prevenir la AF crónica, que causa dificultad para restaurar el ritmo sinusal y aumenta el riesgo de embolia cerebral cardiogénica, se requiere una desfibrilación temprana y la subsiguiente prevención de la recurrencia (mantenimiento del ritmo sinusal). Las drogas antiarrítmicas (clases I y III) se usan más comúnmente como farmacoterapia, pero estas drogas logran efectos terapéuticos insuficientes, mientras que causan serios efectos colaterales tales como un efecto proarrítmico (Am. J. Cardiol., 72, B44-B49 (1993)).

La aparición de la AF es activada por la contracción prematura atrial con causas subyacentes tales como retardo de la conducción intraatrial, acortamiento y heterogeneidad del período refractario atrial (Nature Reviews DRUG DISCOVERY 4, 899-910 (2005)). Es conocido que la prolongación del período refractario del músculo atrial puede terminar la AF (desfibrilación) o evitar que ocurra la AF. La duración del potencial de acción del músculo cardíaco en mamíferos es

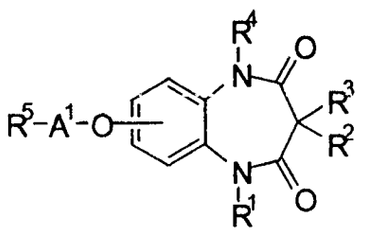
determinada predominantemente por canales de K^+ dependientes del voltaje. La inhibición del canal de K^+ prolonga la duración del potencial de acción miocárdico, lo que da por resultado la prolongación del período refractario (Nature Reviews DRUG DISCOVERY 5, 1034-49 (2006)). El mecanismo de acción de las drogas antiarrítmicas de clase III (por ej., Dofetilida) consiste en inhibir la corriente de K^+ (I_{Kr}) del tipo rectificador retardado de activación rápida, la corriente de K^+ codificada por HERG. Sin embargo, como la I_{Kr} está presente en el atrio y los ventrículos, tales drogas podrían causar arritmias ventriculares, tales como la taquicardia ventricular polimorfa ("torsades de pointes") (Trends Pharmacol. Soc., 22, 240-246 (2001)).

La corriente de K^+ (I_{Kur}) del tipo rectificador retardado de activación ultra-rápida, la corriente de K^+ codificada por Kv1.5, ha sido identificada como el canal de K^+ que se expresa específicamente sólo en el atrio humano (Cric. Res., 73, 1061-1076 (1993), J. Physiol., 491, 31-50 (1996) y Cric. Res., 80, 572-579 (1997)). La corriente de potasio muscarínica (I_{KACh}) codificada por dos genes denominados GIRK1 y GIRK4 es conocida como un canal de K^+ que se expresa específicamente en el atrio humano (Nature 374, 135-141 (1995)). Por consiguiente, una substancia farmacológicamente aceptable que bloquea selectivamente la corriente I_{Kur} (el canal Kv1.5) o la corriente I_{KAch} (canal GIRK1/4) puede actuar selectivamente sobre el músculo atrial y es considerada efectiva para excluir el efecto proarrítmico causado por la duración del potencial de acción prolongada del músculo ventricular.

Los presentes inventores realizaron una amplia investigación para desarrollar un compuesto que bloquee la corriente I_{Kur} (canal Kv1.5) y/o la corriente I_{KAch} (canal GIRK1/4) en forma potente y más selectiva que otros canales de K^+. Como resultado, los inventores hallaron que un nuevo compuesto de benzodiazepina representado por la Fórmula general (1) indicada más abajo podría ser el compuesto deseado. La presente invención se ha logrado en base a los hallazgos arriba mencionados.

La presente invención provee compuestos de benzodiazepina y composiciones farmacéuticas que comprenden los compuestos de benzodiazepina como se resume en los ítems 1 a 13 a continuación.

Ítem 1. Un compuesto de benzodiazepina representado por la Fórmula general (1):



(1)

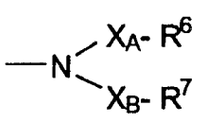
o una sal del mismo,

en donde R^1, R^2, R^3 y R^4 son cada uno independientemente hidrógeno o alquilo inferior;

R^2 y R^3 pueden estar unidos para formar alquileno inferior;

A^1 es alquileno inferior opcionalmente substituido con uno o más hidroxi; y

R^5 es un grupo representado por:



en donde R^6 y R^7 son cada uno independientemente hidrógeno o un grupo orgánico;

X_A y X_B son cada uno independientemente un enlace, alquileno inferior, alquenileno inferior, -CO-, $-SO_2-$, $-SO_2-$ alquileno inferior, -CO-alquileno inferior, -CO-alquenileno inferior, alquileno inferior-N(alquilo inferior)-CO-alquileno inferior, alquileno inferior-N-(alquilo inferior)-, alquileno inferior-N(alquilo inferior)-CO- o alquileno inferior-O-.

Ítem 2. Un compuesto de benzodiazepina representado por la Fórmula general (1) o una sal del mismo de acuerdo con el ítem 1,

en donde R^6 y R^7 son cada uno independientemente hidrógeno, alquilo inferior, ciclo alquilo inferior, arilo o un grupo heterocíclico.

Ítem 3. Un compuesto de benzodiazepina representado por la Fórmula general (1) o una sal del mismo de acuerdo con el ítem 2,

en donde R^6 y R^7 son cada uno independientemente hidrógeno, alquilo inferior, ciclo alquilo inferior, arilo o un grupo heterocíclico monocíclico o policíclico saturado o insaturado que contiene por lo menos un heteroátomo seleccionado entre oxígeno, azufre y nitrógeno.

Ítem 4. Un compuesto de benzodiazepina representado por la Fórmula general (1) o una sal del mismo de acuerdo con el ítem 3,

en donde R^6 y R^7 son cada uno independientemente hidrógeno, alquilo inferior, ciclo alquilo inferior, fenilo, naftilo,

furilo, tienilo, pirazolilo, oxazolilo, isoxazolilo, tiazolilo, pirrolilo, triazolilo, piridilo, pirimidinilo, piridazinilo, pirazinilo, imidazo[2,1-b]-tiazolilo, tieno[2,3-b]pirazinilo, 2,3-dihidroimidazo[2,1-b]tiazolilo, benzotiazolilo, indolilo, imidazo[1,2-a]-piridilo, benzotienilo, benzimidazolilo, 2,3-dihidrobenzo[b]furilo, benzofurilo, indazolilo, furo[2,3-c]piridilo, furo[3,2-c]piridilo, tieno[2,3-c]piridilo, tieno[3,2-c]piridilo, tieno[2,3-b]piridilo, benzo[1,3]-dioxolilo, benz-isoxazolilo, pirazolo[2,3-a]piridilo, indolizinilo, 2,3-dihidroindolilo, isoquinolilo, 1,2,3,4-tetrahidro-1H-isoquinolilo, carboestirilo, 3,4-dihidrocarboestirilo, quinolilo, cromanilo, 5,6,7,8-tetrahidroisoquinolilo, 3,4-dihidro-1H-isoquinolilo, naftiridinilo, 1,4-benzodioxanilo, cinolinilo, quinoxalinilo o 2,3-dihidrobenz-1,4-oxazinilo, cada uno de los cuales está opcionalmente substituido.

Ítem 5. Un compuesto de benzodiazepina representado por la Fórmula general (1) o una sal del mismo de acuerdo con el ítem 4,

en donde R^6 y R^7 son cada uno, uno de los siguientes (1) a (52):

(1) hidrógeno,

(2) alquilo inferior,

(3) ciclo alquilo inferior,

(4) fenilo opcionalmente substituido con uno o más substituyentes seleccionados entre el grupo que consiste en los siguientes (4-1) a (4-25):

(4-1) ciano,

(4-2) hidroxi,

(4-3) halógeno,

(4-4) alquilo inferior opcionalmente substituido con uno o más substituyentes seleccionados entre el grupo que consiste en halógeno, imidazolilo y morfolinilo,

(4-5) alcoxi inferior opcionalmente substituido con uno o más substituyentes seleccionados entre el grupo que consiste en amino y alquilo inferior amino,

(4-6) piridilo,

(4-7) tienilo,

(4-8) piperazinilo opcionalmente substituido con uno o más alquilo inferior,

(4-9) fenilo,

(4-10) pirazolilo opcionalmente substituido con uno o más alquilo inferior,

(4-11) pirimidinilo opcionalmente substituido con uno o más alquilo inferior,

(4-12) piperidilo opcionalmente substituido con uno o más alquilo inferior,

(4-13) furilo,

(4-14) carboxi,

(4-15) alcoxicarbonilo inferior,

(4-16) amino opcionalmente substituido con uno o más substituyentes seleccionados entre el grupo que consiste en alcanoilo inferior y alquilsulfonilo inferior,

(4-17) alquiltio inferior,

(4-18) triazolilo,

(4-19) imidazolilo,

(4-20) pirrolidinilo opcionalmente substituido con uno o más oxo,

(4-21) alquilsulfonilo inferior,

(4-22) alquilenodioxi inferior opcionalmente substituido con uno o más de halógeno,

(4-23) nitro,

(4-24) oxazolilo, y

(4-25) tiazolilo opcionalmente substituido con uno o más alquilo inferior,

(5) naftilo,

(6) furilo opcionalmente substituido con uno o más substituyentes seleccionados entre el grupo que consiste en alquilo inferior opcionalmente substituido con halógeno, carboxi, sulfo, piridiloxi, alcoxicarbonilo inferior y fenilo,

(7) tienilo opcionalmente substituido con uno o más substituyentes seleccionados entre el grupo que consiste en alquilo inferior, alquilenodioxi inferior, carboxi, halógeno, piridilo, alcoxi inferior, alcoxicarbonilo inferior, oxazolilo y furilo,

(8) imidazolilo opcionalmente substituido con uno o más substituyentes seleccionados entre el grupo que consiste en fenilo, alquilo inferior y halógeno,

(9) pirazolilo opcionalmente substituido con uno o más substituyentes seleccionados entre el grupo que consiste en alquilo inferior opcionalmente substituido con halógeno, halógeno, fenilo opcionalmente substituido con alcoxi inferior, furilo y tienilo,

(10) oxazolilo opcionalmente substituido con uno o más substituyentes seleccionados entre el grupo que consiste en alquilo inferior y fenilo,

(11) isoxazolilo opcionalmente substituido con uno o más substituyentes seleccionados entre el grupo que consiste en fenilo, alquilo inferior, tienilo y furilo,

(12) tiazolilo opcionalmente substituido con uno o más substituyentes seleccionados entre el grupo que consiste en alquilo inferior opcionalmente substituido con alcoxi inferior, fenilo y alcanoilamino inferior,

(13) pirrolilo opcionalmente substituido con uno o más substituyentes seleccionados entre el grupo que consiste en alquilo inferior y alcoxicarbonilo inferior,

(14) triazolilo opcionalmente substituido con uno o más alquilo inferior,

(15) piridilo opcionalmente substituido con uno o más substituyentes seleccionados entre el grupo que consiste en alquilo inferior opcionalmente substituido con halógeno, oxo, hidroxi, alcoxi inferior, halógeno, pirrolidinilo, morfolinilo y tienilo,

(16) pirimidinilo opcionalmente substituido con uno o más substituyentes seleccionados entre el grupo que consiste en alquilo inferior y fenilo,

(17) piridazinilo,

(18) pirazinilo,

(19) imidazo[2,1-b]tiazolilo opcionalmente substituido con uno o más halógeno,

(20) tieno[2,3-b]pirazinilo,

(21) 2,3-dihidroimidazo[2,1-b]tiazolilo opcionalmente substituido con uno o más fenilo,

(22) benzotiazolilo opcionalmente substituido con uno o más alquilo inferior,

(23) indolilo opcionalmente substituido con uno o más substituyentes seleccionados entre el grupo que consiste en alquilo inferior, alcanoilo inferior y halógeno,

(24) imidazo[1,2-a]piridilo opcionalmente substituido con uno o más alquilo inferior,

(25) benzotienilo opcionalmente substituido con uno o más alquilo inferior,

(26) benzimidazolilo opcionalmente substituido con uno o más alquilo inferior,

(27) 2,3-dihidrobenzo[b]furilo,

(28) benzofurilo opcionalmente substituido con uno o más de halógeno,

(29) indazolilo opcionalmente substituido con uno o más alquilo inferior,

(30) furo[2,3-c]piridilo opcionalmente substituido con uno o más substituyentes seleccionados entre el grupo que consiste en oxo y alquilo inferior,

(31) furo[3,2-c]piridilo opcionalmente substituido con uno o más substituyentes seleccionados entre el grupo que consiste en oxo, alquilo inferior opcionalmente substituido con halógeno, halógeno, furilo, piridilo y fenilo opcionalmente substituido con uno o más substituyentes seleccionados entre el grupo que consiste en amino y alcoxi inferior,

(32) tieno[2,3-c]piridilo opcionalmente substituido con uno o más substituyentes seleccionados entre el grupo que consiste en oxo grupo y alquilo inferior,

(33) tieno[3,2-c]piridilo opcionalmente substituido con uno o más substituyentes seleccionados entre el grupo que consiste en oxo y alquilo inferior,

(34) tieno[2,3-b]piridilo,

(35) benzo[1,3]dioxolilo opcionalmente substituido con uno o más halógeno,

(36) benzisoxazolilo,

(37) pirazolo[2,3-a]piridilo,

(38) indolizinilo,

(39) 2,3-dihidroindolilo opcionalmente substituido con uno o más substituyentes seleccionados entre el grupo que consiste en oxo, alquilo inferior y alcanoilo inferior,

(40) isoquinolilo opcionalmente substituido con uno o más substituyentes seleccionados entre el grupo que consiste en alquilo inferior, halógeno y oxo,

(41) 1,2,3,4-tetrahidro-1H-isoquinolilo opcionalmente substituido con uno o más oxo,

(42) carboestirilo opcionalmente substituido con uno o más de alcoxi inferior,

(43) 3,4-dihidrocarboestirilo opcionalmente substituido con uno o más de alcoxi inferior,

(44) quinolilo opcionalmente substituido con uno o más substituyentes seleccionados entre el grupo que consiste en amino opcionalmente substituido con uno o dos alquilo inferior, alcoxi inferior, alquilo inferior y oxo,

(45) cromanilo opcionalmente substituido con uno o más alquilo inferior,

(46) 5,6,7,8-tetrahidroisoquinolilo opcionalmente substituido con uno o más oxo,

(47) 3,4-dihidro-1H-isoquinolilo opcionalmente substituido con uno o más oxo,

(48) naftiridinilo,

(49) 1,4-benzodioxanilo,

(50) cinolinilo,

(51) quinoxalinilo, o

(52) 2,3-dihidrobenz-1,4-oxazinilo opcionalmente substituido con uno o más substituyentes seleccionados entre el grupo que consiste en alquilo inferior y oxo.

Ítem 6. Un compuesto de benzodiazepina representado por la Fórmula general (1) o una sal del mismo de acuerdo con el ítem 5,

en donde R^6 y R^7 son cada uno, uno de los siguientes (4a), (6a), (7a), (15a), (30a), (31a), (32a), (33a), (40a) y (44a):

(4a) fenilo opcionalmente substituido con uno o más substituyentes seleccionados entre el grupo que consiste en los siguientes (4a-1), (4a-4) y (4a-6):

(4a-1) ciano,

(4a-4) alquilo inferior opcionalmente substituido con uno o más de halógeno, y

(4a-6) piridilo,

(6a) furilo,

(7a) tienilo,

(15a) piridilo opcionalmente substituido con uno o más alquilo inferior,

(30a) furo[2,3-c]piridilo opcionalmente substituido con uno o más oxo,

(31a) furo[3,2-c]piridilo opcionalmente substituido con uno o más substituyentes seleccionados entre el grupo que consiste en oxo y alquilo inferior,

(32a) tieno[2,3-c]piridilo opcionalmente substituido con uno o más oxo,

(33a) tieno[3,2-c]piridilo opcionalmente substituido con uno o más oxo,

(40a) isoquinolilo opcionalmente substituido con uno o más oxo, y

(44a) quinolilo opcionalmente substituido con uno o más oxo.

Ítem 7. Un compuesto de benzodiazepina representado por la Fórmula general (1) o una sal del mismo de acuerdo con el ítem 6, que es seleccionado entre el grupo que consiste en los siguientes compuestos:

- triclorhidrato de 1-etil-3,3,5-trimetil-7-{3-[(2-piridin-3-iletil)piridin-4-ilmetilamino]propoxi}-1,5-dihidrobenzo[b]-[1,4]diazepina-2,4-diona,
- triclorhidrato de 3,3,5-trimetil-1-propil-7-{3-[(2-piridin-3-iletil)piridin-4-ilmetilamino]propoxi}-1,5-dihidrobenzo-[b][1,4]diazepina-2,4-diona,
- triclorhidrato de 1,5-dietil-3,3-dimetil-7-{3-[(2-piridin-3-iletil)piridin-4-ilmetilamino]propoxi}-1,5-dihidrobenzo-[b][1,4]diazepina-2,4-diona,
- triclorhidrato de 1,3,3,5-tetrametil-7-{3-[(2-piridin-3-iletil)piridin-4-ilmetilamino]propoxi}-1,5-dihidrobenzo[b]-[1,4]diazepina-2,4-diona,
- diclorhidrato de 1-etil-3,3,5-trimetil-7-(3-{[2-(1-oxo-1H-isoquinolin-2-il)etil]piridin-4-ilmetilamino}propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona,
- diclorhidrato de 1-etil-3,3,5-trimetil-7-(3-{[2-(7-oxo-7H-furo[2,3-c]piridin-6-il)etil]piridin-4-ilmetilamino}-propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona
- diclorhidrato de N-metil-N-(2-{piridin-4-ilmetil-[3-(1,3,3,5-tetrametil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo-

[b][1,4]diazepin-7-iloxi)propil]amino}etil)benzamida,

- diclorhidrato de 1,3,3,5-tetrametil-7-{3-[(2-metilbencil)-(2-piridin-3-iletil)amino]propoxi}-1,5-dihidrobenzo[b]-[1,4]diazepina-2,4-diona,

- triclorhidrato de 1,3,3,5-tetrametil-7-{3-[(2-piridin-3-iletil)-(quinolin-4-ilmetil)amino]propoxi}-1,5-dihidro-benzo[b][1,4]diazepina-2,4-diona,

- triclorhidrato de 1-etil-3,3,5-trimetil-7-{3-[(3-metilpiridin-4-ilmetil)-(2-piridin-3-iletil)amino]propoxi}-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona,

- diclorhidrato de 1-etil-3,3,5-trimetil-7-(3-{[2-(2-oxo-2H-quinolin-1-il)etil]piridin-4-ilmetilamino}propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona,

- diclorhidrato de 1-etil-3,3,5-trimetil-7-(3-{[2-(7-oxo-7H-tieno[2,3-c]piridin-6-il)etil]piridin-4-ilmetilamino}-propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona,

- 4-({[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil]-[2-(1-oxo-1H-isoquinolin-2-il)etil]amino}metil)benzonitrilo,

1-etil-3,3,5-trimetil-7-(3-{[2-(1-oxo-1H-isoquinolin-2-il)etil]tiofen-3-ilmetilamino}propoxi)-1,5-dihidrobenzo[b]-[1,4]diazepina-2,4-diona,

- 1-etil-7-(3-{furan-2-ilmetil-[2-(1-oxo-1H-isoquinolin-2-il)etil]amino}propoxi)-3,3,5-trimetil-1,5-dihidrobenzo-[b][1,4]diazepina-2,4-diona,

- 7-{3-[bencil-(2-piridin-3-iletil)amino]propoxi}-1-etil-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona,

- 3-{[[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetra-hidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil]-(2-piridin-3-

iletil)amino]metil}benzonitrilo,

- 1-etil-3,3,5-trimetil-7-{3-[(2-piridin-3-ilbencil)-(2-piridin-3-iletil)amino]propoxi}-1,5-dihidrobenzo[b][1,4]-diazepina-2,4-diona,

- 4-({[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetra-hidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil]-[2-(7-oxo-7H-furo[2,3-c]piridin-6-il)etil]amino}metil)benzonitrilo,

- 1-etil-3,3,5-trimetil-7-{3-[[2-(7-oxo-7H-furo[2,3-c]-piridin-6-il)etil]-(4-trifluorometilbencil)amino]-propoxi}-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona,

- 1-etil-3,3,5-trimetil-7-(3-{(2-metilbencil)-[2-(7-oxo-7H-furo[2,3-c]piridin-6-il)etil]amino}propoxi)-1,5-dihidro-benzo[b][1,4]diazepina-2,4-diona,

- 1-etil-3,3,5-trimetil-7-(3-{[2-(7-oxo-7H-furo[2,3-c]-piridin-6-il)etil]tiofen-2-ilmetilamino}propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona,

- diclorhidrato de 1-etil-3,3,5-trimetil-7-(3-{[2-(2-metil-4-oxo-4H-furo[3,2-c]piridin-5-il)etil]piridin-4-ilmetil-amino}propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona,

- 1-etil-3,3,5-trimetil-7-(3-{[2-(4-oxo-4H-furo[3,2-c]-piridin-5-il)etil]piridin-3-ilmetilamino}propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona,

- 1-etil-3,3,5-trimetil-7-(3-{[2-(4-oxo-4H-tieno[3,2-c]piridin-5-il)etil]piridin-3-ilmetilamino}propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona,

- 1-etil-3,3,5-trimetil-7-{3-[[2-(2-metil-4-oxo-4H-furo-[3,2-c]piridin-5-il)etil]-(4-metilpiridin-3-ilmetil)amino]-propoxi}-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona,

- 1-etil-3,3,5-trimetil-7-(3-{(2-metilpiridin-3-ilmetil)-[2-(4-oxo-4H-furo[3,2-c]piridin-5-il)etil]amino}-propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona,
- 1-etil-3,3,5-trimetil-7-(3-{(4-metilpiridin-3-il-metil)-[2-(4-oxo-4H-furo[3,2-c]piridin-5-il)etil]amino}-propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona,
- 1-etil-3,3,5-trimetil-7-(3-{(2-metilpiridin-3-il-metil)-[2-(4-oxo-4H-tieno[3,2-c]piridin-5-il)etil]amino}-propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona,
- diclorhidrato de 1-etil-3,3,5-trimetil-7-{3-[[2-(2-metil-4-oxo-4H-furo[3,2-c]piridin-5-il)etil]-(2-propil-piridin-3-ilmetil)amino]-propoxi}-1,5-dihidrobenzo[b][1,4]-diazepina-2,4-diona,
- clorhidrato de N-[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)-propil]-N-(2-piridin-3-iletil)bencenosulfonamida,
- diclorhidrato de 7-(3-{(2,6-dimetilpiridin-3-ilmetil)-[2-(4-oxo-4H-furo[3,2-c]piridin-5-il)etil]amino}propoxi)-1-etil-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona,
- clorhidrato de N-[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)-propil]-N-(2-piridin-3-iletil)benzamida, y
- N-[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil]-N-[2-(1-oxo-1H-isoquinolin-2-il)etil]bencenosulfonamida.

Ítem 8. Una composición farmacéutica que comprende un compuesto de benzodiazepina representado por la Fórmula (1) o una sal del mismo de acuerdo con la reivindicación 1, y un

vehículo farmacológicamente aceptable.

Ítem 9. Una composición farmacéutica de acuerdo con el ítem 8 para prevenir y/o tratar la arritmia.

Ítem 10. Un compuesto de benzodiazepina representado por la Fórmula (1) o una sal del mismo de acuerdo con el ítem 1 para usar en la composición farmacéutica.

Ítem 11. Uso de un compuesto de benzodiazepina representado por la Fórmula (1) o una sal del mismo de acuerdo con el ítem 1 como una composición farmacéutica.

Ítem 12. Uso de un compuesto de benzodiazepina representado por la Fórmula (1) o una sal del mismo de acuerdo con el ítem 1 para la producción de una composición farmacéutica.

Ítem 13. Un método para prevenir y/o tratar la arritmia, que comprende administrar a un paciente un compuesto de benzodiazepina representado por la Fórmula (1) o una sal del mismo de acuerdo con el ítem 1.

Los grupos representados por R^1, R^2, R^3, R^4, R^5, R^6, R^7, A^1, X_A y X_B, en la memoria se describen más abajo.

Ejemplos de "grupo orgánico" incluyen alquilo inferior, ciclo alquilo inferior, arilo tal como fenilo y naftilo, un grupo heterocíclico tal como el (6) a (52) para R^6 y R^7.

Ejemplos de "grupo heterocíclico" incluyen grupos heterocíclicos monocíclicos o policíclicos saturados o insaturados que contienen por lo menos un heteroátomo seleccionado entre oxígeno, azufre y nitrógeno. El grupo heterocíclico que más se prefiere puede ser un grupo tal como:

- un grupo heteromonocíclico de 3 a 8 miembros,

preferentemente de 5 o 6 miembros, insaturado, que contiene 1 a 4 átomos de nitrógeno, por ejemplo, pirrolilo, pirrolinilo, imidazolilo, pirazolilo, piridilo y su N-óxido, pirimidinilo, pirazinilo, piridazinilo, triazolilo (por ej., 4H-1,2,4-triazolilo, 1H-1,2,3-triazolilo, 2H-1,2,3-triazolilo, etc.), tetrazolilo (por ej., 1H-tetrazolilo, 2H-tetrazolilo, etc.), dihidrotriazinilo (por ej., 4,5-dihidro-1,2,4-triazinilo, 2,5-dihidro-1,2,4-triazinilo, etc.), etc.;

- un grupo heteromonocíclico de 3 a 8 miembros, preferentemente 5 o 6 miembros, saturado, que contiene 1 a 4 átomos de nitrógeno, por ejemplo, azetidinilo, pirrolidinilo, imidazolidinilo, piperidinilo, pirazolidinilo, piperazinilo, etc.;

- un grupo heterocíclico de 7 a 12 miembros, insaturado, condensado, que contiene 1 a 5 átomos de nitrógeno, por ejemplo, indolilo, dihidroindolilo (por ej., 2,3-dihidroindolilo, etc.), isoindolilo, indolizinilo, benzimidazolilo, quinolilo, isoquinolilo, dihidroisoquinolilo (por ej., 3,4-dihidro-1H-isoquinolilo, etc.), tetrahidroisoquinolilo (por ej., 1,2,3,4-tetrahidro-1H-isoquinolilo, 5,6,7,8-tetrahidroisoquinolilo, etc.), carboestirilo, dihidrocarboestirilo (por ej., 3,4-dihidrocarboestirilo, etc.), indazolilo, benzotriazolilo, tetrazolopiridilo, tetrazolopiridazinilo (por ej., tetrazolo[1,5-b]piridazinilo, etc.), dihidrotriazolopiridazinilo, imidazopiridilo (por ej., imidazo[1,2-a]-piridilo, etc.), naftiridinilo, cinolinilo, quinoxalinilo, pirazolopiridilo (por ej., pirazolo[2,3-a]piridilo, etc.) etc.;

- un grupo heteromonocíclico de 3 a 8 miembros, preferentemente 5 o 6 miembros, insaturado, que contiene 1 a 2 átomos de oxígeno, por ejemplo, furilo, etc.;
- un grupo heterocíclico de 7 a 12 miembros, insaturado, condensado, que contiene 1 a 3 átomos de oxígeno, por ejemplo, benzofurilo, dihidrobenzofurilo (por ej. 2,3-dihidrobenzo[b]furilo, etc.), cromanilo, benzodioxanilo (por ej., 1,4-benzodioxanilo, etc.), dihidrobenzoxazinilo (por ej., 2,3-dihidrobenz-1,4-oxazinil, etc.), benzodioxolil-(benzo[1,3]dioxolilo, etc.), etc.;
- un grupo heteromonocíclico de 3 a 8 miembros, preferentemente 5 o 6 miembros, insaturado, que contiene 1 a 2 átomos de oxígeno y 1 a 3 átomos de nitrógeno, por ejemplo, oxazolilo, isoxazolilo, oxadiazolilo (por ej., 1,2,4-oxadiazolilo, 1,3,4-oxadiazolilo, 1,2,5-oxadiazolilo, etc.), etc.;
- un grupo heteromonocíclico, de 3 a 8 miembros, preferentemente 5 o 6 miembros, saturado, que contiene 1 a 2 átomos de oxígeno y 1 a 3 átomos de nitrógeno, por ejemplo, morfolinilo, etc.;
- un grupo heterocíclico de 7 a 12 miembros, insaturado, condensado, que contiene 1 a 2 átomos de oxígeno y 1 a 3 átomos de nitrógeno, por ejemplo, benzoxazolilo, benzoxadiazolilo, benzisoxazolilo, furopiridilo (por ej., furo[2,3-b]piridilo, furo[3,2-c]piridilo, etc.), etc.;
- un grupo heteromonocíclico de 3 a 8 miembros, preferentemente 5 o 6 miembros, insaturado, que contiene 1 a 2 átomos de azufre y 1 a 3 átomos de nitrógeno, por ejemplo, tiazolilo, 1,2-tiazolilo, tiazolinilo, tiadiazolilo (por ej.,

1,2,4-tiadiazolilo, 1,3,4-tiadiazolilo, 1,2,5-tiadiazolilo, 1,2,3-tiadiazolilo, etc.), etc.;

- un grupo heteromonocíclico de 3 a 8 miembros, preferentemente 5 o 6 miembros, saturado, que contiene 1 a 2 átomos de azufre y 1 a 3 átomos de nitrógeno, por ejemplo, tiazolidinilo, etc.;

- un grupo heteromonocíclico de 3 a 8 miembros, preferentemente 5 o 6 miembros, insaturado, que contiene un átomo de azufre, por ejemplo, tienilo, etc.;

- un grupo heterocíclico de 7 a 12 miembros, insaturado, condensado, que contiene 1 a 3 átomos de azufre, por ejemplo, benzotienilo (por ej., benzolb]tienilo, etc.),

- un grupo heterocíclico de 7 a 12 miembros, insaturado, condensado, que contiene 1 a 2 átomos de azufre y 1 a 3 átomos de nitrógeno, por ejemplo, benzotiazolilo, benzotiadiazolilo, tienopiridilo (por ej., tieno[2,3-b]-piridilo, tieno[2,3-c]piridilo, tieno[3,2-c]piridilo, etc.), imidazotiazolilo (por ej., imidazo[2,1-b]tiazolilo, etc.), dihidroimidazotiazolilo (por ej., 2,3-dihidroimidazo[2,1-b]tiazolilo, etc.), tienopirazinilo (por ej., tieno[2,3-b]pirazinilo, etc.), etc. y similares; en donde dicho grupo heterocíclico puede ser substituido por uno o más substituyentes adecuados.

Ejemplos de "alquilo inferior" incluyen grupos alquilo lineales o ramificados, que tienen 1 a 6 átomos de carbono, tales como metilo, etilo, n-propilo, isopropilo, n-butilo, isobutilo, tert-butilo, sec-butilo, n-pentilo, neopentilo, n-hexilo, isohexilo y 3-metilpentilo.

Ejemplos de "alquileno inferior" incluyen grupos

alquileno lineales o ramificados que tienen 1 a 6 átomos de carbono, tales como metileno, etileno, trimetileno, 2-metiltrimetileno, 2,2-dimetiltrimetileno, 1-metil-trimetileno, metilmetileno, etilmetileno, tetrametileno, pentametileno y hexametileno.

Ejemplos de "ciclo alquilo inferior" incluyen grupos ciclo alquilo lineales o ramificados que tienen 3 a 6 átomos de carbono, tales como ciclopropilo, ciclobutilo, ciclopentilo y ciclohexilo.

Ejemplos de "alcoxi inferior" incluyen grupos alcoxi lineales o ramificados que tienen 1 a 6 átomos de carbono, tales como metoxi, etoxi, n-propoxi, isopropoxi, n-butoxi, isobutoxi, tert-butoxi, sec-butoxi, n-pentiloxi, neopentiloxi, n-hexiloxi, isohexiloxi y 3-metilpentiloxi.

Ejemplos de "halógeno" incluyen flúor, cloro, bromo y yodo.

Ejemplos de "alquilenodioxi inferior" incluyen grupos alquileno lineales o ramificados que tienen 1 a 4 átomos de carbono, tales como metilenodioxi, etilenodioxi, trimetilenodioxi y tetrametilenodioxi.

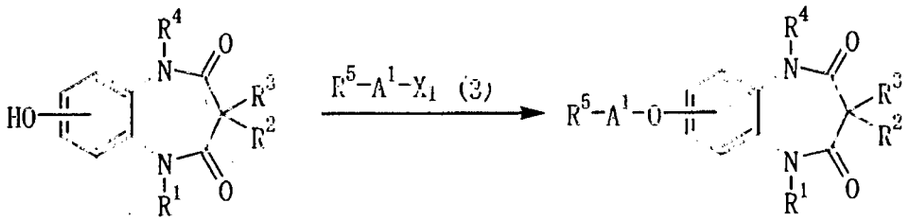
Ejemplos de "alcanoilo inferior" incluyen grupos alcanoilo lineales o ramificados que tienen 1 a 6 átomos de carbono, tales como formilo, acetilo, propionilo, butirilo, isobutirilo, pentanoilo, tert-butilcarbonilo y hexanoilo.

El término "uno o más" puede ser preferentemente 1 a 6, más preferentemente 1 a 3.

El compuesto de benzodiazepina de la presente invención representado por la Fórmula (1) o su sal puede ser producido, por ejemplo, por los procedimientos mostrados en las

siguientes fórmulas de reacción.

Fórmula de reacción 1



en donde R^1, R^2, R^3, R^4, R^5 y A^1 son iguales a los mencionados más arriba, y X_1 es halógeno o hidroxilo.

La reacción del compuesto de Fórmula (2) con el compuesto de Fórmula (3) en donde X_1 es halógeno se puede llevar a cabo en un solvente inerte usual o sin usar solventes en presencia o ausencia de un compuesto básico.

Ejemplos de solventes inertes incluyen agua; éteres tales como dioxano, tetrahidrofurano, dietil éter, dietilenglicol dimetil éter y etilenglicol dimetil éter; hidrocarburos aromáticos tales como benceno, tolueno y xileno; hidrocarburos halogenados tales como diclorometano, dicloroetano, cloroformo y tetracloruro de carbono; alcoholes inferiores tales como metanol, etanol e isopropanol; cetonas tales como acetona y metil etil cetona; solventes polares tales como dimetilformamida (DMF), dimetil sulfóxido (DMSO), triamida hexametilfosfórica y acetonitrilo; y solventes mixtos de tales solventes.

El compuesto básico puede ser seleccionado entre varios compuestos conocidos. Ejemplos de tales compuestos incluyen bases inorgánicas, por ejemplo, hidróxidos de metales alcalinos tales como hidróxido de sodio, hidróxido de

potasio, hidróxido de cesio e hidróxido de litio; carbonatos de metales alcalinos tales como carbonato de sodio, carbonato de potasio, carbonato de cesio, carbonato de litio, hidrógeno carbonato de litio, hidrógeno carbonato de sodio e hidrógeno carbonato de potasio; metales alcalinos tales como sodio y potasio; amida de sodio; hidruro de sodio; e hidruro de potasio; y bases orgánicas, por ejemplo, alcoholatos de metales alcalinos tales como metóxido de sodio, etóxido de sodio, metóxido de potasio y etóxido de potasio; trietilamina; tripropilamina; piridina; quinolina; 1,5-diazabiciclo[4.3.0]noneno-5 (DBN); 1,8-diazabiciclo[5.4.0]undeceno-7 (DBU); y 1,4-diazabiciclo-[2.2.2]octano (DABCO). Estos compuestos básicos se pueden usar solos o en una combinación de dos o más.

La reacción arriba mencionada se puede llevar a cabo agregando un yoduro de metal alcalino tal como yoduro de potasio o yoduro de sodio al sistema de reacción, como se requiera.

El compuesto de Fórmula (3) se usa usualmente en una cantidad de por lo menos 0,5 moles y preferentemente 0,5 a 10 moles, por mol del compuesto de Fórmula (2).

El compuesto básico se usa usualmente en una cantidad de 0,5 a 10 moles, y preferentemente 0,5 a 6 moles, por mol del compuesto de Fórmula (2).

La reacción se lleva a cabo usualmente a una temperatura de 0°C a 250°C, y preferentemente 0°C a 200°C, y es completada usualmente en aprox. 1 a aprox. 80 horas.

La reacción del compuesto de Fórmula (2) con el compuesto de Fórmula (3) en donde X_1 es hidroxilo se lleva a

cabo en un solvente apropiado en presencia de un agente de condensación.

Ejemplos de solventes que se pueden usar en la presente incluyen agua; hidrocarburos halogenados tales como cloroformo, diclorometano, dicloroetano, y tetracloruro de carbono; hidrocarburos aromáticos tales como benceno, tolueno y xileno; éteres tales como dietil éter, diisopropil éter, tetrahidrofurano y dimetoxietano; ésteres tales como acetato de metilo, acetato de etilo y acetato de isopropilo; alcoholes tales como metanol, etanol, isopropanol, propanol, butanol, 3-metoxi-1-butanol, etil cellosolve y metil cellosolve; solventes polares apróticos tales como acetonitrilo, piridina, acetona, N,N-dimetil formamida, dimetil sulfóxido y triamida hexametilfosfórica; y mezclas de tales solventes.

Ejemplos de agentes de condensación incluyen azocarboxilatos tales como di-tert-butil azodicarboxilato, N,N,N',N'-tetrametil azodicarboxamida, 1,1'-(azodicarbonil)dipiperidina, dietil azodicarboxilato; y compuestos de fósforo tales como trifenilfosfina y tri-n-butilfosfina.

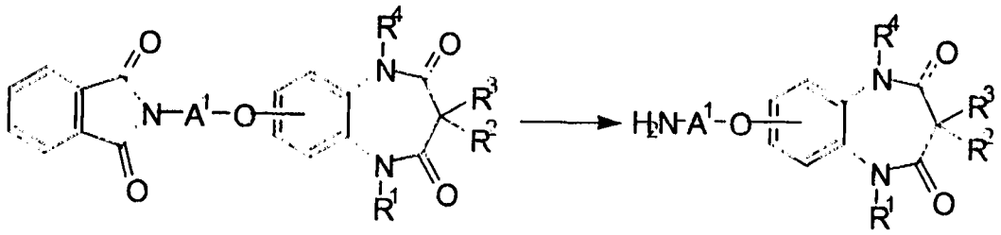
En esta reacción, el compuesto (3) se usa usualmente en una cantidad de por lo menos 1 mol, y preferentemente 1 a 2 moles, por mol del compuesto (2).

El agente de condensación se usa usualmente en una cantidad de por lo menos 1 mol, y preferentemente 1 a 2 moles, por mol del compuesto (2).

La reacción se realiza usualmente a 0 a 200°C, y preferentemente a aprox. 0 a aprox. 150°C, y se completa en

aprox. 1 a aprox. 10 horas.

Fórmula de reacción 2



(1a) (1b)

en donde R^1, R^2, R^3, R^4, R^5 y A^1 son iguales a los mencionados más arriba.

La reacción que convierte el compuesto de Fórmula (1a) en el compuesto de Fórmula (1b) se puede llevar a cabo ya sea haciendo reaccionar el compuesto (1a) con hidrazina en un solvente adecuado, o por hidrólisis. Aquí se puede usar hidrato de hidrazina como la hidrazina.

Ejemplos de solventes usados para la reacción de la hidrazina incluyen agua; hidrocarburos halogenados tales como cloroformo, diclorometano y dicloroetano; hidrocarburos aromáticos tales como benceno, tolueno, y xileno; éteres tales como dietil éter, diisopropil éter, tetrahidrofurano y dimetoxietano; ésteres tales como acetato de metilo y acetato de etilo; y solventes polares apróticos tales como N,N-dimetilformamida, dimetilsulfóxido y triamida hexametilfosfórica; y mezclas de tales solventes. Otros ejemplos de solventes usados para la reacción incluyen alcoholes tales como metanol, etanol, propanol, butanol, 3-metoxi-1-butanol, etil cellosolve o metil cellosolve; acetonitrilo, piridina, acetona, y mezclas de tales solventes.

La hidrazina se usa usualmente en una cantidad de por lo menos aprox. 1 mol, y preferentemente aprox. 1 a aprox. 5 moles, por mol del compuesto (1a).

La reacción se realiza usualmente a aprox. 0 a aprox. 120°C, y preferentemente a aprox. 0 a aprox. 100°C, y es completada usualmente en aprox. 0,5 a aprox. 5 horas.

La hidrólisis del compuesto de Fórmula (1a) se lleva a cabo en un solvente apropiado o sin usar ningún solvente en presencia de un compuesto ácido o básico.

Ejemplos de solventes que se pueden usar en la presente incluyen agua; alcoholes inferiores tales como metanol, etanol e isopropanol; cetonas tales como acetona y metil etil cetona; éteres tales como dioxano, tetrahidrofurano y etilenglicol dimetil éter; ácidos grasos tales como ácido acético y ácido fórmico; y mezclas de tales solventes.

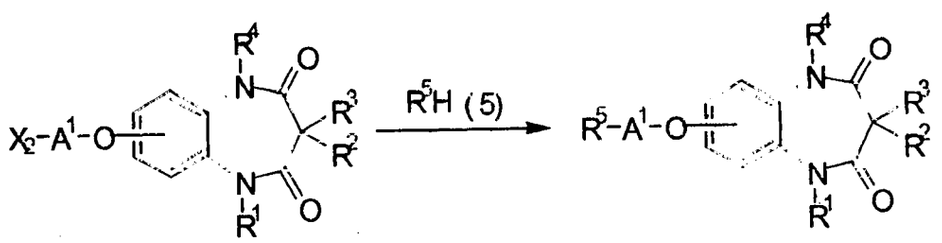
Ejemplos de ácidos incluyen ácidos minerales tales como ácido clorhídrico, ácido sulfúrico y ácido bromhídrico; ácidos alifáticos tales como ácido fórmico, ácido acético; y ácidos sulfónicos tales como el ácido p-toluenosulfónico.

Ejemplos de compuestos básicos incluyen carbonatos de metales tales como carbonato de sodio y carbonato de potasio; e hidróxidos de metales tales como hidróxido de sodio e hidróxido de potasio.

La reacción se lleva a cabo usualmente a temperatura ambiente hasta aprox. 200°C, y preferentemente a temperatura ambiente hasta aprox. 150°C, y se completa usualmente en aprox. 10 minutos a 25 horas.

Fórmula de reacción 3

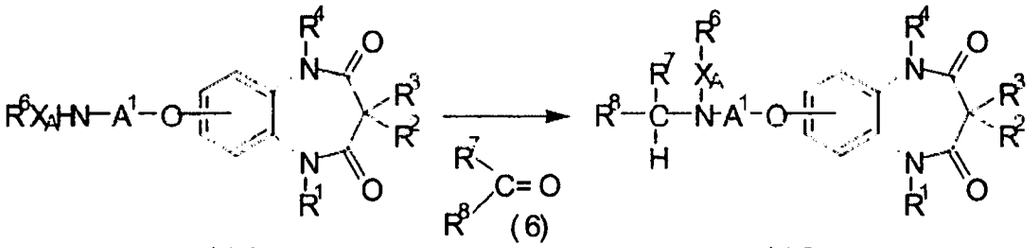
en



(A) (I)

donde R^1, R^2, R^3, R^4, R^5 y A^1 son iguales a los mencionados más arriba, y X_2 es halógeno, alcanosulfoniloxi o arilsulfoniloxi.

La reacción del compuesto de Fórmula (4) con el compuesto de Fórmula (5) se lleva a cabo bajo las mismas condiciones de reacción que aquellas para la reacción del compuesto de Fórmula (3), en donde X_1 es halógeno, con el



compuesto de Fórmula (2) en la Fórmula de reacción 1.

Fórmula de reacción 4

en donde R^1, R^2, R^3, R^4, R^6, R^7 y A^1 son iguales a los mencionados más arriba; y R^8 es hidrógeno o alquilo inferior; con la condición de que la parte de alquileno de $-CHR^7R^8$ contiene no más de 6 átomos de carbono, y $-CHR^8$ es igual a X_B en donde está contenido alquileno.

La reacción del compuesto de Fórmula (1c) y del compuesto de Fórmula (6) se lleva a cabo, por ejemplo, en presencia de un agente reductor en un solvente adecuado o sin usar solventes.

Ejemplos de solventes que se pueden usar en la presente son agua; alcoholes inferiores tales como metanol, etanol, isopropanol, butanol, tert-butanol y etilenglicol; acetonitrilo; ácidos alifáticos tales como ácido fórmico y ácido acético; éteres tales como dietil éter, tetrahidrofurano, dioxano, monoglima y diglima; hidrocarburos

aromáticos tales como benceno, tolueno y xileno; hidrocarburos halogenados tales como diclorometano, dicloroetano, cloroformo y tetracloruro de carbono; y mezclas de tales solventes, etc.

Ejemplos de agentes reductores son ácidos alifáticos tales como ácido fórmico y ácido acético; sales de metales alcalinos de ácidos alifáticos tales como formato de sodio y acetato de sodio; agentes reductores de hidruros tales como borohidruro de sodio, cianoborohidruro de sodio, triacetoxiborohidruro de sodio e hidruro de aluminio y litio; mezclas de tales agentes reductores de hidruros; mezclas de ácidos alifáticos o sales de metales alcalinos de ácidos alifáticos con agentes reductores hidruros; agentes reductores de hidrogenación catalítica tales como negro de paladio, paladio sobre carbono, óxido de platino, negro de platino, níquel de Raney, etc.

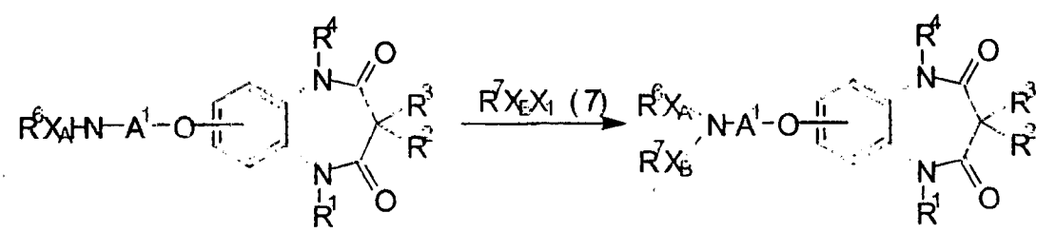
Cuando se usa un ácido alifático tal como ácido fórmico o una sal de metal alcalino de un ácido alifático tal como formato de sodio o acetato de sodio, como un agente reductor, una temperatura de reacción adecuada es usualmente de aprox. temperatura ambiente a aprox. 200°C, y preferentemente de aprox. 50 a aprox. 150°C. La reacción se completa usualmente en aprox. 10 minutos a aprox. 10 horas. Tales ácidos alifáticos y sales de metales alcalinos de ácidos alifáticos se usan usualmente en un gran exceso con relación al compuesto de Fórmula (1c).

Cuando se usa un agente reductor hidruro, una temperatura de reacción adecuada es usualmente de aproximadamente -80 a aprox. 100°C, y preferentemente de

aprox. -30 a aprox. 70°C. La reacción se completa usualmente en aprox. 30 minutos a aprox. 60 horas. El agente reductor hidruro se usa usualmente en una cantidad de aprox. 1 a aprox. 20 moles, y preferentemente de aprox. 1 a aprox. 10 moles, por mol del compuesto de Fórmula (1c). En particular, cuando se usa hidruro de aluminio y litio como un agente reductor hidruro, es preferible usar dietil éter, tetrahidrofurano, dioxano, monoglima, diglima, o éteres similares; o benceno, tolueno, xileno, o hidrocarburos aromáticos similares como un solvente. Trimetilamina, trietilamina, N-etil-diisopropilamina, o aminas similares; o tamices moleculares 3A (MS-3A), tamices moleculares 4A (MS-4A), o tamices moleculares similares se pueden introducir en el sistema de reacción de la reacción.

Cuando se usa un agente reductor de hidrogenación catalítica, la reacción se lleva a cabo usualmente a aprox. -30 hasta aprox. 100°C, y preferentemente a aprox. 0 hasta aprox. 60°C, en una atmósfera de hidrógeno usualmente a aprox. 1 hasta aprox. 20 atm, y preferentemente a aprox. 1 hasta aprox. 10 atm, o en presencia de ácido fórmico, formato de amonio, ciclohexeno, hidrato de hidrazina, o un dador de hidrógeno similar. La reacción se completa usualmente en aprox. 1 a aprox. 12 horas. El agente reductor de hidrogenación catalítica se usa usualmente en una cantidad de aprox. 0,1 a aprox. 40% en peso, y preferentemente de aprox. 1 a aprox. 20% en peso, con relación al compuesto de Fórmula (1c).

En la reacción del compuesto de Fórmula (1c) con el



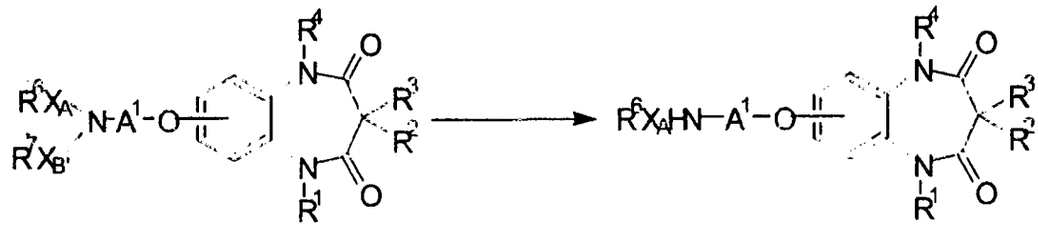
compuesto de Fórmula (6), el compuesto de Fórmula (6) se usa usualmente en una cantidad de por lo menos 1 mol, y preferentemente 1 a 5 moles, por mol del compuesto de Fórmula (1c).

Fórmula de reacción 5

en donde R^1, R^2, R^3, R^4, R^6, R^6, X_A, X_B, A^1 y X_1 son iguales a los mencionados más arriba.

La reacción del compuesto de Fórmula (1c) con el compuesto de Fórmula (7) se lleva a cabo bajo las mismas condiciones de reacción que aquellas para la reacción del compuesto de Fórmula (3) con el compuesto de Fórmula (2) en la Fórmula de reacción 1.

Fórmula de reacción 6



(1f) (1c)

en donde R^1, R^2, R^3, R^4, R^6, R^7, X_A y A^1 son iguales a los de más arriba, y X_B' es $-SO_2-$ o $-CO-$.

La reacción que convierte el compuesto de Fórmula (1f) en el compuesto de Fórmula (1c) se puede llevar a cabo por hidrólisis. La reacción de hidrólisis se lleva a cabo en un solvente apropiado o sin usar solventes en presencia de un compuesto ácido o básico.

Ejemplos de solventes útiles incluyen agua; alcoholes inferiores tales como metanol, etanol, isopropanol y tert-butanol; cetonas tales como acetona y metiletil cetona;

éteres tales como dietil éter, dioxano, tetrahidrofurano, monoglima y diglima; ácidos alifáticos tales como ácido acético y ácido fórmico; ésteres tales como acetato de metilo y acetato de etilo; hidrocarburos halogenados tales como cloroformo, diclorometano, dicloroetano y tetracloruro de carbono; dimetil sulfóxido; N,N-dimetilformamida; y triamida hexametilfosfórica; y mezclas de tales solventes.

Ejemplos de ácidos útiles incluyen ácidos minerales tales como ácido clorhídrico, ácido sulfúrico y ácido bromhídrico; y ácidos orgánicos tales como ácido fórmico, ácido acético, ácido tioglicólico, ácido trifluoroacético y ácido sulfónico (por ej., ácido p-toluenosulfónico). Tales ácidos se pueden usar solos o en combinación.

Ejemplos de compuestos básicos útiles incluyen carbonatos tales como carbonato de sodio, carbonato de potasio, hidrógeno carbonato de sodio e hidrógeno carbonato de potasio; e hidróxidos de metales tales como hidróxido de sodio, hidróxido de potasio, hidróxido de calcio e hidróxido de litio. Tales compuestos básicos se pueden usar solos o en combinación.

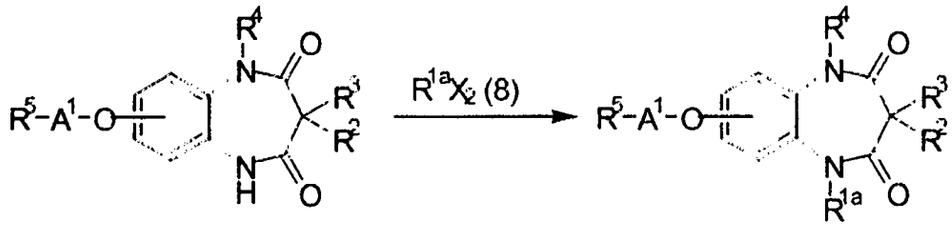
Un compuesto ácido o básico se usa usualmente en una cantidad de por lo menos aprox. 1 mol, y preferentemente aprox. 1 a aprox. 10 moles, por mol del compuesto de Fórmula (1f).

La reacción se lleva a cabo ventajosamente usualmente a aprox. 0 hasta aprox. 200°C, y preferentemente a aprox. 0 hasta aprox. 150°C, y usualmente termina en aprox. 10 minutos a aprox. 80 horas.

En la Fórmula de reacción 6, cuando X_B, en el compuesto

de Fórmula (1f) es $-SO_2-$, el compuesto de Fórmula (1c) se puede producir fácilmente a partir del compuesto de Fórmula (1f) cuando el tiol actúa sobre el compuesto bajo condiciones básicas. Se puede usar cualquier compuesto básico usado en la reacción de hidrólisis antes mencionada. Ejemplos de tioles incluyen mercaptanos aromáticos tales como tiofenol; tioles de alquilo inferior tales como ácido tioglicólico; etc. La reacción se lleva a cabo bajo las mismas condiciones de reacción que las mencionadas más arriba para la reacción de hidrólisis, excepto que se usa tiol usualmente en una cantidad de por lo menos 0,5 moles, y preferentemente aprox. 1 a aprox. 3 moles por mol del compuesto de Fórmula (1f).

Fórmula de reacción 7



(1g) (1h)

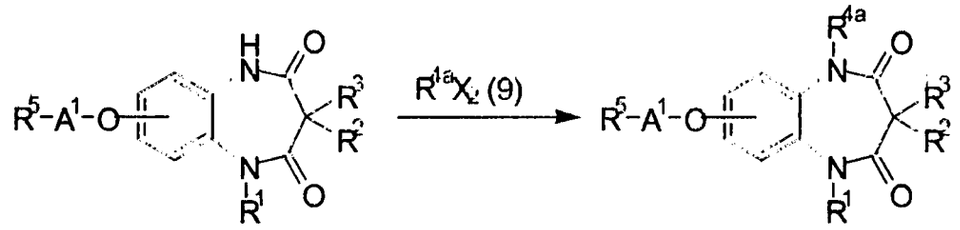
en donde R^2, R^3, R^4, R^5, A^1 y X_2 son iguales a los mencionados más arriba, y R^{1a} es alquilo inferior.

La reacción del compuesto de Fórmula (1g) con el compuesto de Fórmula (8) se lleva a cabo bajo las mismas condiciones de reacción que aquellas para la reacción del compuesto de Fórmula (3), en donde X^1 es halógeno, con el compuesto de Fórmula (2) en la Fórmula de reacción 1.

Cuando R^4 en el compuesto de Fórmula (1g) es hidrógeno en la reacción, se puede producir un compuesto en donde la primera y la quinta posiciones del esqueleto de

benzodiazepina son substituidos simultáneamente con R^{1a}.

Fórmula de reacción 8



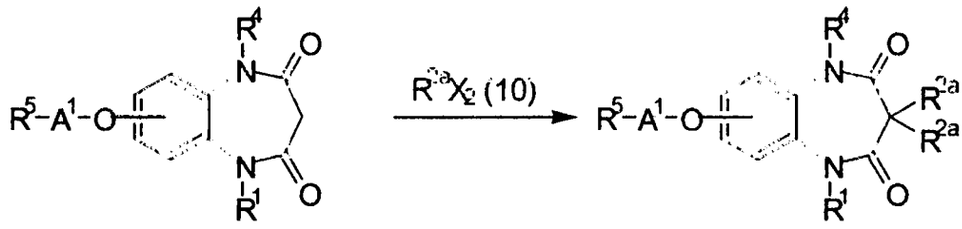
(1i) (1j)

en donde R^1, R^2, R^3, R^5, A^1 y X_2 son iguales a los mencionados más arriba, y R^{4a} es alquilo inferior.

La reacción del compuesto de Fórmula (1i) con el compuesto de Fórmula (9) se lleva a cabo bajo las mismas condiciones de reacción que aquellas para la reacción del compuesto de Fórmula (3), en donde X_1 es halógeno, con el compuesto de Fórmula (2) en la Fórmula de reacción 1.

Cuando R^1 en el compuesto de Fórmula (1i) es hidrógeno en la reacción, se puede producir un compuesto en donde la primera y la quinta posiciones del esqueleto de benzodiazepina son substituidas simultáneamente con R^{4a}.

Fórmula de reacción 9



(1k) (1l)

en donde R^1, R^4, R^5, A^1 y X_2 son iguales a los mencionados más arriba, y R^{2a} es alquilo inferior.

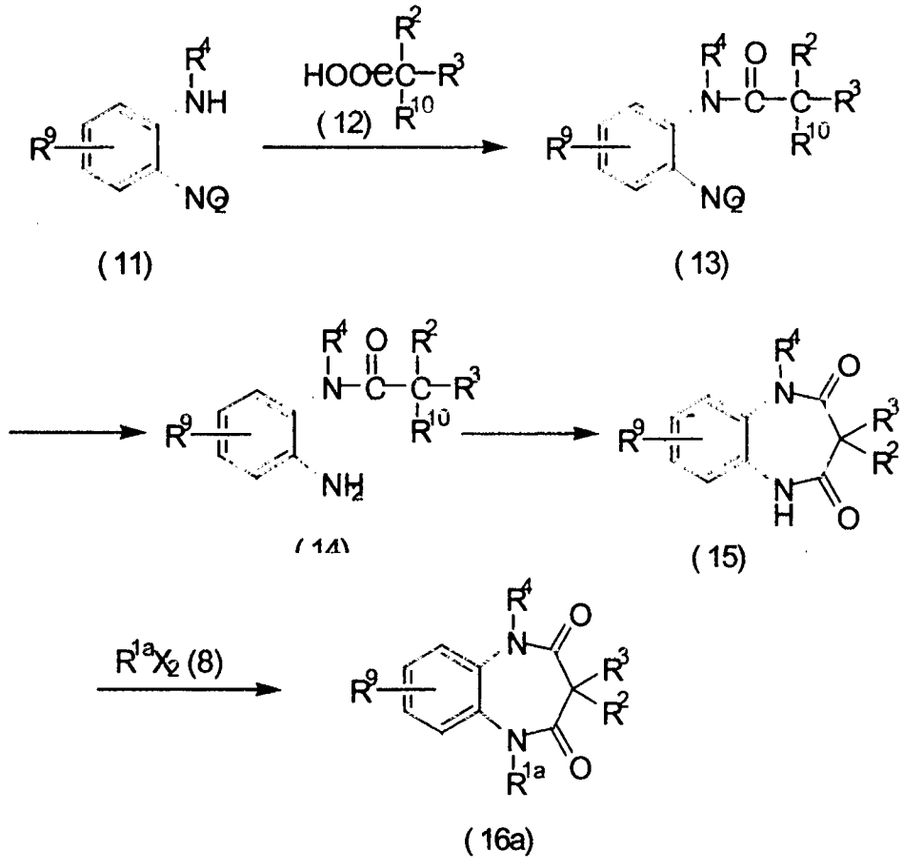
La reacción del compuesto de Fórmula (1k) con el

compuesto de Fórmula (10) se lleva a cabo bajo las mismas condiciones de reacción que aquellas para la reacción del compuesto de Fórmula (3), en donde X_1 es halógeno, con el compuesto de Fórmula (2) en la Fórmula de reacción 1.

Cuando R^1 y/o R^4 es hidrógeno en la reacción del compuesto de Fórmula (1k) y el compuesto de Fórmula (10), el hidrógeno puede ser reemplazado con R^{2a}.

El compuesto de Fórmula (2), que se usa como un material de partida en la Fórmula de reacción arriba mencionada, puede ser producido fácilmente mediante el procedimiento mostrado en la siguiente Fórmula de reacción.

Fórmula de reacción 10



en donde R^2, R^3, R^4, R^{1a} y X_2 son iguales que los mencionados

más arriba. R^9 es alcoxi inferior, y R^{10} es alcoxicarbonilo inferior.

En la reacción del compuesto de Fórmula (11) y el compuesto de Fórmula (12), el compuesto de Fórmula (11) se hace reaccionar con ácido carboxílico del compuesto de Fórmula (12) a través de la reacción de formación de unión amida usual. Las condiciones para las reacciones de formación de la unión amida conocida pueden ser empleadas fácilmente en la reacción de formación de amida indicada más arriba. Por ejemplo, se pueden emplear los siguientes métodos de reacción: (A) un método de anhídrido ácido mixto, en donde se hace reaccionar ácido carboxílico (12) con un halocarboxilato de alquilo para formar un anhídrido ácido mixto, el cual se hace reaccionar luego con una amina (11); (B) un método de éster activo, en donde el ácido carboxílico (12) es convertido en un éster activado tal como un fenil éster, p-nitrofenil éster, N-hidroxisuccinimida éster, 1-hidroxibenzotriazol éster o similares, o una amida activada con benzoxazolina-2-tiona, y el éster o la amida activado se hace reaccionar con una amina (11); (C) un método de carbodiimida, en donde el ácido carboxílico (12) es sometido a una reacción de condensación con una amina (11) en presencia de un agente activador tal como diciclohexilcarbodiimida, 1-(3-dimetilaminopropil)-3-etilcarbodiimida (WSC), carbonil-diimidazol o similares; (D) otros métodos, por ejemplo, un método en donde el ácido carboxílico (12) se convierte en un anhídrido carboxílico usando un agente deshidratante tal como anhídrido acético, y el anhídrido carboxílico se hace reaccionar luego con una

amina (11), un método en donde un éster del ácido carboxílico (12) con un alcohol inferior se hace reaccionar con una amina (11) a una alta presión y una alta temperatura, un método en donde un haluro ácido del ácido carboxílico (12), es decir, un haluro de un ácido carboxílico, se hace reaccionar con una amina (11), etc.

El anhídrido ácido mixto usado en el método del anhídrido ácido mixto (A) se puede obtener mediante la conocida reacción de Schotten-Baumann, y el anhídrido ácido mixto obtenido se hace reaccionar con una amina (11), usualmente sin ser aislado, para producir de esta modo el compuesto de Fórmula (13). La reacción de Schotten-Baumann se lleva a cabo en presencia de un compuesto básico. Los compuestos básicos que se pueden usar incluyen compuestos usados convencionalmente en la reacción de Schotten-Baumann, tales como trietilamina, trimetilamina, piridina, dimetilanilina, N-etildiisopropilamina, dimetilamino-piridina, N-metilmorfolina, 1,5-diazabiciclo[4.3.0]noneno-5 (DBN), 1,8-diazabiciclo[5.4.0]undeceno-7 (DBU), 1,4-diazabiciclo[2.2.2]octano (DABCO) y otras bases orgánicas; carbonato de sodio, carbonato de potasio, hidrógeno carbonato de sodio, hidrógeno carbonato de potasio y otros carbonatos; hidróxido de sodio, hidróxido de potasio, hidróxido de calcio y otros hidróxidos de metales; hidruro de potasio, hidruro de sodio, potasio, sodio, amida de sodio, alcoholatos de metales tales como metilato de sodio y etilato de sodio, y otras bases inorgánicas; etc. La reacción se lleva a cabo usualmente a aprox. -20 hasta aprox. 150°C, y preferentemente a aprox. 0 hasta aprox. 100°C, usualmente durante aprox. 5

minutos hasta aprox. 10 horas, y preferentemente durante aprox. 5 minutos hasta aprox. 5 horas. La reacción del anhídrido ácido mixto obtenido con la amina (11) se lleva a cabo usualmente a aprox. -20 hasta aprox. 150°C, y preferentemente a aprox. 10 hasta aprox. 50°C, usualmente durante aprox. 5 minutos hasta aprox. 30 horas, y preferentemente durante aprox. 5 minutos hasta aprox. 25 horas. Generalmente, el método de anhídrido ácido mixto se lleva a cabo en un solvente. Se pueden usar los solventes usados para los métodos de anhídrido ácido mixto convencionales. Ejemplos de solventes que se pueden usar incluyen cloroformo, diclorometano, dicloroetano, tetracloruro de carbono y otros hidrocarburos halogenados; benceno, tolueno, xileno y otros hidrocarburos aromáticos; dietil éter, diisopropil éter, tetrahidrofurano, dimetoxietano y otros éteres; acetato de metilo, acetato de etilo, acetato de isopropilo y otros ésteres; N,N-dimetilformamida, dimetilsulfóxido, triamida hexametilfosfórica y otros solventes polares apróticos; mezclas de los mismos; etc. Ejemplos de halocarboxilatos de alquilo que se pueden usar en el método del anhídrido ácido mixto incluyen cloroformato de metilo, bromoformato de metilo, cloroformato de etilo, bromoformato de etilo, cloroformato de isobutilo, etc. En este método, se usan el ácido carboxílico (12), un halocarboxilato de alquilo, y una amina (11) preferentemente en cantidades equimolares, pero cada uno de halocarboxilato de alquilo y ácido carboxílico (12) también se puede usar en una cantidad de aprox. 1 a aprox. 1,5 moles por mol de amina (11).

El método (C), en donde se lleva a cabo una reacción de condensación en presencia de un agente activador, se puede realizar en un solvente adecuado en presencia o ausencia de un compuesto básico. Los solventes y compuestos básicos que se pueden usar en este método incluyen aquellos mencionados a continuación como solventes y compuestos básicos que se pueden usar en el método en donde un haluro de ácido carboxílico se hace reaccionar con una amina (11) mencionada más arriba como uno de los otros métodos (D). Una cantidad adecuada de agente activador es por lo menos 1 mol, y preferentemente 1 a 5 moles por mol de amina (11). Cuando se usa WSC como un agente activador, la adición de 1-hidroxibenzotriazol al sistema de reacción permite que la reacción se realice ventajosamente. La reacción se realiza usualmente a aprox. -20 hasta aprox. 180°C, y preferentemente a aprox. 0 hasta aprox. 150°C, y se completa usualmente en aprox. 5 minutos hasta aprox. 90 horas.

Cuando se emplea el método en donde un haluro de ácido carboxílico se hace reaccionar con una amina (11), mencionado más arriba como uno de los otros métodos (D), la reacción se realiza en presencia de un compuesto básico en un solvente adecuado. Los compuestos básicos que se pueden usar incluyen una amplia variedad de compuestos básicos conocidos, tales como aquellos que se usan en la reacción de Schotten-Baumann descripta más arriba. Los solventes que se pueden usar incluyen, además de aquellos que se pueden usar en el método del anhídrido ácido mixto, metanol, etanol, isopropanol, propanol, butanol, 3-metoxi-1-butanol, etil cellosolve, metil cellosolve y otros alcoholes; acetonitrilo; piridina;

acetona; agua; etc. La relación entre el haluro de ácido carboxílico y la amina (11) no esta limitada y puede ser seleccionada adecuadamente entre un amplio rango. Usualmente es adecuado usar, por ejemplo, por lo menos aprox. 1 mol, y preferentemente aprox. 1 a aprox. 5 moles del haluro de ácido carboxílico por mol de amina (11). La reacción se realiza usualmente a aprox. -20 hasta aprox. 180°C, y preferentemente a aprox. 0 hasta aprox. 150°C, y usualmente se completa en aprox. 5 minutos hasta aprox. 30 horas.

La reacción de formación de unión amida mostrada en la Fórmula de reacción 10 también se puede llevar a cabo haciendo reaccionar ácido carboxílico (12) con una amina (11) en presencia de un compuesto de fósforo que sirve como un agente de condensación, tal como trifenilfosfina, difenilfosfinil cloruro, fenil-N-fenilfosforamida cloridrato, dietil clorofosfato, dietil cianofosfato, azida difenilfosfórica, cloruro bis(2-oxo-3-oxazolidinil)-fosfínico o similares.

La reacción se lleva a cabo en presencia de un solvente y un compuesto básico que se puede usar para el método en donde un haluro de ácido carboxílico se hace reaccionar con una amina (11), usualmente a aprox. -20 hasta aprox. 150°C, y preferentemente a aprox. 0 hasta aprox. 100°C, y se completa usualmente en aprox. 5 minutos hasta aprox. 30 horas. Es adecuado usar cada uno del agente de condensación y el ácido carboxílico (12) en cantidades de por lo menos aprox. 1 mol, y preferentemente aprox. 1 a aprox. 2 moles por mol de amina (11).

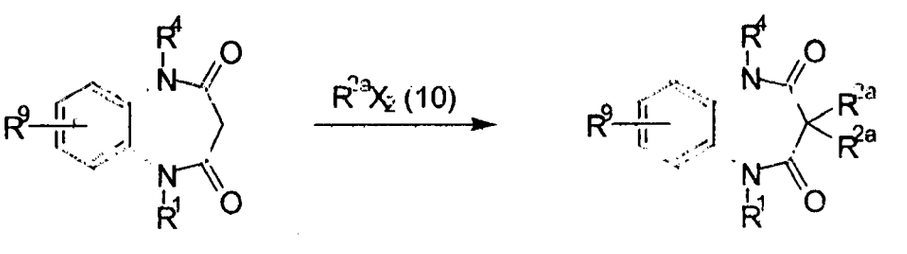
La reacción que convierte el compuesto de Fórmula (13)

en el compuesto de Fórmula (14) puede ser llevada a cabo, por ejemplo, (1) reduciendo el compuesto de Fórmula (13) en un solvente adecuado usando un agente reductor de hidrogenación catalítica, o (2) reduciendo el compuesto de Fórmula (13) en un solvente adecuado inerte usando como un agente reductor una mezcla de un ácido con un metal o una sal metálica, una mezcla de un metal o una sal metálica con un hidróxido de metal alcalino, un sulfuro, o una sal de amonio, o similares.

Cuando se usa el método (1), en donde se usa un agente reductor de hidrogenación catalítica, los ejemplos de solventes que se pueden usar son agua; ácido acético; alcoholes tales como metanol, etanol e isopropanol; hidrocarburos tales como n-hexano y ciclohexano; éteres tales como dioxano, tetrahidrofurano, dietil éter y dietilenglicol dimetil éter; ésteres tales como acetato de etilo y acetato de metilo; solventes polares apróticos tales como N,N-dimetilformamida; mezclas de tales solventes; etc. Los ejemplos de agentes reductores de hidrogenación catalítica incluyen paladio, negro de paladio, paladio sobre carbono, platino sobre carbono, platino, negro de platino, óxido de platino, cromita de cobre, níquel de Raney, etc. Un agente reductor se usa usualmente en una cantidad de aprox. 0,02 veces a igual al peso del compuesto de Fórmula (13). La temperatura de reacción es usualmente de aprox. -20 a aprox. 150°C, y preferentemente de aprox. 0 a aprox. 100°C. La presión de hidrógeno es usualmente de aprox. 1 a 10 atm. La reacción se completa usualmente en aprox. 0,5 a aprox. 100 horas. Un ácido tal como el ácido clorhídrico se puede introducir en el sistema de reacción de la reacción.

Cuando se usa el método (2) mencionado más arriba, se puede usar una mezcla de hierro, zinc, estaño, o cloruro de estaño (II), con un ácido mineral tal como ácido clorhídrico, o ácido sulfúrico; o una mezcla de hierro, sulfato de hierro (II), zinc, o estaño, con un hidróxido de metal alcalino tal como hidróxido de sodio, un sulfuro tal como sulfuro de amonio, una solución acuosa de amoníaco, o una sal de amonio tal como cloruro de amonio, o similares como un agente reductor. Ejemplos de solventes inertes son agua; ácido acético; alcoholes tales como metanol y etanol; éteres tales como dioxano; mezclas de tales solventes, etc. Las condiciones para la reacción de reducción pueden ser seleccionadas adecuadamente de acuerdo con el agente reductor que se use. Por ejemplo, cuando se usa una mezcla de cloruro de estaño (II) y ácido clorhídrico como un agente reductor, es ventajoso llevar a cabo la reacción a aprox. 0 hasta aprox. 150°C durante aprox. 0,5 hasta aprox. 10 horas. Se usa un agente reductor en una cantidad de por lo menos 1 mol, y preferentemente aprox. 1 a 5 moles, por mol del compuesto de Fórmula (13).

La reacción que convierte el compuesto de Fórmula (14) en el compuesto de Fórmula (15) se realiza bajo las mismas condiciones de reacción que aquellas para la reacción del compuesto de Fórmula (11) con el compuesto de Fórmula (12).
La reacción del compuesto de Fórmula (15) con el compuesto de Fórmula (8) se realiza bajo las mismas condiciones de reacción que aquellas para la reacción del compuesto de Fórmula (1g) con el compuesto de Fórmula (8) en la Fórmula de reacc



ión 7.

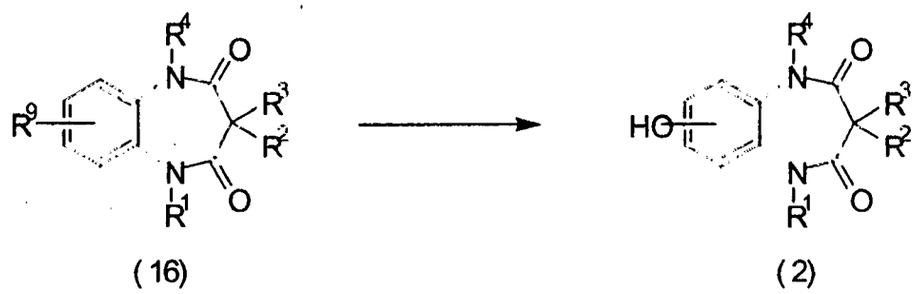
Fórmula de reacción 11

en donde R^1, R^{2a}, R^4, R^9 y X_2 son los mismos que los mencionados más arriba.

La reacción del compuesto de Fórmula (17) con el compuesto de Fórmula (10) se realiza bajo las mismas condiciones de reacción que aquellas para la reacción del compuesto de Fórmula (3), en donde X_1 es halógeno, con el compuesto de Fórmula (2) en la Fórmula de reacción 1.

Cuando R^1 y/o R^4 es hidrógeno en la reacción del compuesto de Fórmula (17) y el compuesto de Fórmula (10), el átomo de hidrógeno puede ser reemplazado con R^{2a}.

Fórmula de reacción 12



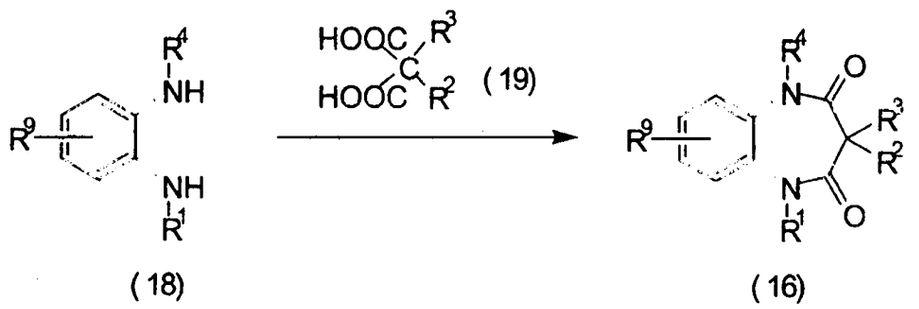
en donde R^1, R^2, R^3, R^4 y R^9 son los mismos que los mencionados más arriba.

La reacción que convierte el compuesto de Fórmula (16) en el compuesto de Fórmula (2) se puede llevar a cabo en un solvente adecuado en presencia de un ácido. Ejemplos de

solventes incluyen agua; alcoholes inferiores tales como metanol, etanol e isopropanol; éteres tales como dioxano, tetrahidrofurano y dietil éter; hidrocarburos halogenados tales como diclorometano, cloroformo y tetracloruro de carbono; solventes polares tales como acetonitrilo; y mezclas de tales solventes. Ejemplos de ácidos incluyen ácidos minerales tales como ácido clorhídrico, ácido sulfúrico y ácido bromhídrico; ácidos alifáticos tales como ácido fórmico y ácido acético; ácidos sulfónicos tales como ácido p-toluenosulfónico; ácidos de Lewis tales como fluoruro de boro, cloruro de aluminio y tribromuro de boro; yoduros tales como yoduro de sodio y yoduro de potasio; mezclas de tales yoduros y ácidos de Lewis. La reacción se realiza usualmente a aprox. 0 hasta aprox. 200°C, y preferentemente a aprox. 0 hasta aprox. 150°C, y se completa usualmente en aprox. 0,5 a aprox. 25 horas. Se usa usualmente un ácido en una cantidad de 1 a 10 moles, y preferentemente aprox. 1 mol a aprox. 2 moles por mol del compuesto de Fórmula (16).

El compuesto de Fórmula (16) se puede preparar usando los procedimientos mostrados en las Fórmulas de reacción 13 y 14 indicadas más abajo.

Fórmula de reacción 13



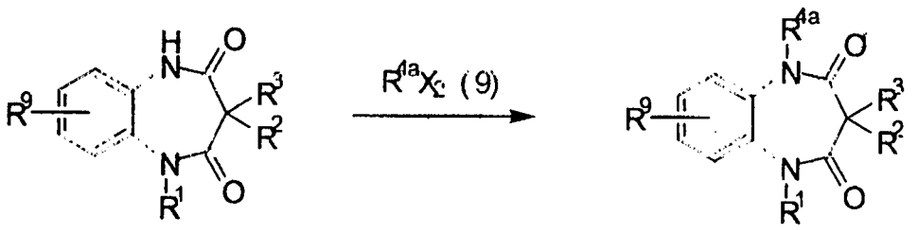
(18) (16)

en donde R^1, R^2, R^3, R^4 y R^9 son los mismos que los mencionados

más arriba.

La reacción del compuesto de Fórmula (18) con el compuesto de Fórmula (19) se realiza bajo las mismas condiciones de reacción que aquellas para la reacción del compuesto de Fórmula (11) con el compuesto de Fórmula (12) en la Fórmula de reacción 10.

Fórmula de reacción 14



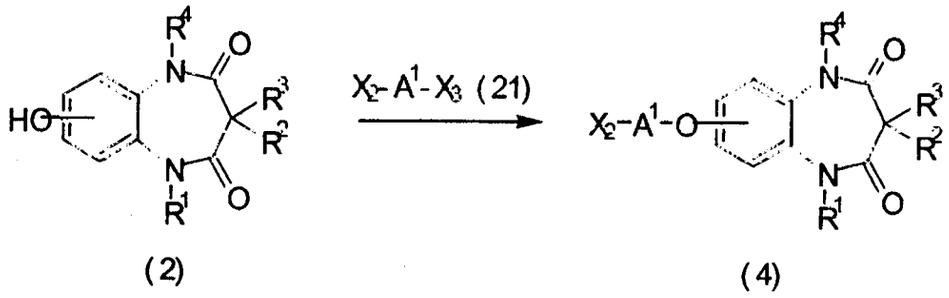
en donde R^1, R^2, R^3, R^{4a} y R^9 son los mismos que los mencionados más arriba.

La reacción del compuesto de Fórmula (20) con el compuesto de Fórmula (9) se realiza bajo las mismas condiciones de reacción que aquellas para la reacción del compuesto de Fórmula (1i) con el compuesto de Fórmula (9) en la Fórmula de reacción 8.

Cuando R^1 en el compuesto de Fórmula (20) es hidrógeno en la reacción, se puede producir un compuesto en donde la primera y la quinta posiciones del esqueleto de benzodiazepina están substituidas simultáneamente con R^{4a}.

El compuesto de Fórmula 4, que se usa como un material de partida en la Fórmula de reacción arriba mencionada, puede ser preparado fácilmente mediante el procedimiento mostrado en la siguiente Fórmula de reacción.

Fórmula de reacción 15



(2) (4)

en donde R^1, R^2, R^3, R^4, A^1 y X_2 son los mismos que los mencionados más arriba, y X_3 es halógeno.

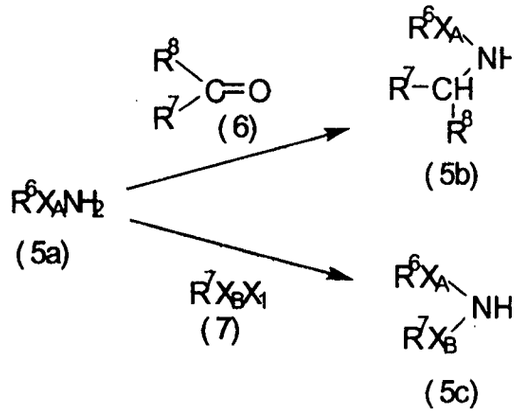
La reacción del compuesto de Fórmula (2) con el compuesto de Fórmula (21) se realiza bajo las mismas condiciones de reacción que aquellas para la reacción del compuesto de Fórmula (3), en donde X_1 es halógeno, con el compuesto de Fórmula (2) en la Fórmula de reacción 1.

X_2 en el compuesto de Fórmula (4) puede ser reemplazado con otro átomo de halógeno agregándolo a un solvente apropiado con un haluro de metal alcalino, y calentando bajo reflujo. Ejemplos de haluros de metales alcalinos incluyen yoduro de sodio, bromuro de sodio, fluoruro de sodio, cloruro de sodio, yoduro de potasio, bromuro de potasio, fluoruro de potasio, cloruro de potasio, etc. Ejemplos de solventes para intercambio de halógenos incluyen cetonas tales como acetona, 2-butanona; éteres tales como dioxano, tetrahidrofurano, dietil éter, dietilenglicol dimetil éter y etilenglicol dimetil éter; y ésteres tales como acetato de metilo y acetato de etilo. Tales solventes se pueden usar solos o en una combinación de dos o más. Un haluro de metal alcalino se usa usualmente en una cantidad de por lo menos 1 mol, y preferentemente aprox. 1 mol a aprox. 10 moles, por mol del compuesto de Fórmula (4). Se continúa el reflujo bajo

calentamiento hasta que termina la reacción. Por ejemplo, el reflujo bajo calentamiento se continúa preferentemente durante aprox. 1 a aprox. 15 horas. La temperatura de reflujo bajo calentamiento varía de acuerdo con el solvente que se use, y es usualmente de aprox. 0 a aprox. 150°C, y preferentemente de aprox. 0 a aprox. 100°C.

El compuesto de Fórmula (5), que se usa como un material de partida, puede ser preparado fácilmente mediante el procedimiento mostrado en la siguiente Fórmula de reacción.

Fórmula de reacción 16



en donde R^6, R^7, X_A, X_B, X_1 y R^8 son los mismos que los mencionados más arriba.

La reacción del compuesto de Fórmula (5a) con el compuesto de Fórmula (6) se realiza bajo las mismas condiciones de reacción que aquellas para la reacción del compuesto de Fórmula (1c) con el compuesto de Fórmula (6) en la Fórmula de reacción 4.

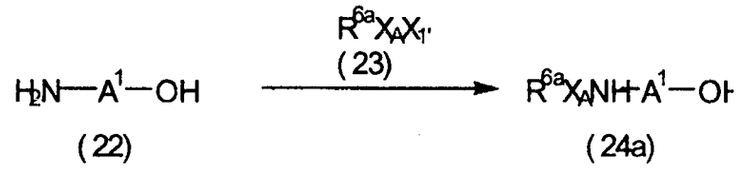
La reacción del compuesto de Fórmula (5a) con el compuesto de Fórmula (7) se realiza bajo las mismas condiciones de reacción que aquellas para la reacción del compuesto de Fórmula (1c) con el compuesto de Fórmula (7) en

la Fórmula de reacción 5.

El compuesto de Fórmula (3), que se usa como un material de partida, puede ser preparado fácilmente mediante el procedimiento mostrado en la siguiente Fórmula de reacción.

El material de partida (24) usado en la siguiente Fórmula de reacción 18 puede ser preparado fácilmente mediante el procedimiento mostrado en la Fórmula de reacción 17.

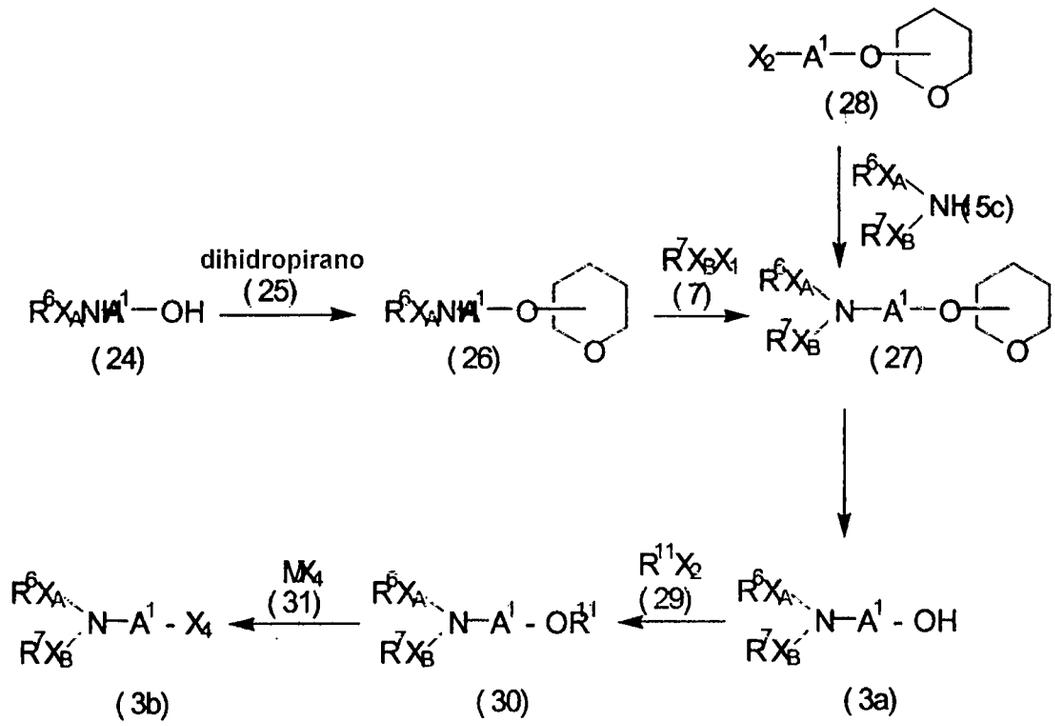
Fórmula de reacción 17



en donde A^1 y X_A son los mismos que los mencionados más arriba, $X_{1'}$ es halógeno, y R^{6a} es el mismo que R^6 como se definió más arriba, excluyendo el átomo de hidrógeno.

La reacción del compuesto de Fórmula (22) con el compuesto de Fórmula (23) se realiza bajo las mismas condiciones de reacción que aquellas para la reacción del compuesto de Fórmula (2) con el compuesto de Fórmula (3) en la Fórmula de reacción 1.

Fórmula de reacción 18



en donde R^6, R^7, X_A, X_B, A^1, X_1 y X_2 son los mismos que los mencionados más arriba, y R^{11} es alquilsulfonilo inferior. X_4 es halógeno, y M es un metal alcalino tal como sodio, potasio, etc.

Ejemplos de los grupos alquilsulfonilo inferior representados por R^{11} incluyen grupos alquilsulfonilo C_{1-6} lineales o ramificados, tales como metilsulfonilo, etilsulfonilo, n-propilsulfonilo, isopropilsulfonilo, n-butilsulfonilo, isobutilsulfonilo, tert-butilsulfonilo, sec-butilsulfonilo, n-pentilsulfonilo, isopentilsulfonilo, neopentilsulfonilo, n-hexilsulfonilo, isohexilsulfonilo, y 3-metilpentilsulfonilo.

La reacción del compuesto de Fórmula (24) y el compuesto de Fórmula (25) se realiza en un solvente adecuado o sin usar

solventes en presencia de un ácido. Ejemplos de solventes incluyen los solventes usados en la reacción del compuesto de Fórmula (2) y el compuesto de Fórmula (3) en la Fórmula de reacción 1. Ejemplos de ácidos que se pueden usar incluyen ácidos minerales tales como ácido clorhídrico, ácido sulfúrico y ácido bromhídrico; y ácidos orgánicos tales como ácido fórmico, ácido acético, ácido tioglicólico, ácido trifluoroacético y ácido sulfónico (por ej., ácido p-toluenosulfónico). Tales ácidos se pueden usar solos o en una combinación. Las condiciones diferentes de las descriptas más arriba pueden ser iguales a las de la reacción entre el compuesto de Fórmula (2) y el compuesto de Fórmula (3) en la Fórmula de reacción 1.

La reacción del compuesto de Fórmula (26) con el compuesto de Fórmula (7) se realiza bajo las mismas condiciones de reacción que aquellas para la reacción del compuesto de Fórmula (2) con el compuesto de Fórmula (3) en la Fórmula de reacción 1.

La reacción del compuesto de Fórmula (5c) con el compuesto de Fórmula (28) se realiza bajo las mismas condiciones de reacción que aquellas para la reacción del compuesto de Fórmula (3), en donde X_1 es halógeno, con el compuesto de Fórmula (2) en la Fórmula de reacción 1.

La reacción que convierte el compuesto de Fórmula (27) en el compuesto de Fórmula (3a) se puede llevar a cabo en un solvente apropiado o sin usar solventes en presencia de un compuesto ácido o básico.

Ejemplos de solventes útiles incluyen agua; alcoholes inferiores tales como metanol, etanol, isopropanol y tert-

butanol; cetonas tales como acetona y metil etil cetona; éteres tales como dietil éter, dioxano, tetrahidrofurano, monoglima y diglima; ácidos alifáticos tales como ácido acético y ácido fórmico; ésteres tales como acetato de metilo y acetato de etilo; hidrocarburos halogenados tales como cloroformo, diclorometano, dicloroetano, y tetracloruro de carbono; dimetil sulfóxido; N,N-dimetilformamida; y triamida hexametilfosfórica; y mezclas de tales solventes.

Ejemplos de ácidos incluyen ácidos miñerales tales como ácido clorhídrico, ácido sulfúrico, y ácido bromhídrico; y ácidos orgánicos tales como ácido fórmico, ácido acético, ácido trifluoroacético y ácido sulfónico (por ej., ácido p-toluenosulfónico y p-toluenosulfonato de piridinio); ácidos de Lewis tales como tribromuro de boro y tricloruro de boro. Tales ácidos se pueden usar solos o en una combinación.

Ejemplos de compuestos básicos útiles incluyen carbonatos tales como carbonato de sodio, carbonato de potasio, hidrógeno carbonato de sodio e hidrógeno carbonato de potasio; e hidróxidos de metales tales como hidróxido de sodio, hidróxido de potasio, hidróxido de calcio e hidróxido de litio. Tales compuestos básicos se pueden usar solos o en una combinación.

La reacción se realiza ventajosamente usualmente a aprox. 0 hasta aprox. 200°C, y preferentemente a aprox. 0 hasta aprox. 150°C, y se completa usualmente en aprox. 10 minutos hasta aprox. 50 horas.

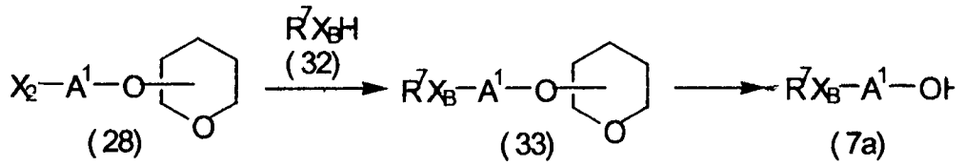
La reacción del compuesto de Fórmula (3a) con el compuesto de Fórmula (29) se realiza bajo las mismas condiciones de reacción que aquellas para la reacción del

compuesto de Fórmula (5c) con el compuesto de Fórmula (28).

La reacción que convierte el compuesto de Fórmula (30) en el compuesto de Fórmula (3b) se realiza bajo las mismas condiciones de reacción que aquellas para la reacción del compuesto de Fórmula (3), en donde X_1 es halógeno, con el compuesto de Fórmula (2) en la Fórmula de reacción 1.

El compuesto de Fórmula (7), que se usa como un material de partida, puede ser preparado fácilmente mediante el procedimiento mostrado en la siguiente Fórmula de reacción.

Fórmula de reacción 19



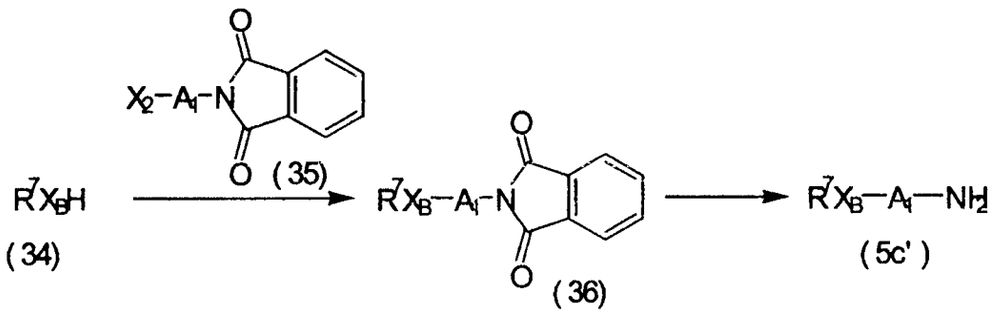
en donde R^7, X_B, X_2 y A^1 son los mismos que los mencionados más arriba.

La reacción del compuesto de Fórmula (32) con el compuesto de Fórmula (28) se realiza bajo las mismas condiciones de reacción que aquellas para la reacción del compuesto de Fórmula (5c) con el compuesto de Fórmula (28) en la Fórmula de reacción 18.

La reacción que convierte el compuesto de Fórmula (33) en el compuesto de Fórmula (7a) se puede llevar a cabo bajo las mismas condiciones de reacción que aquellas para la reacción que convierte el compuesto de Fórmula (27) en el compuesto de Fórmula (3a) en la Fórmula de reacción 18.

El compuesto de Fórmula (5), que se usa como un material de partida, puede ser preparado fácilmente mediante el procedimiento mostrado en la siguiente Fórmula de reacción.

Fórmula de reacción 20

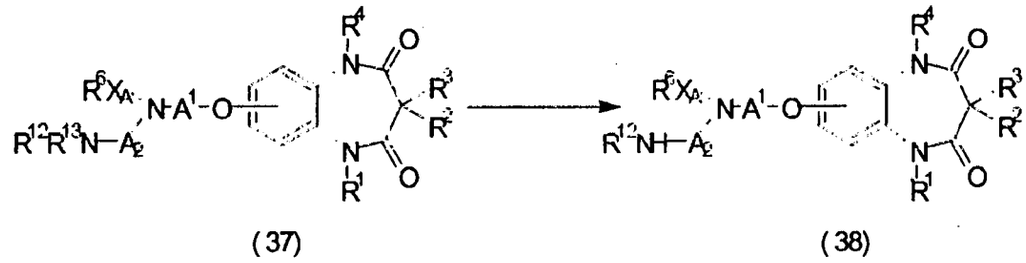


en donde A^1, R^7, X_B y X_2 son los mismos que los indicados más arriba.

La reacción del compuesto de Fórmula (34) con el compuesto de Fórmula (35) se realiza bajo las mismas condiciones de reacción que aquellas para la reacción del compuesto de Fórmula (3), en donde X_1 es halógeno, con el compuesto de Fórmula (2) en la Fórmula de reacción 1.

La reacción que convierte el compuesto de Fórmula (36) en el compuesto de Fórmula (5c) se puede llevar a cabo bajo las mismas condiciones de reacción que aquellas para la reacción que convierte el compuesto de Fórmula (1a) en el compuesto de Fórmula (1b) en la Fórmula de reacción 2.

Fórmula de reacción 21

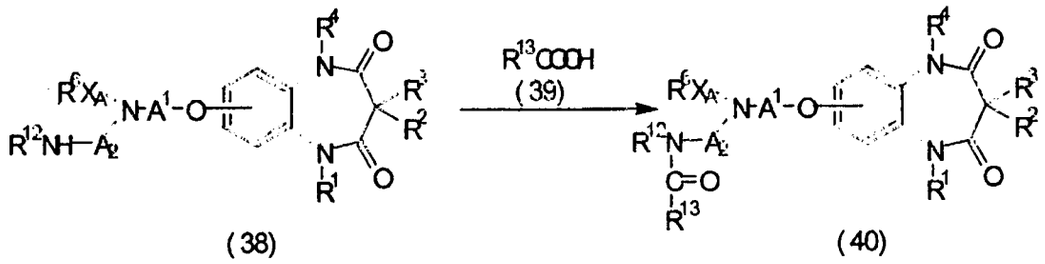


en donde R^1, R^2, R^3, R^4, R^6, X_A y A^1 son los mismos que los mencionados más arriba. R^{12} es hidrógeno, alquilo inferior, alcoxicarbonilo inferior, 2,3-dihidrobenzo[b]furilcarbonilo o

benzoilo. R^{13} es alcoxicarbonilo inferior, 2,3-dihidrobenzo[b]furil carbonilo o benzoilo y A^2 es alquileno inferior.

La reacción que convierte el compuesto de Fórmula (37) en el compuesto de Fórmula (38) se puede llevar a cabo bajo las mismas condiciones de reacción que aquellas para la reacción que convierte el compuesto de Fórmula (1f) en el compuesto de Fórmula (1c) en la Fórmula de reacción 6.

Fórmula de reacción 22



(38) (40)

en donde R^1, R^2, R^3, R^4, R^6, X_A, R^{12}, A^1 y A^2 son los mismos que los mencionados más arriba. R^{13} es 2,3-dihidrobenzo[b]furilo o fenilo.

La reacción del compuesto de Fórmula (38) con el compuesto de Fórmula (39) se realiza bajo las mismas condiciones de reacción que aquellas para la reacción del compuesto de Fórmula (11) con el compuesto de Fórmula (12) en la Fórmula de reacción 10.

Además, los compuestos en la forma en donde un solvato (por ejemplo, un hidrato, etanolato, etc.) se agregó a los compuestos del material de partida y los compuestos objetivo mostrados en cada una de las Fórmulas de reacción están incluidos en cada una de las fórmulas.

El compuesto de Fórmula (1) de acuerdo con la presente invención incluye estereoisómeros e isómeros ópticos.

Los compuestos del material de partida y los compuestos objetivo representados por cada una de las Fórmulas de reacción se pueden usar en una forma de sal apropiada.

Cada uno de los compuestos objetivo obtenidos de acuerdo con las Fórmulas de reacción arriba mencionadas puede ser aislado y purificado a partir de la mezcla de reacción, por ejemplo, después de enfriar la mezcla de reacción, realizando un procedimiento de aislamiento tal como filtración, concentración, extracción, etc., para separar un producto de reacción crudo, y luego sometiendo el producto de reacción crudo a un procedimiento de purificación usual tal como cromatografía en columna, recristalización, etc.

Entre los compuestos de la presente invención, aquellos que tienen un grupo o grupos básicos pueden formar fácilmente sales con ácidos comunes farmacéuticamente aceptables. Ejemplos de tales ácidos incluyen ácido clorhídrico, ácido bromhídrico, ácido nítrico, ácido sulfúrico, ácido fosfórico y otros ácidos inorgánicos, ácido metanosulfónico, ácido p-toluenosulfónico, ácido acético, ácido cítrico, ácido tartárico, ácido maleico, ácido fumárico, ácido málico, ácido láctico y otros ácidos orgánicos, etc.

Entre los compuestos de la presente invención, aquellos que tienen un grupo o grupos ácidos pueden formar fácilmente sales reaccionando con compuestos básicos farmacéuticamente aceptables. Ejemplos de tales compuestos básicos incluyen hidróxido de sodio, hidróxido de potasio, hidróxido de calcio, carbonato de sodio, carbonato de potasio, hidrógeno carbonato de sodio, hidrógeno carbonato de potasio, etc.

La siguiente es una explicación de preparados

farmacéuticos que comprenden el compuesto de la presente invención como un ingrediente activo.

Tales preparados farmacéuticos se obtienen formulando el compuesto de la presente invención como preparados farmacéuticos usuales, usando diluyentes o excipientes que se emplean usualmente tales como cargas, extendedores, ligantes, agentes humectantes, desintegrantes, tensioactivos, lubricantes, etc.

La forma de tales preparados farmacéuticos se puede seleccionar entre varias formas de acuerdo con el propósito del tratamiento. Ejemplos típicos incluyen comprimidos, píldoras, polvos, soluciones, suspensiones, emulsiones, gránulos, cápsulas, supositorios, inyecciones (soluciones, suspensiones, etc.) y similares.

Para formar comprimidos se puede usar cualquiera de los diversos vehículos conocidos, incluyendo, por ejemplo, lactosa, azúcar blanca, cloruro de sodio, glucosa, urea, almidón, carbonato de calcio, kaolín, celulosa cristalina y otros excipientes; agua, etanol, propanol, jarabe simple, soluciones de glucosa, soluciones de almidón, soluciones de gelatina, carboximetilcelulosa, goma laca, metilcelulosa, fosfato de potasio, polivinilpirrolidona y otros ligantes; almidón seco, alginato de sodio, agar en polvo, laminarán en polvo, hidrógeno carbonato de sodio, carbonato de calcio, ésteres de ácidos grasos de polioxietilenosorbitán, laurilsulfato de sodio, monoglicérido del ácido esteárico, almidón, lactosa y otros desintegrantes; azúcar blanca, estearina, manteca de cacao, aceites hidrogenados y otros inhibidores de desintegración; base de amonio cuaternario,

lauril sulfato de sodio y otros promotores de absorción; glicerina, almidón y otros agentes humectantes; almidón, lactosa, kaolín, bentonita, ácido silícico coloidal y otros adsorbentes; talco purificado, estearatos, ácido bórico en polvo, polietilenglicol y otros lubricantes; etc.

Los comprimidos de este tipo pueden ser recubiertos con materiales de recubrimiento usuales, según se requiera, para preparar, por ejemplo, comprimidos recubiertos con azúcar, comprimidos recubiertos con gelatina, comprimidos con recubrimiento entérico, comprimidos recubiertos con película, comprimidos con capas dobles o múltiples, etc.

Para formar píldoras, se puede usar cualquiera de los diversos vehículos conocidos, incluyendo, por ejemplo, glucosa, lactosa, almidón, manteca de cacao, aceites vegetales hidrogenados, kaolín, talco y otros excipientes; goma arábiga en polvo, tragacanto en polvo, gelatina, etanol y otros ligantes; laminarán, agar y otros desintegrantes; etc.

Para formar supositorios, se puede usar cualquiera de los diversos vehículos conocidos, incluyendo, por ejemplo, polietilenglicol, manteca de cacao, alcoholes superiores, ésteres de alcoholes superiores, gelatina, glicéridos semisintéticos, etc.

Para formar una inyección, una solución, emulsión o suspensión se esteriliza y preferentemente se hace isotónica con la sangre. Se puede emplear cualquiera de varios diluyentes conocidos usados ampliamente, para preparar la solución, emulsión o suspensión. Ejemplos de tales diluyentes incluyen agua, etanol, propilenglicol, alcohol isoestearílico

etoxilado, alcohol isoestearílico polioxilado, ésteres de ácidos grasos de polioxietileno sorbitán, etc. En este caso, el preparado farmacéutico puede contener cloruro de sodio, glucosa o glicerina en una cantidad suficiente para preparar una solución isotónica, y puede contener solubilizantes, búferes, agentes analgésicos, etc., usuales, y además, si es necesario, agentes colorantes, conservantes, saborizantes, agentes edulcorantes, etc., y/u otras medicinas.

La proporción del compuesto de la presente invención en el preparado farmacéutico no está limitada y puede ser seleccionada adecuadamente entre un amplio rango. Es usualmente preferible que el preparado farmacéutico contenga el compuesto de la presente invención en una proporción de 1 a 7% en peso.

La vía de administración del preparado farmacéutico de acuerdo con la presente invención no está limitada, y el preparado puede ser administrado por una vía adecuada para la forma del preparado, la edad y el sexo del paciente, las condiciones de la enfermedad, y otras condiciones.

Por ejemplo, los comprimidos, píldoras, soluciones, suspensiones, emulsiones, gránulos y cápsulas son administrados oralmente.

Las inyecciones son administradas endovenosamente solas o como mezcladas con infusiones inyectables usuales tales como soluciones de glucosa, soluciones de aminoácidos o similares, o solas administradas intramuscularmente, intracutáneamente, subcutáneamente o intraperitonealmente, como se requiera. Los supositorios son administrados intrarrectalmente.

La dosificación del preparado farmacéutico es seleccionada adecuadamente de acuerdo con el método de uso, la edad y el sexo del paciente, la gravedad de la enfermedad, y otras condiciones, y es usualmente de aprox. 0,001 a aprox. 100 mg/kg de peso corporal/día, y preferentemente de 0,001 a 50 mg/kg de peso corporal/día, en dosis únicas o divididas.

Como la dosificación varía dependiendo de varias condiciones, una dosis más pequeña que la del rango mencionado más arriba puede ser suficiente, o se puede requerir una dosis más grande que el rango indicado más arriba.

Cuando se administra al cuerpo humano como un producto farmacéutico, el compuesto de la presente invención se puede usar en forma simultánea con, o antes o después, de antitrombóticos tales como inhibidores de la coagulación sanguínea y agentes antiplaquetarios (por ej., warfarina, aspirina, etc.). Además, el presente compuesto se puede usar en forma simultánea con, o antes o después, de fármacos para tratar enfermedades crónicas, tales como los fármacos antihipertensivos (inhibidores de ACE, bloqueadores beta, antagonistas de los receptores de angiotensina II), fármacos para la insuficiencia cardíaca (agentes cardiotónicos, diuréticos) y agentes para el tratamiento de la diabetes.

El compuesto de la presente invención tiene potentes efectos bloqueadores sobre los canales Kv1.5 y/o GIRK1/4 humanos, y débiles efectos bloqueadores sobre los canales HERG. Así, el compuesto de la invención tiene características como un agente bloqueador del canal K+ atrio-selectivo.

Por lo tanto, el compuesto de la invención se puede usar

como una substancia farmacológicamente activa que es más segura y provee un efecto más potente sobre la prolongación del período refractario atrial que los agentes antiarrítmicos convencionales. El compuesto de la invención se usa preferentemente como un agente terapéutico para la arritmia tal como la fibrilación atrial, el aleteo atrial, y la taquicardia atrial (eliminación de la arritmia y/o prevención de la aparición de la arritmia). El compuesto de la invención se usa particularmente como un agente terapéutico para la fibrilación atrial (desfibrilación y mantenimiento del ritmo sinusal). El compuesto de la invención también se puede usar como un agente profiláctico para la tromboembolia, como por ejemplo, el infarto cerebral, y como un agente terapéutico para la insuficiencia cardíaca.

El compuesto que tiene potentes efectos bloqueadores sobre los canales Kv1.5 humano y GIRK1/4 humano tiene efectos de prolongación del período refractario atrial más potentes y es muy seguro, en comparación con los compuestos que inhiben cualquiera de los canales. Además, este compuesto tiene mayores efectos terapéuticos sobre la fibrilación atrial (desfibrilación y mantenimiento del ritmo sinusal) que los compuestos que inhiben cualquiera de los canales. Por lo tanto, el compuesto que tiene potentes efectos bloqueadores sobre los canales Kv1.5 humano y GIRK1/4 humano es particularmente útil como un agente terapéutico para la arritmia tal como fibrilación atrial, aleteo atrial y taquicardia atrial (terminación de la arritmia y/o prevención de la aparición de la arritmia). Este compuesto es particularmente útil como un agente terapéutico para la

fibrilación atrial (desfibrilación y mantenimiento del ritmo sinusal).

Los siguientes ejemplos pretenden ilustrar la presente invención con mayores detalles.

Ejemplo de referencia 1

Síntesis de etil N-(5-metoxi-2-nitrofenil)-N-metil malonamato

Se suspendió hidruro de sodio (60% en aceite, 96 mg, 2,4 mmoles) en 10 ml de dimetilformamida (DMF). Se agregó N-metil-5-metoxi-2-nitroanilina (364 mg, 2 mmoles) a 0°C, y se agitó durante 30 minutos a temperatura ambiente. Se agregó etil malonil cloruro (0,38 ml, 3 mmoles) a 0°C a la mezcla agitada, y la mezcla de reacción se agitó a temperatura ambiente durante la noche. Se agregó agua y se realizó la extracción con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio, y se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (n-hexano:acetato de etilo = 2:1→1:2). El producto purificado se concentró bajo presión reducida para obtener de este modo 554 mg (rendimiento: 90%) de etil N-(5-metoxi-2-nitrofenil)-N-metil malonamato como un aceite amarillo.

^{1}H-NMR ($CDCl_3$) δppm:

1,24 (3H, t, J = 7,1 Hz), 3,15 - 3,17 (2H, m), 3,25 (3H, s), 3,92 (3H, s), 4,13 (2H, q, J = 7,1 Hz), 6,93 (1H, d, J = 2,8 Hz), 7,02 (1H, dd, J = 2,8 y 9,2 Hz), 8,15 (1H, d, J = 9,2 Hz).

Ejemplo de referencia 2

Síntesis de etil N-etil-N-(5-metoxi-2-nitrofenil) malonamato

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo de referencia 1, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

1,11 (3H, t, J = 7,2 Hz), 1,24 (3H, t, J = 7,1 Hz), 3,11-3,25 (2H, m), 3,39-3,46 (1H, m), 3,92 (3H, s), 3,98-4,17 (3H, m),

6,89 (1H, d, J = 2,8 Hz), 7,03 (1H, dd, J = 9,2 y 2,8 Hz), 8,13 (1H, d, J = 9,2 Hz).

Ejemplo de referencia 3

Síntesis de etil N-(2-amino-5-metoxifenil)-N-metil malonamato

Se agregó paladio sobre carbono (10%, 0,5 g) a una solución de etanol (150 ml) de etil N-(5-metoxi-2-nitrofenil)-N-metil malonamato (3,0 g, 10 mmol) y se realizó la reducción catalítica a temperatura ambiente y presión normal. La mezcla de reacción se filtró a través de Celite para retirar el catalizador. El filtrado se concentró bajo presión reducida para obtener de este modo 2,68 g (rendimiento: cuantitativo) de etil N-(2-amino-5-metoxifenil)-N-metil malonamato como un aceite amarillo.

^{1}H-NMR ($CDCl_3$) δppm:

1,22 (3H, t, J = 7,1 Hz), 3,19 - 3,27 (5H, m), 3,52-3,68 (2H, br), 3,74 (3H, s), 4,11 (2H, q, J = 7,1 Hz), 6,62 (1H, d, J = 2,7 Hz), 6,73 (1H, d, J = 8,7 Hz), 6,79 (1H, dd, J = 2,7 y 8,7 Hz).

Ejemplo de referencia 4

Síntesis de 8-metoxi-1-metil-1,5-dihidrobenzo[b][1,4]-diazepina-2,4-diona

Se agregó etóxido de sodio (204 mg, 3,0 mmoles) a una solución de etanol (15 ml) de etil N-(2-amino-5-metoxifenil)-N-metil malonamato (266 mg, 1,0 mmol), y se agitó a 65°C durante 2,5 horas. La mezcla de reacción se enfrió a temperatura ambiente y se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (diclorometano:metanol = 1:0→ 10:1). El producto purificado se concentró a sequedad bajo presión reducida para

obtener de este modo 176,3 mg (rendimiento: 80%) de 8-metoxi-1-metil-1,5-dihidrobenzo-[b][1,4]diazepina-2,4-diona como un polvo blanco.

^{1}H-NMR ($CDCl_3$) δppm:

3,36 (2H, s), 3,43 (3H, s), 3,84 (3H, s), 6,79-6,83 (1H, m), 7,06-7,09 (1H, m), 8,72 (1H, br-s).

Ejemplo de referencia 5

Síntesis de 1-etil-8-metoxi-1,5-dihidrobenzo[b][1,4]-diazepina-2,4-diona

Se agregó paladio sobre carbono (10%, 1,1 g) a una solución de etanol (250 ml) de etil N-etil-N-(5-metoxi-2-nitrofenil) malonamato (21,05 g, 67,8 mmol), y se enfrió en un baño de agua helada. Se realizó luego la reducción catalítica a aproximadamente temperatura ambiente. La filtración en Celite se realizó para retirar el catalizador, y el filtrado se concentró bajo presión reducida. El residuo se disolvió en tetrahidrofurano (THF) (200 ml). Se agregó etóxido de sodio (6,9 g, 102 mmoles), y luego se realizó el calentamiento bajo reflujo durante 15 minutos. La mezcla de reacción se enfrió a temperatura ambiente, y la materia insoluble precipitada se recogió por filtración. El filtrado se concentró bajo presión reducida. Se agregó agua al residuo y la materia insoluble recogida, y la mezcla se neutralizó con ácido clorhídrico. Luego se realizó la extracción con acetato de etilo. La capa orgánica se lavó con una solución acuosa de cloruro de sodio saturada, se secó sobre sulfato de sodio anhidro, y se concentró bajo presión reducida. El residuo se recristalizó a partir de etanol para obtener de este modo 7,9 g (rendimiento: 50%) de 1-etil-8-metoxi-1,5-

dihidrobenzo[b][1,4]diazepina-2,4-diona como un polvo blanco. Luego se concentró la solución madre y el residuo se purificó usando una columna flash de gel de sílice (n-hexano : acetato de etilo = 1:1→0:1) para obtener de este modo 2,9 g del compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

1,19 (3H, t, J = 7,1 Hz), 3,33 (2H, s), 3,78-3,84 (1H, m), 3,84 (3H, s), 4,13 - 4,25 (1H, m), 6,82 (1H, dd, J = 8,8 y 2,7 Hz), 6,87 (1H, d, J = 2,7 Hz), 7,09 (1H, d, J = 8,8 Hz), 8,82 (1H, br-s).

Ejemplo de referencia 6

Síntesis de 1-etil-7-metoxi-5-metil-1,5-dihidrobenzo[b]-[1,4]diazepina-2,4-diona

Se suspendió hidruro de sodio (60% en aceite, 44 mg, 1,1 mmoles) en dimetilformamida (DMF) (8 ml) y se enfrió en un baño de agua helada a 0°C. Se agregó 8-metoxi-1-metil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona (220 mg, 1,0 mmoles) a la suspensión a la misma temperatura, y se agitó a 0°C durante 1 hora. Se agregó yoduro de etilo (187 mg, 1,2 mmoles) a la mezcla y se agitó a temperatura ambiente durante la noche. Se agregó agua a la mezcla de reacción, y se realizó la extracción con acetato de etilo. Se secó la capa orgánica sobre sulfato de sodio, y se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (n-hexano:acetato de etilo = 4:1→1:1). El producto purificado se concentró a sequedad bajo presión reducida para obtener de este modo 190,2 mg (rendimiento: 77%) de 1-etil-7-metoxi-5-metil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona como un sólido

amarillo.

^{1}H-NMR ($CDCl_3$) δppm:

1,11 (3H, t, J = 7,1 Hz), 3,31 - 3,32 (2H, m), 3,40 (3H, s), 3,59-3,68 (1H, m), 3,85 (3H, s), 4,18-4,30 (1H, m), 6,78 (1H, d, J = 2,8 Hz), 6,84 (1H, dd, J = 9,0 y 2,8 Hz), 7,26 (1H, d, J = 9,0 Hz).

Ejemplo de referencia 7

Síntesis de 1,5-dietil-7-metoxi-1,5-dihidrobenzo[b][1,4] diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo de referencia 6, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

1.04-1,14 (6H, m), 3,28 (2H, s), 3,50-3,64 (2H, m), 3,85 (3H, s), 4,35-4,47 (2H, m), 6,83-6,88 (2H, m), 7,25-7,27 (1H, m).

Ejemplo de referencia 8

Síntesis de 7-metoxi-5-metil-1-propil-1,5-dihidrobenzo[b]-[1,4] diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo de referencia 6, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,76 (3H, t, J = 7,3 Hz), 1,35-1,62 (2H, m), 3,32 (2H, s), 3,40 (3H, s), 3,33-3,51 (1H, m), 3,49 (3H, s), 4,21-4,38 (1H, m), 6,78 (1H, d, J = 2,8 Hz), 6,84 (1H, dd, J = 9,0 y 2,8 Hz), 7,25 (1H, d, J = 9,0 Hz).

Ejemplo de referencia 9

Síntesis de 1-isobutil-7-metoxi-5-metil-1,5-dihidrobenzo-[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo de referencia 6, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,69 (3H, d, J = 6,7 Hz), 0,77 (3H, d, J = 6,7 Hz), 1,56-1,90 (1H, m), 3,24 (1H, dd, J = 13,6 y 5,9 Hz), 3,33 (2H, s), 3,40 (3H, s), 3,85 (3H, s), 4,32 (1H, dd, J = 13,6 y 9,0 Hz), 6,78 (1H, d, J = 2,8 Hz), 6,84 (1H, dd, J = 9,0 y 2,9 Hz), 7,24 (1H, d, J = 9,0 Hz).

Ejemplo de referencia 10

Síntesis de 7-metoxi-5-metil-1-(3-metilbutil)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo de referencia 6, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,80 (3H, d, J = 6,3 Hz), 0,86 (3H, d, J = 6,3 Hz), 1,22-1,53 (3H, m), 3,32 (2H, s), 3,39 (3H, s), 3,36-3,62 (1H, m), 3,85 (3H, s), 4,31-4,48 (1H, m), 6,78 (1H, d, J = 2,8 Hz), 6,85 (1H, dd, J = 8,8 y 2,8 Hz), 7,25 (1H, d, J = 8,8 Hz).

Ejemplo de referencia 11

Síntesis de 7-metoxi-5-metil-1-(3-metilbut-2-enil)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo de referencia 6, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

1,63 (6H, s), 3,32 - 3,34 (2H, m), 3,38 (3H, s), 3,84 (3H, s), 4,33 (1H, dd, J = 13,6 y 6,2 Hz), 4,51 (1H, dd, J = 13,6

y 6,9 Hz), 5,14 - 5,19 (1H, m), 6,76 (1H, d, J = 2,8 Hz), 6,81 (1H, dd, J = 9,0 y 2,8 Hz), 7,27 (1H, d, J = 9,0 Hz).

Ejemplo de referencia 12

Síntesis de 1-etil-7-metoxi-3,3,5-trimetil-1,5-dihidro-benzo-[b][1,4]diazepina-2,4-diona

Se suspendió hidruro de sodio (60% en aceite, 76 mg, 1,9 mmoles) en DMF (8 ml). Se agregó 1-etil-7-metoxi-5-metil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona (190 mg, 0,76 mmoles) a 0°C, y se realizó la agitación a la misma temperatura durante 1 hora. Se agregó yoduro de metilo (0,19 ml, 3,1 mmoles) a la mezcla, y se agitó a temperatura ambiente durante 3 días. Se agregó agua a la mezcla de reacción, y se realizó la extracción con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio, y se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna en gel de sílice (acetato de etilo). El producto purificado se concentró a sequedad bajo presión reducida para obtener de este modo 169 mg (rendimiento: 80%) de 1-etil-7-metoxi-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona como un polvo amarillo.

^{1}H-NMR ($CDCl_3$) δppm:

0,86 (3H, s), 1,15 (3H, t, J = 7,1 Hz), 1,53 (3H, s), 3,40 (3H, s), 3,65-3,76 (1H, m), 3,85 (3H, s), 4,12-4,24 (1H, m), 6,73 (1H, d, J = 2,8 Hz), 6,83 (1H, dd, J = 9,0 y 2,8 Hz), 7,22 (1H, d, J = 9,0 Hz).

Ejemplo de referencia 13

Síntesis de 7-metoxi-3,3,5-trimetil-1-propil-1,5-dihidro-benzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el

procedimiento del Ejemplo de referencia 12, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,76 (3H, t, J = 7,3 Hz), 0,85 (3H, s), 1,52 (3H, s), 1,38-1,68 (2H, m), 3,41 (3H, s), 3,42-3,58 (1H, m), 3,85 (3H, s), 4,19-4,31 (1H, m), 6,72 (1H, d, J = 2,8 Hz), 6,81 (1H, dd, J = 9,0 y 2,8 Hz), 7,20 (1H, d, J = 9,0 Hz).

Ejemplo de referencia 14

Síntesis de 7-metoxi-3,3,5-trimetil-1-(3-metilbutil)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo de referencia 12, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,82 (3H, d, J = 6,2 Hz), 0,85 (3H, s), 0,86 (3H, d, J = 6,2 Hz), 1,30-1,49 (3H, m), 1,52 (3H, s), 3,40 (3H, s), 3,49-3,62 (1H, m), 3,85 (3H, s), 4,21-4,36 (1H, m), 6,71 (1H, d, J = 2,8 Hz), 6,80 (1H, dd, J = 9,0 y 2,8 Hz), 7,20 (1H, d, J = 9.0 Hz).

Ejemplo de referencia 15

Síntesis de 1,5-dietil-7-metoxi-3,3-dimetil-1,5-dihidro-benzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo de referencia 12, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,84 (3H, s), 1,06-1,18 (6H, m), 1,51 (3H, s), 3,56-3,83 (2H, m), 3,85 (3H, s), 4,29-4,42 (2H, m), 6,79-6,86 (2H, m), 7,21 (1H, d, J = 8,9 Hz).

Ejemplo de referencia 16

Síntesis de 1,3-dietil-7-metoxi-5-metil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo de referencia 12, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,86 (3H, t, J = 7,3 Hz), 1,06 (3H, t, J = 7,0 Hz), 1,94-2,05 (2H, m), 2,97 (1H, t, J = 6,9 Hz), 3,40 (3H, s), 3,55-3,66 (1H, m), 3,86 (3H, s), 4,20-4,33 (1H, m), 6,79 (1H, d, J = 2,8 Hz), 6,84-6,88 (1H, m), 7,26-7,29 (1H, m).

Ejemplo de referencia 17

Síntesis de 3,3-dietil-7-metoxi-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Se agregó dicloruro de dietilmalonilo (0,95 ml, 5,5 mmoles) a una solución de diclorometano (20 ml) de 4-metoxi-o-fenilendiamina (691 mg, 5 mmoles) y trietilamina (1,7 ml, 12,5 mmoles) a 0°C, y se agitó a temperatura ambiente durante la noche. Se agregó a la mezcla de reacción, y se realizó la extracción con diclorometano. La capa orgánica se lavó con una solución acuosa de cloruro de sodio saturada, se secó sobre sulfato de sodio, y se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (n-hexano:acetato de etilo = 9:1→1:1). El producto purificado se concentró a sequedad bajo presión reducida para obtener de este modo 452,3 mg (rendimiento: 34%) de 3,3-dietil-7-metoxi-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona como un aceite amarillo.

^{1}H-NMR ($CDCl_3$) δppm:

1,10 (6H, t, J = 7,5 Hz), 1,86 (4H, q, J = 7,5 Hz), 3,76 (3H, s), 4,18 (2H, br), 6,30 (1H, d, J = 2,7 Hz), 6,35 (1H, dd, J = 8,7 y 2,7 Hz), 7,23 (1H, d, J = 8,7 Hz).

Ejemplo de referencia 18

Síntesis de 3,3-dietil-7-metoxi-1,5-dimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Se suspendió hidruro de sodio (60% en aceite, 170 mg, 4,3 mmoles) en DMF (15 ml). Se agregó 3,3-dietil-7-metoxi-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona (452 mg, 1,7 mmoles) a 0°C, y se realizó la agitación a la misma temperatura durante 1 hora. Se agregó yoduro de metilo (0,42 ml, 6,8 mmoles) a la mezcla, y se agitó a temperatura ambiente durante 3 días. Se agregó agua a la mezcla de reacción y se realizó la extracción con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio y se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (n-hexano:acetato de etilo = 2:1→1:1). El producto purificado se concentró a sequedad bajo presión reducida para obtener de este modo 373 mg (rendimiento: 76%) de 3,3-dietil-7-metoxi-1,5-dimetil-1,5-dihidrobenzo[b][1,4]-diazepina-2,4-diona como un polvo blanco.

^{1}H-NMR ($CDCl_3$) δppm:

0,56 (3H, t, J = 7,4 Hz), 1,02 (3H, t, J = 7,3 Hz), 1,20-1,31 (2H, m), 2,15 (2H, q, J = 7,3 Hz), 3,38 (3H, s), 3,41 (3H, s), 3,85 (3H, s), 6,71 (1H, d, J = 2,8 Hz), 6,81 (1H, dd, J = 9,0 y 2,8 Hz), 7,14 (1H, d, J = 9,0 Hz).

Ejemplo de referencia 19

Síntesis de 7-metoxi-1,3,3,5-tetrametil-1,5-dihidrobenzo-

[b][1,4]diazepina-2,4-diona

Se suspendió hidruro de sodio (60% en aceite, 128 mg, 3,2 mmoles) en DMF (10 ml). Se agregó 8-metoxi-1-metil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona (176 mg, 0,8 mmoles) a 0°C, y se realizó la agitación a la misma temperatura durante 1 hora. Se agregó yoduro de metilo (0,25 ml, 4,0 mmoles) a la mezcla, y se agitó a temperatura ambiente durante la noche. Se agregó agua a la mezcla de reacción y se realizó la extracción con acetato de etilo. La capa orgánica se lavó con agua, se secó sobre sulfato de sodio y se concentró bajo presión reducida. El residuo se recristalizó a partir de n-hexano para obtener de este modo 161,6 mg (rendimiento: 77%) de 7-metoxi-1,3,3,5-tetrametil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona como un polvo blanco.

^{1}H-NMR ($CDCl_3$) δppm:

0,87 (3H, s), 1,54 (3H, s), 3,40 (3H, s), 3,42 (3H, s), 3,84 (3H, s), 6,73 (1H, s), 6,84 (1H, d, J = 8,9 Hz), 7,14 (1H, d, J = 8,9 Hz).

Ejemplo de referencia 20

Síntesis de 5-etil-7-metoxi-1,3,3-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo de referencia 19, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,86 (3H, s), 1,19 (3H, t, J = 7,1 Hz), 1,53 (3H, s), 3,38 (3H, s), 3,75-3,82 (1H, m), 3,84 (3H, s), 4,12-4,19 (1H, m), 6,80-6,85 (2H, m), 7,16 (1H, dd, J = 8,6 y 0,5 Hz).

Ejemplo de referencia 21

Síntesis de 1,3,3,5-tetraetil-7-metoxi-1,5-dihidrobenzo-[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo de referencia 19, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,56 (3H, t, J = 7,4 Hz), 0,98 (3H, t, J = 7,4 Hz), 1,07-1,26 (6H, m), 2,10-2,17 (2H, m), 3,59-3,74 (2H, m), 3,85 (3H, s), 4,24-4,32 (2H, m), 6,78-6,85 (2H, m), 7,20 (1H, d, J = 8,9 Hz).

Ejemplo de referencia 22

Síntesis de 1,3,3-trietil-7-metoxi-5-metil-1,5-dihidrobenzo-[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo de referencia 19, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,57 (3H, t, J = 7,4 Hz), 1,00 (3H, t, J = 7,3 Hz), 1,16 (3H, t, J = 7,2 Hz), 1,21-1,29 (2H, m), 2,10-2,19 (2H, m), 3,40 (3H, s), 3,72-3,83 (1H, m), 3,85 (3H, s), 4,06-4,14 (1H, m), 6,71 (1H, d, J = 2,8 Hz), 6,82 (1H, dd, J = 9,0 y 2,8 Hz), 7,21 (1H, d, J = 9,0 Hz).

Ejemplo de referencia 23

Síntesis de 1,3,5-trietil-7-metoxi-1,5-dihidrobenzo[b][1,4] diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo de referencia 19, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,85 (3H, t, J = 7,5 Hz), 0,88-1,11 (6H, m), 2,92-2,97 (1H, m), 3,50-3,65 (2H, m), 3,86 (3H, s), 4,12 (2H, q, J = 7,2 Hz), 4,38-4,45 (2H, m), 6,84-6,89 (2H, m), 7,25-7,28 (1H, m).

Ejemplo de referencia 24

Síntesis de 1-etil-7-hidroxi-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Una solución de 1,0 M tribromuro de boro/diclorometano (1,22 ml) se agregó a una solución de diclorometano (3 ml) de 1-etil-7-metoxi-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]-diazepina-2,4-diona (169 mg, 1,0 mmol) a 0°C, y se agitó a temperatura ambiente durante la noche. Se agregaron agua y metanol a la mezcla de reacción y se realizó la extracción con la mezcla de solventes (diclorometano:metanol = 10:1). La capa orgánica se secó sobre sulfato de sodio anhidro y se concentró a sequedad bajo presión reducida para obtener de este modo 156,4 mg (rendimiento: 98%) de 1-etil-7-hidroxi-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona como un polvo blanco.

^{1}H-NMR ($CDCl_3$) δppm:

0,90 (3H, s), 1,16 (3H, t, J = 7,0 Hz), 1,55 (3H, s), 3,41 (3H, s), 3,66-3,78 (1H, m), 4,12-4,23 (1H, m), 6,79 (1H, d, J = 2,7 Hz), 6,84 (1H, dd, J = 8,8 y 2,7 Hz), 6,88 (1H, d, J = 2,7 Hz), 7,18 (1H, d, J = 8,8 Hz).

Ejemplo de referencia 25

Síntesis de 3,3-dietil-7-hidroxi-1,5-dimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo de referencia 24, se sintetizó el

compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,55 (3H, t, J = 7,3 Hz), 1,00 (3H, t, J = 7,3 Hz), 1,15-1,29 (2H, m), 2,12 (2H, q, J = 7,3 Hz), 3,37 (3H, s), 3,38 (3H, s), 6,69 (1H, d, J = 2,7 Hz), 6,76 (1H, dd, J = 8,8 y 2,7 Hz), 7,06 (1H, d, J = 8,8 Hz).

Ejemplo de referencia 26

Síntesis de 1,3,3-trietil-7-hidroxi-5-metil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo de referencia 24, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,59 (3H, t, J = 7,3 Hz), 1,01 (3H, t, J = 7,3 Hz), 1,18 (3H, t, J = 7,1 Hz), 1,21-1,34 (2H, m), 2,13-2,24 (2H, m), 3,40 (3H, s), 3,71-3,82 (1H, m), 4,05-4,16 (1H, m), 6,78 (1H, d, J = 2,7 Hz), 6,84 (1H, dd, J = 8,8 y 2,7 Hz), 7,04 (1H, br-s), 7,17 (1H, d, J = 8,8 Hz).

Ejemplo de referencia 27

Síntesis de 1,3-dietil-7-hidroxi-5-metil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo de referencia 24, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,87 (3H, t, J = 7,4 Hz), 1,07 (3H, t, J = 7,1 Hz), 1,95-2,05 (2H, m), 3,00 (1H, t, J = 6,9 Hz), 3,39 (3H, s), 3,58-3,64 (1H, m), 4,22-4,29 (1H, m), 5,87 (1H, br-s), 6,80-6,84 (2H, m), 7,21-7,24 (1H, m).

Ejemplo de referencia 28

Síntesis de 1,3-dietil-7-hidroxi-3,5-dimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo de referencia 24, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,64 (3H, t, J = 7,3 Hz), 1,11-1,26 (5H, m), 1,54 (3H, s), 3,40 (3H, s), 3,70-3,82 (1H, m), 4,06-4,17 (1H, m), 6,39 (1H, br-s), 6,75-6,83 (2H, m), 7,17-7,24 (1H, d, J = 8,8 Hz).

Ejemplo de referencia 29

Síntesis de 5-etil-7-hidroxi-1,3,3-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo de referencia 24, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,88 (3H, s), 1,20 (3H, t, J = 7,1 Hz), 1,53 (3H, s), 3,38 (3H, s), 3,73-3,84 (1H, m), 4,07-4,19 (1H, m), 6,76-6,81 (2H, m), 7,11 (1H, d, J = 8,7 Hz).

Ejemplo de referencia 30

Síntesis de 7-hidroxi-3,3,5-trimetil-1-propil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo de referencia 24, se sintetizó el compuesto objetivo.

^{1}H-NMR (CD_3OD) δppm:

0,74 (3H, t, J = 7,4 Hz), 0,85 (3H, s), 1,43 (3H, s), 1,38-1,61 (2H, m), 3,36 (3H, s), 3,53-3,61 (1H, m), 4,21-4,29 (1H,

m), 6,76-6,82 (2H, m), 7,26 (1H, d, J = 8,5 Hz).

Ejemplo de referencia 31

Síntesis de 7-hidroxi-3,3,5-trimetil-1-(3-metilbutil)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo de referencia 24, se sintetizó el compuesto objetivo.

^{1}H-NMR (CD_3OD) δppm:

0,79 (3H, d, J = 6,1 Hz), 0,85 (3H, s), 0,85 (3H, d, J = 6,1 Hz), 1,26-1,40 (3H, m), 1,42 (3H, s), 3,35 (3H, s), 3,56-3,63 (1H, m), 4,34-4,41 (1H, m), 6,76-6,82 (2H, m), 7,28 (1H, d, J = 8,7 Hz).

Ejemplo de referencia 32

Síntesis de 1,3,3,5-tetraetil-7-hidroxi-1,5-dihidrobenzo-[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo de referencia 24, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,58 (3H, t, J = 7,4 Hz), 0,98 (3H, t, J = 7,3 Hz), 1,08-1,29 (8H, m), 2,12-2,19 (2H, m), 3,57-3,76 (2H, m), 4,20-4,34 (2H, m), 6,09 (1H, br-s), 6,78-6,82 (2H, m), 7,14-7,17 (1H, m).

Ejemplo de referencia 33

Síntesis de 1,5-dietil-7-hidroxi-3,3-dimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo de referencia 24, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,87 (3H, s), 1,08-1,17 (6H, m), 1,54 (3H, s), 3,57-3,73 (2H, m), 4,27-4,39 (2H, m), 6,85-6,87 (2H, m), 7,15-7,18 (1H, m).

Ejemplo de referencia 34

Síntesis de 1,3,5-trietil-7-hidroxi-1,5-dihidrobenzo[b]-[1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo de referencia 24, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,84 (3H, t, J = 7,4 Hz), 1,02-1,12 (6H, m), 1,95-2,19 (2H, m), 3,03 (1H, t, J = 6,9 Hz), 3,51-3,70 (2H, m), 4,33-4,46 (2H, m), 6,89-6,93 (2H, m), 7,23 (1H, d, J = 8,5 Hz), 7,57 (1H, s).

Ejemplo de referencia 35

Síntesis de 7-hidroxi-1,3,3,5-tetrametil-1,5-dihidrobenzo-[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo de referencia 24, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,90 (3H, s), 1,49 (3H, s), 3,39 (3H, s), 3,40 (3H, s), 6,73 (1H, d, J = 2,7 Hz), 6,80 (1H, dd, J = 8,9 y 2,7 Hz), 7,13 (1H, d, J = 8,9 Hz).

Ejemplo de referencia 36

Síntesis de 7-hidroxi-1-isobutil-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo de referencia 24, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,69 (3H, d, J = 6,7 Hz), 0,75 (3H, d, J = 6,7 Hz), 0,87 (3H, s), 1,53 (3H, s), 1,72-1,91 (1H, m), 3,24 (1H, dd, J = 6,3 y 13,5 Hz), 3,40 (3H, s), 4,35 (1H, dd, J = 8,6 y 13,5 Hz), 6,72-6,79 (2H, m), 7,13 (1H, d, J = 8,6 Hz).

Ejemplo de referencia 37

Síntesis de 7-(3-cloropropoxi)-1-etil-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Se agregaron 1-etil-7-hidroxi-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona (1,85 g, 7,1 mmoles) y carbonato de potasio (1,2 g, 8,5 mmoles) a acetonitrilo (40 ml) que contenía agua al 50% (40 ml), y se disolvió calentando a 70°C. Se agregó 1-bromo-3-cloropropano (2,1 ml, 21 mmoles) y se realizó el calentamiento bajo reflujo durante 6 horas. La mezcla de reacción se enfrió a temperatura ambiente. Se agregó agua y se realizó la extracción con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio, y se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (n-hexano:acetato de etilo = 2:1→1:1). El producto purificado se concentró a sequedad bajo presión reducida para obtener de este modo 2,18 g (rendimiento: 91%) de 7-(3-cloropropoxi)-1-etil-3,3,5-trimetil-1,5-hidrobenzo[b][1,4]-diazepina-2,4-diona como un aceite incoloro.

^{1}H-NMR ($CDCl_3$) δppm:

0,86 (3H, s), 1,15 (3H, t, J = 7,1 Hz), 1,53 (3H, s), 2,21-2,38 (2H, m), 3,40 (3H, s), 3,63-3,89 (4H, m), 4,10-4,26 (2H, m), 6,74 (1H, d, J = 2,8 Hz), 6,83 (1H, dd, J = 2,8 y 9,0 Hz), 7,21 (1H, d, J = 9,0 Hz).

Ejemplo de referencia 38

Síntesis de 7-(3-cloropropoxi)-1,3,3,5-tetrametil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo de referencia 37, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,88 (3H, s), 1,53 (3H, s), 2,20-2,32 (2H, m), 3,40 (3H, s), 3,42 (3H, s), 3,77 (2H, t, J = 6,1 Hz), 4,15 (2H, t, J = 5,8 Hz), 6,74 (1H, d, J = 2,7 Hz), 6,83 (1H, dd, J = 2,7 y 9,0 Hz), 7,15 (1H, d, J = 9,0 Hz).

Ejemplo de referencia 39

Síntesis de 1-etil-7-(3-yodopropoxi)-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Se agregaron 7-(3-cloropropoxi)-1-etil-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona (2,18 g, 6,4 mmoles) y yoduro de sodio (4,8 g, 32 mmoles) a acetona (50 ml), y se calentó bajo reflujo durante 8,5 horas. La mezcla de reacción se enfrió a temperatura ambiente, se agregó agua y se realizó la extracción con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio, y se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (n-hexano:acetato de etilo = 1:1). El producto purificado se concentró bajo presión reducida para obtener de este modo 2,76 g (rendimiento: 100%) de 1-etil-7-(3-yodopropoxi)-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona como un aceite incoloro.

^{1}H-NMR ($CDCl_3$) δppm:

0,87 (3H, s), 1,15 (3H, t, J = 7,1 Hz), 1,53 (3H, s), 2,26-2,34 (2H, m), 3,39 (2H, t, J = 6,6 Hz), 3,65-3,76 (1H, m), 3,41 (3H, s), 4,07 (2H, t, J = 5,8 Hz), 4,12-4,24 (1H, m), 6,74 (1H, d, J = 2,8 Hz), 6,83 (1H, dd, J = 9,0 y 2,8 Hz), 7,22 (1H, d, J = 9,0 Hz).

Ejemplo de referencia 40

Síntesis de 7-(3-yodopropoxi)-1,3,3,5-tetrametil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo de referencia 39, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,88 (3H, s), 1,54 (3H, s), 2,22-2,34 (2H, m), 3,39 (2H, t, J = 6,6 Hz), 3,40 (3H, s), 3,42 (3H, s), 4,07 (2H, t, J = 5,8 Hz), 6,74 (1H, d, J = 2,8 Hz), 6,83 (1H, dd, J = 2,8 y 9,0 Hz), 7,15 (1H, d, J = 9,0 Hz).

Ejemplo de referencia 41

Síntesis de (2-piridin-3-iletil)piridin-4-ilmetilamina

Se agregaron 4-piridinacarbaldehído (5,36 g, 50 mmoles) y 3-(2-aminoetil)piridina (6,5 ml, 50 mmoles) a metanol (100 ml), y se agitó a temperatura ambiente durante 7 horas. La mezcla resultante se enfrió a 0°C. Se agregó borohidruro de sodio (2,8 g, 74 mmoles) a la mezcla y se agitó a 0°C durante 1 hora. Se agregó luego agua a la mezcla de reacción para retirar por destilación el metanol bajo presión reducida. El residuo se extrajo con diclorometano. La capa orgánica se lavó con una solución acuosa de cloruro de sodio saturada, se secó sobre sulfato de sodio anhidro y se concentró bajo presión reducida. El residuo se purificó por cromatografía en

columna de gel de sílica básica (acetato de etilo:metanol=95:5→85:5). El producto purificado se concentró bajo presión reducida para obtener de este modo 10,03 g (rendimiento: 94%) de (2-piridin-3-iletil)piridin-4-ilmetilamina como un aceite incoloro.

^{1}H-NMR ($CDCl_3$) δppm:

2,79-2,98 (4H, m), 3,82 (2H, s), 7,21-7,25 (3H, m), 7,51-7,55 (1H, m), 8,47-8,50 (2H, m), 8,52-8,54 (2H, m)

Ejemplo de referencia 42

Síntesis de (2-piridin-3-iletil)piridin-4-ilmetil-[3-(tetrahidropiran-2-iloxi)propil]amina

Se agregó yoduro de sodio (1,5 g, 10 mmoles) a una solución de DMF (20 ml) de 2-(3-bromopropoxi)-tetrahidropirano (0,85 ml, 5 mmoles), y se agitó a 70°C durante 7 horas. La mezcla de reacción se enfrió a temperatura ambiente. Se agregaron luego (2-piridin-3-iletil)piridin-4-ilmetilamina (1,28 g, 6 mmoles) y N-etil diisopropilamina (1,3 ml, 7,5 mmoles) a la mezcla de reacción y se agitó a temperatura ambiente durante la noche. Se agregó agua a la mezcla de reacción, y se realizó la extracción con acetato de etilo. La capa orgánica se lavó con agua y una solución acuosa de cloruro de sodio saturada, en ese orden. La capa orgánica se secó sobre sulfato de sodio anhidro y se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:metanol = 20:1→ 4:1). El producto purificado se concentró bajo presión reducida para obtener de este modo 236 mg (rendimiento: 13%) de (2-piridin-3-iletil)piridin-4-ilmetil-[3-(tetrahidropiran-2-iloxi)propil]amina como un

aceite incoloro.

^{1}H-NMR ($CDCl_3$) δppm:

1,40-1,92 (8H, m), 2,52-2,83 (6H, m), 3,30-3,56 (2H, m), 3,62 (2H, s), 3,66-3,90 (2H, m), 4,51 - 4,53 (1H, m), 7,16 (2H, d, J = 6,0 Hz), 7,19 (1H, d, J = 4,8 Hz), 7,42 (1H, d, J = 6,6 Hz), 8,41-8,49 (4H, m).

Ejemplo de referencia 43

Síntesis de 3-[(2-piridin-3-iletil)piridin-4-ilmetilamino]-propan-1-ol

Se agregó una solución 2N de clorúro de hidrógeno-metanol (1,2 ml) a una solución de metanol (4 ml) de (2-piridin-3-iletil)piridin-4-ilmetil-[3-(tetrahidropiran-2-iloxi)propil]amina (236 mg, 0,66 mmoles), y se agitó a temperatura ambiente durante la noche. Se agregó una solución 2N de cloruro de hidrógeno metanol (0,5 ml) a la mezcla, y se agitó a 50°C durante 3 horas. Se agregó luego trietilamina (0,64 ml) a la mezcla de reacción y se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice básica (diclorometano). El producto purificado se concentró bajo presión reducida para obtener de este modo 186,3 mg (rendimiento: cuantitativo) de 3-[(2-piridin-3-iletil)piridin-4-ilmetilamino]propan-1-ol como un aceite anaranjado.

^{1}H-NMR ($CDCl_3$) δppm:

1,70-1,86 (2H, m), 2,67-2,78 (4H, m), 2,81 (2H, t, J = 6,0 Hz), 3,65 (2H, s), 3,72 (2H, t, J = 5,5 Hz), 7,18 (2H, d, J = 5,9 Hz), 7,21 (1H, d, J = 4,9 Hz), 7,42 (1H, dt, J = 1,8 y 7,8 Hz), 8,42-8,54 (2H, m), 8,54 (2H, d, J = 5,9 Hz).

Ejemplo de referencia 44

Síntesis de 6-[2-(tetrahidropiran-2-iloxi)etil]-6H-furo[2,3-c]piridin-7-ona

Se suspendió hidruro de sodio (60% en aceite, 138 mg, 3,5 mmol) en DMF (10 ml). Se agregó una solución de DMF (5 ml) de 6H-furo[2,3-c]piridin-7-ona (310 mg, 2,3 mmoles) a 0°C, y se realizó la agitación a la misma temperatura durante 1 hora. Se agregó una solución de DMF (5 ml) de 2-(2-yodoetoxi)tetrahidropirano (1175 mg, 4,6 mmoles), y se realizó la agitación a temperatura ambiente durante la noche. Se agregó agua a la mezcla de reacción y se realizó la extracción con acetato de etilo. La capa orgánica se lavó con agua, se secó sobre sulfato de sodio, y se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (n-hexano:acetato de etilo = 2:1→1:1). El producto purificado se concentró bajo presión reducida para obtener de este modo 450 mg (rendimiento: 74%) de 6-[2-(tetrahidropiran-2-iloxi)etil]-6H-furo[2,3-c]piridin-7-ona como un aceite amarillo.

^{1}H-NMR ($CDCl_3$) δppm:

1,46-1,81 (6H, m), 3,40-3,47 (1H, m), 3,63-3,79 (2H, m), 4,00-4,07 (1H, m), 4,16-4,24 (1H, m), 4,34-4,41 (1H, m), 4,54 (1H, t, J = 3,1 Hz), 6,43 (1H, d, J = 7,0 Hz), 6,65 (1H, d, J = 1,9 Hz), 7,26 (1H, d, J = 7,0 Hz), 7,73 (1H, d, J = 1,9 Hz).

Ejemplo de referencia 45

Síntesis de 7-metil-2-[2-(tetrahidropiran-2-iloxi)etil]-2H-isoquinolin-1-ona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo de referencia 44, se sintetizó el

compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

1,39-1,88 (6H, m), 2,49 (3H, s), 3,33-3,48 (1H, m), 3,61-3,81 (2H, m), 4,00-4,21 (2H, m), 4,28-4,39 (1H, m), 4,53-4,56 (1H, m), 6,43 (1H, d, J = 7,4 Hz), 7,15 (1H, d, J = 7,4 Hz), 7,41 (1H, d, J = 8,1 Hz), 7,45 (1H, dd, J = 1,7 y 8,1 Hz), 8,23 (1H, s).

Ejemplo de referencia 46

Síntesis de 6-(2-hidroxietil)-6H-furo[2,3-c]piridin-7-ona

Se agregó p-toluenosulfonato de piridinio (0,21 g, 0,85 mmoles) a una solución de metanol (20 ml) de 6-[2-(tetrahidropiran-2-iloxi)etil]-6H-furo[2,3-c]piridin-7-ona (0,45 g, 1,7 mmoles), y se agitó a temperatura ambiente durante 2 días. Se agregó una solución acuosa de hidrógeno carbonato de sodio a la mezcla de reacción, y se extrajo con diclorometano. La capa orgánica se secó sobre sulfato de sodio anhidro y se concentró bajo presión reducida. Se agregó dietil éter al residuo para precipitar los cristales. Los cristales se recogieron por filtración y se secaron para obtener de este modo 223 mg (rendimiento: 73%) de 6-(2-hidroxietil)-6H-furo[2,3-c]piridin-7-ona como un polvo blanco.

^{1}H-NMR ($CDCl_3$) δppm:

3,15 (1H, t, J = 5,3 Hz), 3,96-4,01 (2H, m), 4,25 (2H, t, J = 5,3 Hz), 6,49 (1H, d, J = 7,0 Hz), 6,66 (1H, d, J = 2,0 Hz), 7,18 (1H, d, J = 7,0 Hz), 7,75 (1H, d, J = 2,0 Hz).

Ejemplo de referencia 47

Síntesis de 2-(2-hidroxietil)-7-metil-2H-isoquinolin-1-ona

Usando un material de partida apropiado y siguiendo el

procedimiento del Ejemplo de referencia 46, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

2,48 (3H, s), 3,29 (1H, t, J = 5,2 Hz), 3,96 - 4,01 (2H, m), 4,16-4,19 (2H, m), 6,49 (1H, d, J = 7,3 Hz), 7,05 (1H, d, J = 7,3 Hz), 7,41 (1H, d, J = 8,1 Hz), 7,46 (1H, dd, J = 1,7 y 8,1 Hz), 8,20 (1H, d, J = 1,7 Hz).

Ejemplo de referencia 48

Síntesis de 2-nitro-N-[3-(tetrahidropiran-2-iloxi)propil]-bencenosulfonamida

Se agregó cloruro de 2-nitrobencenosulfonilo (22,1 g, 0,10 moles) a una solución de diclorometano (400 ml) de 3-aminopropanol (8,2 g, 0,11 moles) y trietilamina (21 ml, 0,15 moles) a 0°C, y se agitó a temperatura ambiente durante la noche. Se agregó agua a la mezcla de reacción y se realizó la extracción con diclorometano. La capa orgánica se secó sobre sulfato de sodio anhidro y se concentró bajo presión reducida. El residuo se disolvió en diclorometano (400 ml), y se agregaron 3,4-dihidro-2H-pirano (9,3 g, 0,11 moles) y ácido p-toluenosulfónico (1,9 g, 0,01 moles). Se realizó la agitación a temperatura ambiente durante la noche. Se agregó una solución acuosa de hidróxido de sodio 1N a la mezcla de reacción, y se realizó la extracción con diclorometano. La capa orgánica se lavó con agua, se secó sobre sulfato de sodio, y se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (n-hexano:acetato de etilo = 2:1→1:2). El producto purificado se concentró bajo presión reducida para obtener de este modo 27,56 g (rendimiento: 80%) de 2-nitro-N-[3-(tetrahidropiran-

2-iloxi)propil]bencenosulfonamida como un aceite marrón pálido.

^{1}H-NMR ($CDCl_3$) δppm:

1,40-1,93 (6H, m), 3,12-3,38 (2H, m), 3,38-3,58 (2H, m), 3,75-3,92 (2H, m), 4,11-4,17 (1H, m), 4,51-4,54 (1H, m), 5,85-5,93 (1H, m), 7,63-7,79 (2H, m), 7,79-7,92 (1H, m), 8,07-8,20 (1H, m).

Ejemplo de referencia 49

Síntesis de 2-nitro-N-[2-(7-oxo-7H-furo[2,3-c]piridin-6-il)etil]-N-[3-(tetrahidropiran-2-iloxi)propil]benceno-sulfonamida

Se agregaron trifenilfosfina (393 mg, 1,5 mmoles) y di-tert-butil éster del ácido azodicarboxílico (345 mg, 1,5 mmoles) a una solución de tetrahidrofurano (THF) (10 ml) de 6-(2-hidroxietil)-6H-furo[2,3-c]piridin-7-ona (179 mg, 1,0 mmol) y 2-nitro-N-[3-(tetrahidropiran-2-iloxi)propil]-bencenosulfonamida (413 mg, 1,2 mmoles), y se agitó durante la noche. La mezcla de reacción resultante se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (n-hexano:acetato de etilo = 1:1→0:1). El producto purificado se concentró a sequedad bajo presión reducida para obtener de este modo 286 mg (rendimiento: 57%) de 2-nitro-N-[2-(7-oxo-7H-furo[2,3-c]piridin-6-il)etil]-N-[3-(tetrahidropiran-2-iloxi)propil]bencenosulfonamida como un sólido blanco amorfo.

^{1}H-NMR ($CDCl_3$) δppm:

1,37-1,91 (8H, m), 3,25-3,59 (4H, m), 3,61-3,88 (4H, m), 4,27 (2H, t, J = 6,5 Hz), 4,45-4,49 (1H, m), 6,43 (1H, d, J = 7,0 Hz), 6,64 (1H, s), 7,19 (1H, d, J = 7,0 Hz), 7,49-7,69 (3H,

m), 7,72 (1H, s), 7,92-8,02 (1H, m).

Ejemplo de referencia 50

Síntesis de 2-nitro-N-[2-(1-oxo-1H-isoquinolin-2-il)etil]-N-[3-(tetrahidropiran-2-iloxi)propil]bencenosulfonamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo de referencia 49, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

1,40-1,91 (8H, m), 3,21-3,61 (4H, m), 3,61-3,86 (4H, m), 4,21 (2H, t, J = 6,6 Hz), 4,45-4,48 (1H, m), 6,45 (1H, d, J = 7,3 Hz), 7,14 (1H, d, J = 7,3 Hz), 7,38-7,79 (6H, m), 7,91-8,01 (1H, m), 8,34 (1H, d, J = 7,5 Hz).

Ejemplo de referencia 51

Síntesis de 2-nitro-N-[2-(1-oxo-3,4-dihidro-1H-isoquinolin-2-il)etil]-N-[3-(tetrahidropiran-2-iloxi)propil]-bencenosulfonamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo de referencia 49, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

1,44-1,98 (8H, m), 3,01 (2H, t, J = 6,6 Hz), 3,28-3,82 (12H, m), 4,46 - 4,49 (1H, m), 7,18 (1H, d, J = 7,6 Hz), 7,29-7,72 (5H, m), 7,98-8,07 (2H, m).

Ejemplo de referencia 52

Síntesis de N-(3-hidroxipropil)-2-nitro-N-[2-(7-oxo-7H-furo[2,3-c]piridin-6-il)etil]bencenosulfonamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo de referencia 46, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

1,73-1,87 (2H, m), 3,51 (2H, t, J = 6,9 Hz), 3,63 (2H, t, J = 5,7 Hz), 3,71 (2H, t, J = 6,8 Hz), 4,27 (2H, t, J = 6,8 Hz), 6,46 (1H, d, J = 7,0 Hz), 6,65 (1H, d, J = 1,9 Hz), 7,20 (1H, d, J = 7,0 Hz), 7,50-7,69 (3H, m), 7,73 (1H, d, J = 1,9 Hz), 7,92-8,01 (1H, m).

Ejemplo de referencia 53

Síntesis de N-(3-hidroxipropil)-2-nitro-N-[2-(1-oxo-1H-isoquinolin-2-il)etil]bencenosulfonamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo de referencia 46, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

1,72-1,89 (2H, m), 3,54 (2H, t, J = 6,7 Hz), 3,65 (2H, t, J = 5,5 Hz), 3,72 (2H, t, J = 6,7 Hz), 4,23 (2H, t, J = 6,8 Hz), 6,49 (1H, d, J = 7,3 Hz), 7,15 (1H, d, J = 7,3 Hz), 7,42-7,70 (6H, m), 7,90-8,00 (1H, m), 8,34 (1H, d, J = 7,9 Hz).

Ejemplo de referencia 54

Síntesis de N-(3-hidroxipropil)-2-nitro-N-[2-(1-oxo-3,4-dihidro-1H-isoquinolin-2-il)etil]bencenosulfonamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo de referencia 46, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

1,75-2,05 (2H, m), 3,01 (2H, t, J = 6,2 Hz), 3,46-3,88 (10H, m), 7,18 (1H, d, J = 7,6 Hz), 7,34 (1H, d, J = 7,7 Hz), 7,39-7,42 (1H, m), 7,57-7,70 (3H, m), 7,97-8,06 (2H, m).

Ejemplo de referencia 55

Síntesis de 3-{(2-nitrobencenosulfonil)-[2-(7-oxo-7H-

furo[2,3-c]piridin-6-il)etil]amino}propil metanosulfonato

Se agregó cloruro de metanosulfonilo (0,14 ml, 1,8 mmoles) a una solución de THF (30 ml) de N-(3-hidroxipropil)-2-nitro-N-[2-(7-oxo-7H-furo[2,3-c]piridin-6-il)etil]bencenosulfonamida (644 mg, 1,5 mmoles) y trietilamina (0,34 ml, 2,3 mmol), y se agitó a temperatura ambiente durante la noche. Se agregó agua a la mezcla de reacción, y se realizó la extracción con diclorometano. La capa orgánica se secó sobre sulfato de sodio anhidro, y se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:metanol = 1:0→10:1). El producto purificado se concentró a sequedad bajo presión reducida para obtener de este modo 480 mg (rendimiento: 64%) of 3-{(2-nitrobencenosulfonil)-[2-(7-oxo-7H-furo[2,3-c]piridin-6-il)etil]amino}propil metanosulfonato como un sólido amorfo blanco.

^{1}H-NMR ($CDCl_3$) δppm:

1,95-2,05 (2H, m), 3,04 (3H, s), 3,50 (2H, t, J = 7,1 Hz), 3,70 (2H, t, J = 6,7 Hz), 4,18 (2H, t, J = 5,8 Hz), 4,26 (2H, t, J = 6,7 Hz), 6,47 (1H, d, J = 7,0 Hz), 6,66 (1H, d, J = 1,9 Hz), 7,19 (1H, d, J = 7,0 Hz), 7,50 - 7,74 (4H, m), 7,94-8,02 (1H, m).

Ejemplo de referencia 56

Síntesis de 3-{(2-nitrobencenosulfonil)-[2-(1-oxo-1H-isoquinolin-2-il)etil]amino}propil metanosulfonato

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo de referencia 55, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

1,98-2,09 (2H, m), 3,01 (3H, s), 3,52 (2H, t, J = 6,9 Hz), 3,71 (2H, t, J = 6,6 Hz), 4,17 (2H, t, J = 5,8 Hz), 4,21 (2H, t, J = 6,9 Hz), 6,47 (1H, d, J = 7,4 Hz), 7,13 (1H, d, J = 7,4 Hz), 7,45-7,70 (6H, m), 7,90-8,00 (1H, m), 8,33 (1H, d, J = 7,7 Hz).

Ejemplo de referencia 57

Síntesis de 3-{(2-nitrobencenosulfonil)-[2-(1-oxo-3,4-dihidro-1H-isoquinolin-2-il)etil]amino}propil metanosulfonato

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo de referencia 55, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

2,04-2,19 (2H, m), 3,01 (2H, t, J = 6,7 Hz), 3,02 (3H, s), 3,39-3,48 (6H, m), 3,75 (2H, t, J = 7,2 Hz), 4,26 (2H, t, J = 5,9 Hz), 7,17 (1H, d, J = 7,4 Hz), 7,28-7,45 (2H, m), 7,60-7,74 (3H, m), 7,96-8,04 (2H, m).

Ejemplo de referencia 58

Síntesis de N-(3-yodopropil)-2-nitro-N-[2-(7-oxo-7H-furo[2,3-c]piridin-6-il)etil]bencenosulfonamida

Se agregaron 3-{(2-nitrobencenosulfonil)-[2-(7-oxo-7H-furo[2,3-c]-piridin-6-il)etil]amino}propil metanosulfonato (480 mg, 0,96 mmoles) y yoduro de sodio (720 mg, 4,8 mmoles) a acetona (20 ml), y se calentó bajo reflujo durante 5 horas. La mezcla de reacción se enfrió a temperatura ambiente, se agregó agua, y se realizó la extracción con diclorometano. La capa orgánica se secó sobre sulfato de sodio, y se concentró bajo presión reducida para obtener de este modo 474 mg

(rendimiento: 93%) de N-(3-yodopropil)-2-nitro-N-[2-(7-oxo-7H-furo[2,3-c]piridin-6-il)etil]bencenosulfonamida como un sólido amorfo amarillo.

^{1}H-NMR (DMSO-D_6) δppm:

1,89-2,02 (2H, m), 3,12 (2H, t, J = 6,9 Hz), 3,42 (2H, t, J = 7,3 Hz), 3,66 (2H, t, J = 5,8 Hz), 4,15 (2H, t, J = 5,9 Hz), 6,49 (1H, d, J = 7,0 Hz), 6,84 (1H, d, J = 1,9 Hz), 7,37 (1H, d, J = 7,0 Hz), 7,69-7,81 (2H, m), 7,87-7,99 (2H, m), 8,09 (1H, d, J = 1,9 Hz).

Ejemplo de referencia 59

Síntesis de N-(3-yodopropil)-2-nitro-N-[2-(1-oxo-1H-isoquinolin-2-il)etil]bencenosulfonamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo de referencia 58, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

2,02-2,18 (2H, m), 3,06 (2H, t, J = 7,0 Hz), 3,44 (2H, t, J = 7,2 Hz), 3,72 (2H, t, J = 6,5 Hz), 4,21 (2H, t, J = 6,5 Hz), 6,46 (1H, d, J = 7,3 Hz), 7,13 (1H, d, J = 7,3 Hz), 7,41-7,70 (6H, m), 7,95-8,06 (1H, m), 8,34 (1H, d, J = 7,9 Hz).

Ejemplo de referencia 60

Síntesis de N-(3-yodopropil)-2-nitro-N-[2-(1-oxo-3,4-dihidro-1H-isoquinolin-2-il)etil]bencenosulfonamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo de referencia 58, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

2,03-2,20 (2H, m), 3,02 (2H, t, J = 6,6 Hz), 3,12 (2H, t, J = 6,6 Hz), 3,50 (2H, t, J = 7,1 Hz), 3,56-3,70 (4H, m), 3,76

(2H, t, J = 7,0 Hz), 7,17 (1H, d, J = 7,5 Hz), 7,28-7,45 (2H, m), 7,60-7,70 (3H, m), 8,00-8,11 (2H, m).

Ejemplo de referencia 61

Síntesis de tert-butil metil-[2-(2-nitrobencenosulfonil-amino)-etil]carbamato

Se agregó cloruro de 2-nitrobencenosulfonilo (4,9 g, 22 mmoles) a una solución de diclorometano (100 ml) de tert-butil (2-aminoetil)metil carbamato (3,5 g, 20 mmoles) y trietilamina (3,3 ml, 24 mmoles) a 0°C, y se agitó a temperatura ambiente durante la noche. Se agregó agua a la mezcla de reacción, y se realizó la extracción con diclorometano. La capa orgánica se secó sobre sulfato de sodio anhidro y se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (n-hexano:acetato de etilo = 3:2→2:3). El producto purificado se concentró bajo presión reducida para obtener de este modo 5,06 g (rendimiento: 70%) de tert-butil metil-[2-(2-nitrobencenosulfonilamino)etil]carbamato como un aceite amarillo.

^{1}H-NMR ($CDCl_3$) δppm:

1,45 (9H, s), 2,84 (3H, s), 3,26-3,41 (4H, m), 7,68-7,79 (2H, m), 7,79-7,90 (1H, m), 8,09-8,19 (1H, m).

Ejemplo de referencia 62

Síntesis de 2-nitro-N-(2-piridin-3-iletil)benceno-sulfonamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo de referencia 61, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

2,88 (2H, t, J = 7,1 Hz), 3,41 (2H, q, J = 7,1 Hz), 5,44 (1H,

t, J = 5,4 Hz), 7,18-7,22 (1H, m), 7,50 (1H, dt, J = 7,8 y 1,8 Hz), 7,71-7,77 (2H, m), 7,82-7,88 (1H, m), 8,07-8,12 (1H, m), 8,35 (1H, d, J = 1,8 Hz), 8,45 (1H, dd, J = 4,8 y 1,8 Hz).

Ejemplo 1

Síntesis de 7-(3-(1,3-dioxo-1,3-dihidroisoindol-2-il)propoxi)-1-etil-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]-diazepina-2,4-diona

Se agregaron carbonato de potasio (2,99 g, 21,6 mmoles) y N-(3-bromopropil)ftalimida (2,32 g, 8,65 mmoles) a una solución de DMF (50 ml) de 1-etil-7-hidroxi-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona (1,89 g, 7,2 mmoles), y se agitó a temperatura ambiente durante la noche. Se agregó agua a la mezcla de reacción, y se realizó la extracción con acetato de etilo. La capa orgánica se lavó con agua y una solución acuosa de cloruro de sodio saturada, en ese orden. La capa orgánica se secó sobre sulfato de magnesio anhidro, y se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (n-hexano:acetato de etilo = 2:1→3:7). El producto purificado se concentró a sequedad bajo presión reducida para obtener de este modo 2,70 g (rendimiento: 83%) de 7-(3-(1,3-dioxo-1,3-dihidroisoindol-2-il)propoxi)-1-etil-3,3,5-trimetil-1,5-dihidrobenzo[b]-[1,4]diazepina-2,4-diona como un polvo blanco.

^{1}H-NMR ($CDCl_3$) δppm:

0,84 (3H, s), 1,13 (3H, t, J = 7,1 Hz), 1,52 (3H, s), 2,18-2,24 (2H, m), 3,33 (3H, s), 3,63-3,75 (1H, m), 3,93 (2H, t, J = 6,8 Hz), 4,06 (2H, t, J = 5,9 Hz), 4,10-4,10 (1H, m), 6,59

(1H, d, J = 2,8 Hz), 6,73 (1H, dd, J = 9,0 y 2,8 Hz), 7,16 (1H, d, J = 9,0 Hz), 7,72-7,76 (2H, m), 7,82-7,88 (2H, m).

Ejemplo 2

Síntesis de 7-(3-aminopropoxi)-1-etil-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Se agregó hidrato de hidrazina (1,17 ml, 24 mmoles) a una solución de metanol (60 ml) de 7-[3-(1,3-dioxo-1,3-dihidroisoindol-2-il)propoxi]-1-etil-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona (2,70 g, 6,0 mmoles), y se agitó mientras se calentaba bajo reflujo durante 2 horas. La mezcla de reacción se concentró bajo presión reducida. Se agregó una solución acuosa de hidróxido de sodio 1N al residuo, y se agitó durante 30 minutos, y se realizó la extracción con diclorometano. La capa orgánica se lavó con agua y una solución acuosa de cloruro de sodio saturada, en ese orden. La capa orgánica se secó sobre sulfato de magnesio anhidro, y se concentró bajo presión reducida para obtener de este modo 1,48 g (rendimiento: 77%) de 7-(3-aminopropoxi)-1-etil-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona como un aceite incoloro.

^{1}H-NMR ($CDCl_3$) δppm:

0,86 (3H, s), 1,14 (3H, t, J = 7,1 Hz), 1,52 (3H, s), 1,90-2,00 (2H, m), 2,94 (2H, t, J = 6,8 Hz), 3,40 (3H, s), 3,66-3,76 (1H, m), 4,08 (2H, t, J = 6,2 Hz), 4,11-4,21 (1H, m), 6,73 (1H, d, J = 2,8 Hz), 6,82 (1H, dd, J = 9,0 y 2,8 Hz), 7,20 (1H, d, J = 9,0 Hz).

Ejemplo 3

Síntesis de clorhidrato de 7-(3-aminopropoxi)-1-etil-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Se agregó una solución 4N de cloruro de hidrógeno acetato de etilo (0,42 ml) a una solución de acetato de etilo (3 ml) de 7-(3-aminopropoxi)-1-etil-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona (264 mg), y se agitó a temperatura ambiente durante 30 minutos. La mezcla de reacción se concentró a sequedad bajo presión reducida para obtener de este modo 0,22 g de clorhidrato de 7-(3-aminopropoxi)-1-etil-3,3,5-trimetil-1,5-dihidrobenzo[b]-[1,4]diazepina-2,4-diona como un sólido amorfo blanco.

^{1}H-NMR (DMSO-D_6) δppm:

0,77 (3H, s), 1,01 (3H, t, J = 6,6 Hz), 1,33 (3H, s), 1,92-2,38 (4H, m), 3,33 (3H, s), 3,67-4,20 (6H, m), 6,95-7,00 (2H, m), 7,42 (1H, d, J = 8,8 Hz), 8,28 (1H, br-s).

Ejemplo 4

Síntesis de N-(3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil)-2-nitrobencenosulfonamida

Se agregó trietilamina (0,8 ml, 5,7 mmoles) a una solución de diclorometano (50 ml) de 7-(3-aminopropoxi)-1-etil-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona (1,22 g, 3,8 mmoles) y se enfrió con hielo. Se agregó cloruro de o-nitrobencenosulfonilo (1,03 g, 4,2 mmoles) a la mezcla resultante, y se agitó a temperatura ambiente durante 2 horas. Se agregó agua a la mezcla de reacción, y se realizó la extracción con diclorometano. La capa orgánica se lavó con agua y una solución acuosa de cloruro de sodio saturada, en ese orden, luego se secó sobre sulfato de magnesio anhidro, y se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (n-

hexano:acetato de etilo = 1:1→0:1). El producto purificado se concentró a sequedad bajo presión reducida para obtener de este modo 1,86 g (rendimiento: 97%) de N-(3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)-propil)-2-nitrobencenosulfonamida como un sólido amorfo blanco.

^{1}H-NMR ($CDCl_3$) δppm:

0,86 (3H, s), 1,15 (3H, t, J = 7,1 Hz), 1,52 (3H, s), 2,05-2,13 (2H, m), 3,34-3,40 (2H, m), 3,40 (3H, s), 3,65-3,77 (1H, m), 4,07-4,21 (3H, m), 5,76 (1H, t, J = 5,9 Hz), 6,77 (1H, d, J = 2,7 Hz), 6,82 (1H, dd, J = 8,9 y 2,8 Hz), 7,21 (1H, d, J = 9,0 Hz), 7,73-7,79 (2H, m), 7,85-7,89 (1H, m), 8,14-8,18 (1H, m).

Ejemplo 5

Síntesis de 1-etil-3,3,5-trimetil-7-[3-(2-piridin-3-iletilamino)propoxi]-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Se agregó 1-etil-7-(3-yodopropoxi)-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona (5,3 mmoles) a una solución de metanol (100 ml) de 3-(2-aminoetil)piridina (3,3 g, 26,7 mmoles), y se agitó a 50°C durante 9 horas. La mezcla de reacción se enfrió a temperatura ambiente, y se concentró bajo presión reducida. Se agregó agua al residuo, y se realizó la extracción con diclorometano. La capa orgánica se secó sobre sulfato de sodio anhidro, y se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (diclorometano:metanol = 20:1→10:1). El producto purificado se concentró bajo presión reducida, y el residuo se purificó por cromatografía en columna de gel de

sílice básica (acetato de etilo:metanol = 1:0→10:1) nuevamente. El producto purificado se concentró bajo presión reducida para obtener de este modo 1,57 g (rendimiento: 70%) de 1-etil-3,3,5-trimetil-7-[3-(2-piridin-3-iletilamino)propoxi]-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona como un aceite amarillo.

^{1}H-NMR ($CDCl_3$) δppm:

0,86 (3H, s), 1,14 (3H, t, J = 7,1 Hz), 1,52 (3H, s), 1,93-2,00 (2H,m), 2,80-2,96 (6H, m), 3,39 (3H, s), 3,66-3,73 (1H, m), 4,04 (2H, t, J = 6,1 Hz), 4,14-4,21 (1H, m), 6,70 (1H, d, J = 2,8 Hz), 6,78 (1H, dd, J = 9,0 y 2,0 Hz), 7,17-7,24 (2H, m), 7,54 (1H, dt, J = 7,8 y 1,9 Hz), 8,46 (1H, dd, J = 4,8 y 1,6 Hz), 8,49 (1H, d, J = 2,0 Hz).

Ejemplo 6

Síntesis de diclorhidrato de 1-etil-3,3,5-trimetil-7-[3-(2-piridin-3-iletilamino)propoxi]-1,5-dihidrobenzo[b][1,4]-diazepina-2,4-diona

Se agregó una solución 4N de cloruro de hidrógeno acetato de etilo (0,37 ml) a una solución de acetato de etilo (10 ml) de 1-etil-3,3,5-trimetil-7-[3-(2-piridin-3-iletilamino)propoxi]-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona (207 mg, 0,49 mmoles), y se agitó durante 30 minutos a temperatura ambiente. La materia insoluble precipitada se recogió por filtración, se lavó con acetato de etilo, y se secó para obtener de este modo 208 mg (rendimiento: 85%) de diclorhidrato de 1-etil-3,3,5-trimetil-7-[3-(2-piridin-3-iletilamino)-propoxi]-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona como un sólido amorfo amarillo pálido.

^{1}H-NMR (DMSO-D_6) δppm:

0,76 (3H, s), 1,01 (3H, t, J = 7,0 Hz), 1,32 (3H, s), 2,14-2,20 (2H, m), 3,10 (2H, br-s), 3,25-3,33 (6H, m), 3,61-3,73 (1H, m), 3,99-4,18 (4H, m), 6,92-6,99 (2H, m), 7,42 (1H, d, J = 8,9 Hz), 7,94-7,89 (1H, m), 8,46 (1H, d, J = 8,0 Hz), 8,80 (1H, dd, J = 5,5 y 1,0 Hz), 8,90 (1H, d, J = 1,0 Hz), 9,46 (2H, br-s).

Ejemplo 7

Síntesis de 1-etil-3,3,5-trimetil-7-{3-[(2-piridin-3-iletil)piridin-4-ilmetilamino]propoxi}-1,5-dihidrobenzo[b]-[1,4]diazepina-2,4-diona

Se agregaron 4-piridinacarbaldehído (1,18 ml, 12,5 mmoles) y una cantidad catalítica de ácido acético a una solución de 1,2-dicloroetano (40 ml) de 1-etil-3,3,5-trimetil-7-[3-(2-piridin-3-iletilamino)propoxi]-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona (4,44 g, 10,5 mmoles), y se agitó durante 30 minutos. Se agregó triacetoxihidroborato de sodio (3,33 g, 15,7 mmoles) a la mezcla resultante y se agitó a temperatura ambiente durante la noche. La mezcla de reacción se diluyó con diclorometano, se lavó con agua y una solución acuosa de cloruro de sodio saturada, en ese orden, luego se secó sobre sulfato de magnesio anhidro, y se concentró bajo presión reducida. El residuo se purificó por cromatografía flash en gel de sílice (acetato de etilo:metanol = 1:0→9:1). El producto purificado se concentró bajo presión reducida para obtener de este modo 4,73 g (rendimiento: 88%) de 1-etil-3,3,5-trimetil-7-{3-[(2-piridin-3-iletil)piridin-4-ilmetilamino]propoxi}-1,5-dihidrobenzo[b]-[1,4]diazepina-2,4-diona como un aceite amarillo pálido.

^{1}H-NMR ($CDCl_3$) δppm:

0,86 (3H, s), 1,15 (3H, t, J = 7,0 Hz), 1,52 (3H, s), 1,87-1,95 (2H, m), 2,67-2,80 (6H, m), 3,40 (3H, s), 3,66-3,77 (3H, m), 3,89 (2H, t, J = 6,0 Hz), 4,09-4,21 (1H, m), 6,63 (1H, d, J = 2,7 Hz), 6,72 (1H, dd, J = 9,0 y 2,7 Hz), 7,12-7,22 (4H, m), 7,42 (1H, dt, J = 7,8 y 1,9 Hz), 8,42-8,46 (4H, m).

Ejemplo 8

Síntesis de triclorhidrato de 1-etil-3,3,5-trimetil-7-{3-[(2-piridin-3-iletil)piridin-4-ilmetilamino]propoxi}-1,5-dihidrobenzo[b]-[1,4]diazepina-2,4-diona

Se agregaron trifenilfosfina (186 mg, 0,71 mmoles) y di-tert-butil azodicarboxilato (163 mg, 0,71 mmoles) a una solución de tetrahidrofurano (THF) (5 ml) de 1-etil-7-hidroxi-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona (156 mg, 0,59 mmoles) y 3-[(2-piridin-3-iletil)piridin-4-ilmetilamino]propan-1-ol (161 mg, 0,59 mmoles), y se agitó durante la noche. La mezcla de reacción se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:metanol = 1:0→4:1), y el producto purificado se concentró bajo presión reducida. Se agregó una solución 4N de cloruro de hidrógeno-acetato de etilo (0,29 ml) al residuo (solución de acetato de etilo), se agitó a temperatura ambiente durante 30 minutos, y se concentró a sequedad bajo presión reducida para obtener de este modo 206 mg (rendimiento: 56%) de triclorhidrato de 1-etil-3,3,5-trimetil-7-{3-[(2-piridin-3-iletil)piridin-4-ilmetil-amino]propoxi}-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona como un sólido amorfo blanco.

^{1}H-NMR (DMSO-D_6) δppm:

0,75 (3H, s), 1,01 (3H, t, J = 7,0 Hz), 1,32 (3H, s), 2,22-2,41 (2H, m), 3,15-3,53 (6H, m), 3,33 (3H, s), 3,64-3,71 (1H, m), 4,07-4,14 (3H, m), 4,62-4,86 (2H, m), 6,88-6,94 (2H, m), 7,42 (1H, d, J = 8,8 Hz), 8,03 (1H, dd, J = 8,0 y 5,7 Hz), 8,27-8,42 (2H, m), 8,54 (1H, d, J = 8,0 Hz), 8,84 (1H, d, J = 4,8 Hz), 8,94-9,02 (3H, m).

Ejemplo 9

Síntesis de triclorhidrato de 1-isobutil-3,3,5-trimetil-7-{3-[(2-piridin-3-iletil)piridin-4-ilmetilamino]propoxi}-1,5-dihidrobenzo[b]-[1,4]diazepina-2,4-diona

Se agregaron N,N,N',N'-tetrametilazodicarboxamide (TMAD)(189 mg, 1,1 mmoles) y tri-n-butil fosfina (0,28 ml, 1,1 mmoles) a una solución de THF (5 ml) de 7-hidroxi-1-isobutil-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona (213 mg, 0,73 mmoles) y 3-[(2-piridin-3-iletil)piridin-4-ilmetilamino]propan-1-ol (199 mg, 0,73 mmoles), y se agitó a temperatura ambiente durante la noche. Se agregó agua a la mezcla de reacción, y se realizó la extracción con diclorometano. La capa orgánica se secó sobre sulfato de sodio anhidro y se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:methanol = 20:1→10:1). El producto purificado se concentró bajo presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (diclorometano:metanol = 40:1→10:1) nuevamente. El producto purificado se concentró bajo presión reducida. Se agregó una solución 4N de cloruro de hidrógeno-acetato de etilo (0,57 ml) al residuo (solución de acetato de etilo), se agitó a temperatura ambiente durante 30 minutos, y se

concentró a sequedad bajo presión reducida para obtener de este modo 480 mg (rendimiento: cuantitativo) de triclorhidrato de 1-isobutil-3,3,5-trimetil-7-{3-[(2-piridin-3-iletil)piridin-4-ilmetilamino]propoxi}-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona como un sólido amorfo blanco.

^{1}H-NMR (DMSO-D_6) δppm:

0,58 (3H, d, J = 6,6 Hz), 0,71 (3H, d, J = 6,6 Hz), 0,75 (3H, s), 1,33 (3H, s), 1,51-1,78 (2H, m), 2,19-2,38 (2H, m), 3,00-3,48 (7H, m), 3,34 (3H, s), 4,02-4,28 (2H, m), 4,38-4,59 (2H, m), 6,86-6,94 (2H, m), 7,45 (1H, d, J = 9,0 Hz), 7,63-7,67 (1H, m), 7,87 (2H, d, J = 5,2 Hz), 8,07 (1H, d, J = 7,9 Hz), 8,62 (1H, d, J = 1,3 Hz), 8,66-8,78 (3H, m).

Ejemplo 10

Síntesis de triclorhidrato de 3,3,5-trimetil-1-propil-7-{3-[(2-piridin-3-iletil)piridin-4-ilmetilamino]propoxi}-1,5-dihidrobenzo[b]-[1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 9, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-D_6) δppm:

0,64 (3H, t, J = 7,4 Hz), 0,75 (3H, s), 1,32 (3H, s), 1,28-1,51 (2H, m), 2,18-2,41 (2H, m), 3,09-3,61 (7H, m), 3,32 (3H, s), 4,02-4,26 (3H, m), 4,47-4,82 (2H, m), 6,82-6,97 (2H, m), 7,42 (1H, d, J = 8,8 Hz), 7,92-8,03 (1H, m), 8,08-8,31 (2H, m), 8,41-8,50 (1H, m), 8,82 (1H, d, J = 5,6 Hz), 8,83-8,98 (3H, m).

Ejemplo 11

Síntesis de triclorhidrato de 3,3,5-trimetil-1-(3-

metilbutil)-7-{3-[(2-piridin-3-iletil)piridin-4-ilmetil-amino]propoxi}-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 9, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-D_6) δppm:

0,68-1,80 (15H, m), 2,28-2,48 (2H, m), 3,19-3,40 (2H, m), 3,31 (3H, s), 3,40-3,64 (5H, m), 4,03-4,18 (2H, m), 4,18-4,33 (1H, m), 4,70-4,92 (2H, m), 6,87-6,99 (2H, m), 7,44 (1H, d, J = 8,9 Hz), 8,00-8,09 (1H, m), 8,38-8,50 (2H, m), 8,51-8,62 (1H, m), 8,86 (1H, d, J = 5,5 Hz), 8,94-9,08 (3H, m).

Ejemplo 12

Síntesis de triclorhidrato de 5-etil-1,3,3-trimetil-7-{3-[(2-piridin-3-iletil)piridin-4-ilmetilamino]propoxi}-1,5-dihidrobenzo[b][1,4] diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 9, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-D_6) δppm:

0,75 (3H, s), 1,03 (3H, t, J = 7,0 Hz), 1,32 (3H, s), 2,21-2,41 (2H, m), 3,15-3,32 (2H, m), 3,28 (3H, s), 3,32-3,58 (4H, m), 3,64-3,82 (1H, m), 4,01-4,18 (3H, m), 4,59-4,82 (2H, m), 6,86-7,00 (2H, m), 7,38 (1H, d, J = 8,9 Hz), 8,02 (1H, dd, J = 5,7 y 8,0 Hz), 8,32 (2H, s), 8,53 (1H, d, J = 8,1 Hz), 8,83 (1H, d, J = 5,2 Hz), 8,90-8,99 (3H, m).

Ejemplo 13

Síntesis de triclorhidrato de 1,3,3,5-tetraetil-7-{3-[(2-piridin-3-iletil)piridin-4-ilmetilamino]propoxi}-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 9, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-D_6) δppm:

0,47 (3H, t, J = 7,1 Hz), 0,76-1,80 (13H, m), 1,80-2,00 (2H, m), 2,25-2,44 (2H, m), 3,22-3,40 (2H, m), 3,40-3,58 (2H, m), 3,58-3,79 (2H, m), 4,02-4,30 (4H, m), 4,70-4,92 (2H, m), 6,93 (2H, dd, J = 2,5 y 9,0 Hz), 6,99 (1H, d, J = 2,5 Hz), 7,44 (1H, d, J = 9,0 Hz), 8,06 (1H, dd, J = 5,8 y 7,9 Hz), 8,49 (1H, s), 8,60 (1H, d, J = 8,1 Hz), 8,86 (1H, d, J = 5,5 Hz), 8,96-9,09 (3H, m).

Ejemplo 14

Síntesis de triclorhidrato de 1,5-dietil-3,3-dimetil-7-{3-[(2-piridin-3-iletil)piridin-4-ilmetilamino]propoxi}-1,5-dihidrobenzo[b][1,4] diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 9, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-D_6) δppm:

0,73 (3H, s), 0,79-1,01 (6H, m), 1,31 (3H, s), 2,20-2,45 (2H, m), 3,18-3,38 (2H, m), 3,38-3,52 (2H, m), 3,52-3,79 (2H, m), 4,09-4,16 (2H, m), 4,16-4,35 (2H, m), 4,63-4,89 (2H, m), 6,92 (1H, dd, J = 2,6 y 9,0 Hz), 6,99 (1H, d, J = 2,6 Hz), 7,43 (1H, d, J = 9,0 Hz), 8,02 (1H, dd, J = 5,7 y 8,0 Hz), 8,34 (2H, s), 8,55 (1H, d, J = 8,0 Hz), 8,84 (1H, d, J = 5,4 Hz), 8,94-8,97 (3H, m).

Ejemplo 15

Síntesis de triclorhidrato de 1,3,5-trietil-7-{3-[(2-piridin-3-iletil)piridin-4-ilmetilamino]propoxi}-1,5-

dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 9, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-D_6) δppm:

0,62-1,80 (11H, m), 2,22-2,41 (2H, m), 2,81-3,00 (1H, m), 3,12-3,37 (2H, m), 3,37-3,55 (4H, m), 3,55-3,85 (2H, m), 4,08-4,19 (2H, m), 4,19-4,38 (2H, m), 4,62-4,88 (2H, m), 6,92 (1H, d, J = 9,1 Hz), 7,05 (1H, s), 7,50 (1H, d, J = 9,1 Hz), 8,03 (1H, dd, J = 5,9 y 7,9 Hz), 8,37 (2H, s), 8,56 (1H, d, J = 8,0 Hz), 8,84 (1H, d, J = 5,5 Hz), 8,92-9,02 (3H, m).

Ejemplo 16

Síntesis de 2-nitro-N-(2-piridin-3-iletil)-N-[3-(1,3,3,5-tetrametil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]-diazepin-7-iloxi)propil]bencenosulfonamida

Se agregaron 2-nitro-N-(2-piridin-3-iletil)-bencenosulfonamida (1,8 g, 5,8 mmoles) y carbonato de potasio (1,0 g, 7,2 mmoles) a una solución de DMF (30 ml) de 7-(3-yodopropoxi)-1,3,3,5-tetrametil-1,5-dihidro-benzo[b][1,4]diazepina-2,4-diona (2,0 g, 4,8 mmoles) y se agitó a temperatura ambiente durante la noche. La mezcla de reacción se agregó a agua helada, y se realizó la extracción con acetato de etilo. La capa orgánica se lavó con agua, se secó sobre sulfato de sodio anhidro, se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (n-hexano:acetato de etilo = 1:2→acetato de etilo→acetato de etilo:metanol= 20:1). El producto purificado se concentró a sequedad bajo presión reducida para obtener de este modo 2,29 g

(rendimiento: 80%) de 2-nitro-N-(2-piridin-3-iletil)-N-[3-(1,3,3,5-tetrametil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo-[b][1,4]diazepin-7-iloxi)propil]bencenosulfonamida como un sólido amorfo amarillo.

^{1}H-NMR ($CDCl_3$) δppm:

0,86 (3H, s), 1,53 (3H, s), 2,02-2,12 (2H, m), 2,91 (2H, t, J = 8,1 Hz), 3,39 (3H, s), 3,41 (3H, s), 3,57 (2H, t, J = 8,4 Hz), 3,60 (2H, t, J = 7,4 Hz), 4,01 (2H, t, J = 5,9 Hz), 6,71 (1H, d, J = 2,7 Hz), 6,77 (1H, d, J = 8,8 Hz), 7,14 (1H, d, J = 8,9 Hz), 7,18-7,24 (1H, m), 7,48-7,64 (4H, m), 8,00 (1H, d, J = 9,2 Hz), 8,41 (1H, d, J = 2,1 Hz), 8,45 (1H, d, J = 4,8 Hz).

Ejemplo 17

Síntesis de clorhidrato de 2-nitro-N-(2-piridin-3-iletil)-N-[3-(1,3,3,5-tetrametil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil]bencenosulfonamida

Se agregó una solución 4N de cloruro de hidrógeno-acetato de etilo (0,57 ml) a una solución de acetato de etilo (1 ml) de 2-nitro-N-(2-piridin-3-iletil)-N-[3-(1,3,3,5-tetrametil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil]bencenosulfonamida (236 mg), y se agitó a temperatura ambiente durante 1 minuto. La materia insoluble precipitada se recogió por filtración, se lavó con acetato de etilo, y luego se secó para obtener de este modo 163 mg (rendimiento: 65%) de clorhidrato de 2-nitro-N-(2-piridin-3-iletil)-N-[3-(1,3,3,5-tetrametil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-il-oxi)propil]bencenosulfonamida como un polvo blanco.

^{1}H-NMR (DMSO-D_6) δppm:

0,76 (3H, s), 1,33 (3H, s), 1,89-2,08 (2H, m), 3,10 (2H, t, J = 7,0 Hz), 3,30 (3H, s), 3,33 (3H, s), 3,55 (2H, t, J = 7,6 Hz), 3,69 (2H, t, J = 6,8 Hz), 4,00 (2H, t, J = 6,0 Hz), 6,82-6,95 (2H, m), 7,34 (1H, d, J = 8,8 Hz), 7,76-7,96 (4H, m), 8,03 (1H, d, J = 7,4 Hz), 8,40 (1H, d, J = 7,8 Hz), 8,75 (1H, d, J = 5,3 Hz), 8,85 (1H, s).

Ejemplo 18

Síntesis de 1,3,3,5-tetrametil-7-[3-(2-piridin-3-iletilamino)propoxi]-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Se agregaron hidróxido de litio (0,36 g, 15 mmoles) y ácido tioglicólico (0,48 ml, 6,9 mmoles) a una solución de DMF (20 ml) de 2-nitro-N-(2-piridin-3-iletil)-N-[3-(1,3,3,5-tetrametil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo-[b][1,4]diazepin-7-iloxi)propil]bencenosulfonamida (2,05 g, 3,4 mmoles), y se agitó a temperatura ambiente durante 3 días. La mezcla de reacción se agregó a agua helada, y se extrajo con acetato de etilo. La capa orgánica se lavó con agua, se secó sobre sulfato de sodio anhidro, y se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:metanol = 20:1→diclorometano:metanol = 10:1→4:1). El producto purificado se concentró bajo presión reducida para obtener de este modo 1,13 g (rendimiento: 81%) de 1,3,3,5-tetrametil-7-[3-(2-piridin-3-iletilamino)propoxi]-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona como un aceite amarillo.

^{1}H-NMR ($CDCl_3$) δppm:

0,87 (3H, s), 1,53 (3H, s), 1,92-2,02 (2H, m), 2,78-2,90 (4H,

m), 2,93 (2H, t, J = 6,5 Hz), 3,39 (3H, s), 3,41 (3H, s), 4,04 (2H, t, J = 6,2 Hz), 6,71 (1H, d, J = 2,7 Hz), 6,78 (1H, dd, J = 2,7 y 8,9 Hz), 7,13 (1H, d, J = 9,0 Hz), 7,16-7,25 (1H, m), 7,54 (1H, d, J = 7,8 Hz), 8,46 (1H, dd, J = 1,6 y 4,8 Hz), 8,49 (1H, d, J = 1,6 Hz).

Ejemplo 19

Síntesis de triclorhidrato de 1,3,3,5-tetrametil-7-{3-[(2-piridin-3-iletil)piridin-4-ilmetilamino]propoxi}-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 8, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-D_6) δppm:

0,76 (3H, s), 1,33 (3H, s), 2,18-2,40 (2H, m), 3,10-3,64 (6H, m), 3,30 (3H, s), 3,33 (3H, s), 3,97-4,14 (2H, m), 4,40-4,72 (2H, m), 6,81-6,92 (2H, m), 7,36 (1H, d, J = 8,6 Hz), 7,73-8,02 (3H, m), 8,28 (1H, d, J = 6,4 Hz), 8,68-8,82 (4H, m).

Ejemplo 20

Síntesis de triclorhidrato de 3,3-dietil-1,5-dimetil-7-{3-[(2-piridin-3-iletil)piridin-4-ilmetilamino]propoxi}-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 8, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,54 (3H, t, J = 7,5 Hz), 1,01 (3H, t, J = 7,5 Hz), 1,12-1,31 (4H, m), 2,09-2,24 (2H, m), 2,99-3,41 (6H, m), 3,38 (3H, s), 3,41 (3H, s), 3,97-4,08 (2H, m), 4,40-4,88 (2H, m), 6,67 (1H, d, J = 2,6 Hz), 6,74 (1H, dd, J = 9,0 y 2,6 Hz), 7,14 (1H, d,

J = 9,0 Hz), 7,51-7,62 (1H, m), 7,70 (2H, d, J = 5,3 Hz), 7,96 (1H, d, J = 7,1 Hz), 8,61 (1H, d, J = 4,7 Hz), 8,70 (2H, d, J = 5,3 Hz), 8,89 (1H, s).

Ejemplo 21

Síntesis de N-[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil]-2-nitro-N-[2-(1-oxo-1H-isoquinolin-2-il)etil]benceno-sulfonamida

Se agregó carbonato de potasio (0,22 g, 1,6 mmol) a una solución de DMF (10 ml) de N-(3-yodopropil)-2-nitro-N-[2-(1-oxo-1H-isoquinolin-2-il)etil]bencenosulfonamida (0,57 g, 1,05 mmoles) y 1-etil-7-hidroxi-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona (0,33 g, 1,26 mmoles), y se agitó a temperatura ambiente durante la noche. La mezcla de reacción se agregó a agua helada y se realizó la extracción con acetato de etilo. La capa orgánica se lavó con una solución acuosa de hidróxido de sodio 1N y agua, se secó sobre sulfato de sodio anhidro y se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (n-hexano:acetato de etilo = 1:1→0:1). El producto purificado se concentró a sequedad bajo presión reducida para obtener de este modo 0,49 g (rendimiento: 69%) de N-[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b]-[1,4]diazepin-7-iloxi)propil]-2-nitro-N-[2-(1-oxo-1H-isoquinolin-2-il)etil]bencenosulfonamida como un sólido amorfo blanco.

^{1}H-NMR ($CDCl_3$) δppm:

0,84 (3H, s), 1,14 (3H, t, J = 7,0 Hz), 1,52 (3H, s), 2,08-2,14 (2H, m), 3,39 (3H, s), 3,62 (2H, t, J = 7,4 Hz), 3,66-3,77 (3H, m), 3,94 (2H, t, J = 5,8 Hz), 4,13-4,22 (1H, m),

4,24 (2H, t, J = 6,7 Hz), 6,46 (1H, d, J = 7,3 Hz), 6,67 (1H, d, J = 2,7 Hz), 6,72 (1H, dd, J = 8,9 y 2,7 Hz), 7,12-7,19 (2H, m), 7,47-7,67 (6H, m), 7,95-7,98 (1H, m), 8,35 (1H, d, J = 7,5 Hz).

Ejemplo 22

Síntesis de 1-etil-3,3,5-trimetil-7-{3-[2-(1-oxo-1H-isoquinolin-2-il)etilamino]propoxi}-1,5-dihidrobenzo[b]-[1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 18, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,84 (3H, s), 1,14 (3H, t, J = 7,0 Hz), 1,52 (3H, s), 1,92-2,00 (2H, m), 2,87 (2H, t, J = 6,7 Hz), 3,06 (2H, t, J = 6,2 Hz), 3,38 (3H, s), 3,63-3,74 (1H, m), 4,02 (2H, t, J = 6,1 Hz), 4,09-4,23 (3H, m), 6,46 (1H, d, J = 7,3 Hz), 6,69 (1H, d, J = 2,7 Hz), 6,74 (1H, dd, J = 9,0 y 2,7 Hz), 7,10-7,16 (2H, m), 7,46-7,51 (2H, m), 7,64 (1H, t, J = 8,1 Hz), 8,41 (1H, d, J = 8,2 Hz).

Ejemplo 23

Síntesis de diclorhidrato de 1-etil-3,3,5-trimetil-7-(3-{[2-(1-oxo-1H-isoquinolin-2-il)etil]piridin-4-ilmetil-amino}propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando materiales de partida apropiados y siguiendo los procedimientos de los Ejemplos 7 y 6, se sintetizó el compuesto objetivo.

^{1}H-NMR ($DMSO-D_6$) δppm:

0,74 (3H, s), 1,01 (3H, t, J = 7,0 Hz), 1,32 (3H, s), 2,01-2,39 (2H, m), 2,89-3,51 (2H, m), 3,30 (3H, s), 3,61-3,73 (1H,

m), 3,89-4,12 (5H, m), 4,19-4,77 (4H, m), 6,67 (1H, d, J = 7,0 Hz), 6,71-6,90 (2H, m), 7,37 (1H, d, J = 9,0 Hz), 7,50-7,54 (2H, m), 7,66-7,76 (2H, m), 8,20 (1H, d, J = 8,0 Hz), 7,87-8,13 (2H, m), 8,60-8,96 (2H, m).

Ejemplo 24

Síntesis de 1-etil-3,3,5-trimetil-7-(3-{[2-(1-oxo-1H-isoquinolin-2-il)etil]piridin-4-ilmetilamino}propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

Polvo blanco (acetato de etilo)

Punto de fusión 119,8-121,6°C

^{1}H-NMR ($CDCl_3$) δppm:

0,86 (3H, s), 1,16 (3H, t, J = 7,0 Hz), 1,53 (3H, s), 1,87-1,96 (2H, m), 2,70-2,74 (2H, m), 2,83-2,93 (2H, m), 3,36 (3H, s), 3,36-3,74 (3H, m), 3,86 (2H, t, J = 6,0 Hz), 4.10 (2H, t, J = 6,1 Hz), 4,12-4,21 (1H, m), 6,41 (1H, d, J = 7,3 Hz), 6,58-6,62 (2H, m), 6,98 (1H, d, J = 7,3 Hz), 7,08-7,17 (3H, m), 7,47-7,52 (2H, m), 7,66 (1H, td, J = 7,5 y 1,7 Hz), 8,27 (2H, dd, J = 4,4 y 1,6 Hz), 8,59 (1H, dt, J = 8,1 y 0,7 Hz).

Ejemplo 25

Síntesis de 2-nitro-N-[2-(7-oxo-7H-furo[2,3-c]piridin-6-il)etil]-N-[3-(1,3,3,5-tetrametil-2,4-dioxo-2,3,4,5-tetra-hidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil]benceno-sulfonamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 21, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,85 (3H, s), 1,53 (3H, s), 2,03-2,15 (2H, m), 3,39 (3H, s), 3,42 (3H, s), 3,59 (2H, t, J = 7,4 Hz), 3,73 (2H, t, J = 6,9 Hz), 3,94 (2H, t, J = 5,8 Hz), 4,29 (2H, t, J = 6,7 Hz), 6,45 (1H, d, J = 7,0 Hz), 6,64 (1H, d, J = 2,0 Hz), 6,69-6,75 (2H, m), 7,12 (1H, d, J = 8,8 Hz), 7,19 (1H, d, J = 7,0 Hz), 7,56-7,66 (3H, m), 7,73 (1H, d, J = 1,9 Hz), 7,98-8,02 (1H, m).

Ejemplo 26

Síntesis de 1,3,3,5-tetrametil-7-{3-[2-(7-oxo-7H-furo[2,3-c]piridin-6-il)etilamino]propoxi}-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 18, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,86 (3H, s), 1,53 (3H, s), 1,90-2,02 (2H, m), 2,87 (2H, t, J = 6,7 Hz), 3,07 (2H, t, J = 6,2 Hz), 3,39 (3H, s), 3,41 (3H, s), 4,03 (2H, t, J = 6,1 Hz), 4,20 (2H, t, J = 6,5 Hz), 6,45 (1H, d, J = 7,0 Hz), 6,65 (1H, d, J = 2,0 Hz), 6,72 (1H, d, J = 2,7 Hz), 6,78 (1H, dd, J = 2,7 y 8,9 Hz), 7,12 (1H, d, J = 8,9 Hz), 7,17 (1H, d, J = 7,0 Hz), 7,74 (1H, d, J = 2,0 Hz).

Ejemplo 27

Síntesis de diclorhidrato de 1,3,3,5-tetrametil-7-(3-{[2-(7-oxo-7H-furo[2,3-c]piridin-6-il)etil]piridin-4-ilmetil-amino}propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando materiales de partida apropiados y siguiendo los procedimientos de los Ejemplos 7 y 6, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-D_6) δppm:

0,76 (3H, s), 1,33 (3H, s), 1,89-2,32 (2H, m), 2,89-3,51 (6H, m), 3,30 (3H, s), 3,33 (3H, s), 3,91-4,12 (2H, m), 4,22-4,61 (2H, m), 6,62 (1H, d, J = 6,5 Hz), 6,72-6,98 (3H, m), 7,35 (1H, d, J = 8,9 Hz), 7,56 (1H, d, J = 7,0 Hz), 8,08 (2H, br-s), 8,13 (1H, s), 8,81 (2H, br-s).

Ejemplo 28

Síntesis de N-[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil]-2-nitro-N-[2-(7-oxo-7H-furo[2,3-c]piridin-6-il)etil]benceno-sulfonamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 21, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,84 (3H, s), 1,14 (3H, t, J = 7,1 Hz), 1,52 (3H, s), 2,06-2,13 (2H, m), 3,40 (3H, s), 3,57-3,75 (5H, m), 3,94 (2H, t, J = 5,8 Hz), 4,11-4,20 (1H, m), 4,29 (2H, t, J = 6,9 Hz), 6,45 (1H, d, J = 7,0 Hz), 6,64 (1H, d, J = 2,0 Hz), 6,70-6,76 (2H, m), 7,18 (1H, d, J = 8,9 Hz), 7,20 (1H, d, J = 7,0 Hz), 7,55-7,66 (3H, m), 7,74 (1H, d, J = 2,0 Hz), 7,99-8,02 (1H, m).

Ejemplo 29

Síntesis de 1-etil-3,3,5-trimetil-7-{3-[2-(7-oxo-7H-furo-[2,3-c]piridin-6-il)etilamino]propoxi}-1,5-dihidrobenzo-[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 18, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,85 (3H, s), 1,14 (3H, t, J = 7,1 Hz), 1,52 (3H, s), 1,92-

2,01 (2H, m), 2,86 (2H, t, J = 6,8 Hz), 3,05 (2H, t, J = 6,2 Hz), 3,39 (3H, s), 3,66-3,75 (1H, m), 4,02 (2H, t, J = 6,1 Hz), 4,12-4,24 (3H, m), 6,43 (1H, d, J = 7,0 Hz), 6,64 (1H, d, J = 2,0 Hz), 6,71 (1H, d, J = 2,8 Hz), 6,78 (1H, dd, J = 9,0 y 2,8 Hz), 7,14 (1H, d, J = 7,0 Hz), 7,18 (1H, d, J = 9,0 Hz), 7,73 (1H, d, J = 2,0 Hz).

Ejemplo 30

Síntesis de 1-etil-3,3,5-trimetil-7-(3-{[2-(7-oxo-7H-furo-[2,3-c]piridin-6-il)etil]piridin-4-ilmetilamino}propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

Polvo blanco (acetato de etilo-n-hexano)

Punto de fusión 80,7-82,8°C

^{1}H-NMR ($CDCl_3$) δppm:

0,86 (3H, s), 1,15 (3H, t, J = 7,1 Hz), 1,52 (3H, s), 1,89-1,97 (2H, m), 2,73 (2H, t, J = 6,8 Hz), 2,87 (2H, t, J = 4,9 Hz), 3,40 (3H, s), 3,66-3,77 (3H, m), 3,91 (2H, t, J = 6,1 Hz), 4,09-4,22 (3H, m), 6,37 (1H, d, J = 7,0 Hz), 6,64-6,72 (3H, m), 6,99 (1H, d, J = 7,0 Hz), 7,09 (2H, d, J = 5,9 Hz), 7,19 (1H, d, J = 8,9 Hz), 7,75 (1H, d, J = 2,0 Hz), 8,33 (2H, dd, J = 4,5 y 1,5 Hz).

Ejemplo 31

Síntesis de diclorhidrato de 1-etil-3,3,5-trimetil-7-(3-{[2-(7-oxo-7H-furo-[2,3-c]piridin-6-il)etil]piridin-4-ilmetilamino}propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el

procedimiento del Ejemplo 3, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-D_6) δppm:

0,75 (3H, s), 1,01 (3H, t, J = 7,0 Hz), 1,32 (3H, s), 1,98-2,20 (2H, m), 2,92-3,40 (4H, m), 3,31 (3H, s), 3,63-3,71 (1H, m), 3,99-4,12 (4H, m), 4,22-4,66 (3H, m), 6,62 (1H, d, J = 6,7 Hz), 6,82-6,90 (3H, m), 7,39 (1H, d, J = 9,0 Hz), 7,55 (1H, d, J = 6,8 Hz), 7,89-8,19 (3H, m), 8,65-8,94 (2H, m).

Ejemplo 32

Síntesis de 2-nitro-N-[2-(1-oxo-3,4-dihidro-1H-isoquinolin-2-il)etil]-N-[3-(1,3,3,5-tetrametil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil]benceno-sulfonamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 21, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,85 (3H, s), 1,53 (3H, s), 2,10-2,20 (2H, m), 2,95 - 3,07 (2H, m), 3,39 (3H, s), 3,41 (3H, s), 3,55-3,69 (6H, m), 3,79 (2H, t, J = 6,9 Hz), 3,99 (2H, t, J = 5,9 Hz), 6,65-6,77 (2H, m), 7,11 (1H, d, J = 8,8 Hz), 7,18 (1H, d, J = 7,8 Hz), 7,30-7,49 (2H, m), 7,58-7,69 (3H, m), 7,98-8,08 (2H, m).

Ejemplo 33

Síntesis de 1,3,3,5-tetrametil-7-{3-[2-(1-oxo-3,4-dihidro-1H-isoquinolin-2-il)etilamino]propoxi}-1,5-dihidrobenzo[b]-[1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 18, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,86 (3H, s), 1,53 (3H, s), 1,92-2,02 (2H, m), 2,87-3,02 (6H, m), 3,38 (3H, s), 3,40 (3H, s), 3,62 (2H, t, J = 6,4 Hz), 3,72 (2H, t, J = 6,5 Hz), 4,06 (2H, t, J = 6,1 Hz), 6,72 (1H, d, J = 2,7 Hz), 6,79 (1H, dd, J = 2,7 y 9,0 Hz), 7,10 (1H, d, J = 8,9 Hz), 7,17 (1H, d, J = 7,4 Hz), 7,29-7,43 (2H, m), 8,05 (1H, d, J = 7,6 Hz).

Ejemplo 34

Síntesis de diclorhidrato de 1,3,3,5-tetrametil-7-(3-{[2-(1-oxo-3,4-dihidro-1H-isoquinolin-2-il)etil]piridin-4-ilmetilamino}propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando materiales de partida apropiados y siguiendo los procedimientos de los Ejemplos 7 y 6, se sintetizó el compuesto objetivo.

^{1}H-NMR ($DMSO-D_6$) δppm:

0,76 (3H, s), 1,33 (3H, s), 2,20-2,41 (2H, m), 2,98-3,08 (2H, m), 3,16-3,45 (4H, m), 3,29 (3H, s), 3,33 (3H, s), 3,53-3,71 (2H, m), 3,82-4,01 (2H, m), 4,03-4,20 (2H, m), 4,55-4,89 (2H, m), 6,81-6,97 (2H, m), 7,28-7,40 (3H, m), 7,42-7,54 (1H, m), 7,87 (1H, d, J = 7,6 Hz), 8,28 (2H, d, J = 4,9 Hz), 8,94 (2H, d, J = 5,6 Hz).

Ejemplo 35

Síntesis de N-[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil]-2-nitro-N-[2-(1-oxo-3,4-dihidro-1H-isoquinolin-2-il)etil]-bencenosulfonamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 21, se sintetizó el compuesto

objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,84 (3H, s), 1,14 (3H, t, J = 7,0 Hz), 1,52 (3H, s), 2,10-2,24 (2H, m), 3,01 (2H, t, J = 6,5 Hz), 3,39 (3H, s), 3,59-3,87 (9H, m), 3,99 (2H, t, J = 5,9 Hz), 4,08-4,23 (1H, m), 6,69 (1H, d, J = 2,9 Hz), 6,74 (1H, dd, J = 2,7 y 8,8 Hz), 7,17 (2H, d, J = 9,0 Hz), 7,29-7,48 (2H, m), 7,57-7,69 (3H, m), 8,00-8,05 (2H, m).

Ejemplo 36

Síntesis de 1-etil-3,3,5-trimetil-7-{3-[2-(1-oxo-3,4-dihidro-1H-isoquinolin-2-il)etilamino]propoxi}-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 18, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,85 (3H, s), 1,14 (3H, t, J = 7,0 Hz), 1,52 (3H, s), 1,91-2,06 (2H, m), 2,82-3,02 (6H, m), 3,38 (3H, s), 3,53-3,78 (5H, m), 4,06 (2H, t, J = 6,1 Hz), 4,09-4,25 (1H, m), 6,72 (1H, d, J = 2,7 Hz), 6,78 (1H, dd, J = 2,7 y 9,0 Hz), 7,16 (2H, d, J = 8,9 Hz), 7,28-7,48 (2H, m), 8,05 (1H, d, J = 7,6 Hz).

Ejemplo 37

Síntesis de diclorhidrato de 1-etil-3,3,5-trimetil-7-(3-{[2-(1-oxo-3,4-dihidro-1H-isoquinolin-2-il)etil]piridin-4-ilmetilamino}-propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando materiales de partida apropiados y siguiendo los procedimientos de los Ejemplos 7 y 6, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-D_6) δppm:

0,75 (3H, s), 1,01 (3H, t, J = 7,0 Hz), 1,32 (3H, s), 2,22-2,43 (2H, m), 2,98-3,10 (2H, m), 3,20-3,49 (4H, m), 3,32 (3H, s), 3,57-3,75 (3H, m), 3,90-4,08 (3H, m), 4,08-4,20 (2H, m), 4,65-4,90 (2H, m), 6,80-6,97 (2H, m), 7,28-7,45 (3H, m), 7,45-7,55 (1H, m), 7,87 (1H, d, J = 7,6 Hz), 8,38 (2H, d, J = 5,7 Hz), 8,99 (2H, d, J = 6,1 Hz).

Ejemplo 38

Síntesis de 2-nitro-N-[2-(1-oxo-1H-isoquinolin-2-il)etil]-N-[3-(1,3,3,5-tetrametil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil]bencenosulfonamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 21, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,85 (3H, s), 1,53 (3H, s), 1,99-2,15 (2H, m), 3,39 (3H, s), 3,41 (3H, s), 3,61 (2H, t, J = 6,9 Hz), 3,74 (2H, t, J = 6,8 Hz), 3,94 (2H, t, J = 5,6 Hz), 4,24 (2H, t, J = 6,7 Hz), 6,45 (1H, d, J = 7,3 Hz), 6,60-6,74 (2H, m), 7,02-7,18 (2H, m), 7,41-7,70 (6H, m), 7,88-8,00 (1H, m), 8,35 (1H, d, J = 8,3 Hz).

Ejemplo 39

Síntesis de 1,3,3,5-tetrametil-7-{3-[2-(1-oxo-1H-isoquinolin-2-il)etilamino]propoxi}-1,5-dihidrobenzo[b]-[1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 18, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,86 (3H, s), 1,53 (3H, s), 1,89-2,04 (2H, m), 2,87 (2H, t, J = 6,8 Hz), 3,07 (2H, t, J = 6,2 Hz), 3,38 (3H, s), 3,39 (3H, s), 4,03 (2H, t, J = 6,1 Hz), 4,08-4,21 (2H, m), 6,47 (1H, d, J = 7,3 Hz), 6,70 (1H, d, J = 2,7 Hz), 6,75 (1H, dd, J = 2,7 y 9,0 Hz), 7,09 (1H, d, J = 8,9 Hz), 7,13 (1H, d, J = 7,4 Hz), 7,41-7,55 (2H, m), 7,60-7,70 (1H, m), 8,41 (1H, d, J = 8,0 Hz).

Ejemplo 40

Síntesis de diclorhidrato de 1,3,3,5-tetrametil-7-(3-{[2-(1-oxo-1H-isoquinolin-2-il)etil]piridin-4-ilmetilamino}-propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando materiales de partida apropiados y siguiendo los procedimientos de los Ejemplos 7 y 6, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-D_6) δppm:

0,75 (3H, s), 1,33 (3H, s), 2,09-2,38 (2H, m), 3,01-3,56 (6H, m), 3,30 (3H, s), 3,32 (3H, s), 3,93-4,18 (2H, m), 4,30-4,54 (2H, m), 6,62-6,73 (1H, m), 6,73-6,96 (2H, m), 7,34 (1H, d, J = 8,9 Hz), 7,48-7,62 (2H, m), 7,62-7,81 (2H, m), 8,12-8,38 (3H, m), 8,76-9,05 (2H, m).

Ejemplo 41

Síntesis de tert-butil metil-(2-{(2-nitrobencenosulfonil)-[3-(1,3,3,5-tetrametil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil]amino}etil)carbamato

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 21, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,86 (3H, s), 1,46 (9H, s), 1,53 (3H, s), 2,01-2,15 (2H, m),

2,87 (3H, s), 3,39 (3H, s), 3,41 (3H, s), 3,43-3,48 (4H, m), 3,58 (2H, t, J = 6,9 Hz), 3,99 (2H, t, J = 5,5 Hz), 6,69 (1H, d, J = 2,7 Hz), 6,75 (1H, dd, J = 2,7 y 8,9 Hz), 7,12 (1H, d, J = 9,1 Hz), 7,57-7,72 (3H, m), 7,98-8,08 (1H, m).

Ejemplo 42

Síntesis de tert-butil metil-{2-[3-(1,3,3,5-tetrametil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)propilamino]etil}carbamato

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 18, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,87 (3H, s), 1,46 (9H, s), 1,53 (3H, s), 1,91-2,04 (2H, m), 2,80 (2H, t, J = 6,5 Hz), 2,84 (2H, t, J = 7,0 Hz), 2,88 (3H, s), 3,35 (2H, t, J = 6,5 Hz), 3,39 (3H, s), 3,41 (3H, s), 4,06 (2H, t, J = 6,2 Hz), 6,73 (1H, d, J = 2,7 Hz), 6,81 (1H, dd, J = 2,7 y 9,0 Hz), 7,13 (1H, d, J = 9,0 Hz).

Ejemplo 43

Síntesis de tert-butil metil-(2-{piridin-4-ilmetil-[3-(1,3,3,5-tetrametil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil]amino}etil)carbamato

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,87 (3H, s), 1,44 (9H, br), 1,53 (3H, s), 1,90-2,02 (2H, m), 2,63 (2H, t, J = 6,9 Hz), 2,67 (2H, t, J = 6,9 Hz), 2,79 (3H, br), 3,33 (2H, br), 3,40 (3H, s), 3,41 (3H, s), 3,65 (2H, s), 4,00 (2H, t, J = 6,1 Hz), 6,66 (1H, d, J = 2,7 Hz), 6,75 (1H,

dd, J = 2,7 y 8,9 Hz), 7,13 (1H, d, J = 8,9 Hz), 7,25 (2H, d, J = 6,5 Hz), 8,48 (2H, d, J = 5,7 Hz).

Ejemplo 44

Síntesis de 1,3,3,5-tetrametil-7-{3-[(2-metilaminoetil)-piridin-4-ilmetilamino]propoxi}-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Se agregó una solución 4N de cloruro de hidrógeno-acetato de etilo (3,2 ml) a una solución de acetato de etilo (30 ml) de tert-butilmetil-(2-{piridin-4-ilmetil-[3-(1,3,3,5-tetrametil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo-[b][1,4]diazepin-7-iloxi)propil]amino}etil)carbamato (1,43 g, 2,5 mmoles) y se agitó a temperatura ambiente durante la noche. La mezcla de reacción se concentró bajo presión reducida. El residuo se disolvió en diclorometano, y se agregó ácido trifluoroacético (3 ml). Se realizó la agitación a temperatura ambiente durante 1 hora. La mezcla de reacción se concentró bajo presión reducida, y el residuo se disolvió en una mezcla de solventes de diclorometano-metanol. Se agregó carbonato de amonio cuaternario unido a polímeros (PL-HCO3MP) para neutralizar la mezcla. La mezcla de reacción resultante se filtró. El filtrado se concentró bajo presión reducida para obtener de este modo 1,44 g (rendimiento: cuantitativo) de 1,3,3,5-tetrametil-7-{3-[(2-metilaminoetil)piridin-4-ilmetilamino]-propoxi}-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona como un aceite marrón pálido.

^{1}H-NMR ($CDCl_3$) δppm:

0,85 (3H, s), 1,53 (3H, s), 1,92-2,06 (2H, m), 2,56 (3H, s), 2,72 (2H, t, J = 7,0 Hz), 2,89 (2H, t, J = 5,6 Hz), 3,03 (2H,

t, J = 5,6 Hz), 3,38 (3H, s), 3,39 (3H, s), 3,68 (2H, s), 4,00 (2H, t, J = 5,6 Hz), 6,67 (1H, d, J = 2,7 Hz), 6,75 (1H, dd, J = 2,7 y 8,9 Hz), 7,12 (1H, d, J = 8,9 Hz), 7,30 (2H, d, J = 5,8 Hz), 8,51 (2H, d, J = 4,6 Hz).

Ejemplo 45

Síntesis de diclorhidrato de N-metil-N-(2-{piridin-4-ilmetil-[3-(1,3,3,5-tetrametil-2,4-dioxo-2,3,4,5-tetra-hidro-1H-benzo[b][1,4]-diazepin-7-iloxi)propil]amino}-etil)benzamida

Se agregaron clorhidrato de 1-(3-dimetilaminopropil)-3-etil carbodiimida (WSC) (144 mg, 0,75 mmol) y 1-hidroxibenzotriazol (HOBt) (115 mg, 0,75 mmoles) a una solución de DMF (5 ml) de 1,3,3,5-tetrametil-7-{3-[(2-metilaminoetil)piridin-4-ilmetilamino]propoxi}-1,5-dihidro-benzo[b][1,4]diazepina-2,4-diona (227 mg, 0,5 mmoles) y ácido benzoico (92 mg, 0,75 mmoles), y se agitó a temperatura ambiente durante la noche. Se agregó agua a la mezcla de reacción, y se realizó la extracción con acetato de etilo. La capa orgánica se lavó con agua, se secó sobre sulfato de sodio anhidro y se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:metanol = 1:0→10:1). El producto purificado se concentró bajo presión reducida y se agregó una solución 4N de cloruro de hidrógeno-acetato de etilo (0,14 ml) al residuo (una solución de acetato de etilo). La materia insoluble precipitada se recogió por filtración, se lavó con acetato de etilo, y se secó para obtener de este modo 120,5 mg (rendimiento: 40%) de diclorhidrato de N-metil-N-(2-{piridin-4-ilmetil-[3-(1,3,3,5-tetrametil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo-[b][1,4]diazepin-7-iloxi)-

propil]amino}etil)benzamida como un polvo blanco.

^{1}H-NMR (DMSO-D_6) δppm:

0,76 (3H, s), 1,34 (3H, s), 2,08-2,31 (2H, m), 2,94 (3H, s), 2,99-3,38 (4H, m), 3,29 (3H, s), 3,32 (3H, s), 3,66-3,89 (2H, m), 4,00-4,15 (2H, m), 4,29-4,55 (2H, m), 6,80-6,89 (2H, m), 7,32 (1H, d, J = 8,7 Hz), 7,41 (5H, br-s), 8,02 (2H, br-s), 7,58-8,78 (2H, m).

Ejemplo 46

Síntesis de diclorhidrato de la metil-(2-{piridin-4-ilmetil-[3-(1,3,3,5-tetrametil-2,4-dioxo-2,3,4,5-tetra-hidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil]amino}-etil)amida del ácido 2,3-dihidrobenzofuran-7-carboxílico

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 45, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-D_6) δppm:

0,77 (3H, s), 1,34 (3H, s), 2,08-2,34 (2H, m), 2,76-3,33 (8H, m), 3,29 (3H, s), 3,32 (3H, s), 3,69-3,92 (2H, m), 3,95-4,18 (3H, m), 4,39-4,63 (4H, m), 6,72-6,92 (3H, m), 6,92-7,10 (1H, m), 7,19-7,37 (2H, m), 7,80-8,18 (2H, m), 8,79 (2H, br-s).

Ejemplo 47

Síntesis de 2-nitro-N-(2-piridin-3-iletil)-N-[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b]-[1,4]diazepin-7-iloxi)propil]bencenosulfonamida

Se agregó carbonato de potasio (1,89 g, 13,7 mmoles) a una solución de DMF (50 ml) de 2-nitro-N-(2-piridin-3-iletil)bencenosulfonamida (1,40 g, 4,56 mmoles) y 1-etil-7-(3-yodopropoxi)-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]-diazepina-2,4-diona (2,16 g, 5,0 mmoles), y se agitó a

temperatura ambiente durante la noche. Se agregó agua a la mezcla de reacción, y luego se realizó la extracción con acetato de etilo. La capa orgánica se lavó con agua y una solución acuosa de cloruro de sodio saturada, en ese orden, se secó sobre sulfato de magnesio anhidro, y se concentró bajo presión reducida. El residuo se purificó por medio de cromatografía en columna en gel de sílice (acetato de etilo: metanol = 1:0→10:1). El producto purificado se concentró bajo presión reducida para obtener de este modo 2,99 g (rendimiento: cuantitativo) de 2-nitro-N-(2-piridin-3-iletil)-N-[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo-[b][1,4]diazepin-7-iloxi)propil]-bencenosulfonamida como un aceite amarillo.

^{1}H-NMR ($CDCl_3$) δppm:

0,84 (3H, s), 1,15 (3H, t, J = 7,0 Hz), 1,52 (3H, s), 2,04-2,12 (2H, m), 2,88 - 2,96 (2H, m), 3,40 (3H, s), 3,55 - 3,62 (4H, m), 3,64 - 3,76 (1H, m), 4,01 (2H, t, J = 5,9 Hz), 4,08 - 4,23 (1H, m), 6,70 (1H, d, J = 2,7 Hz), 6,78 (1H, dd, J = 9,0 y 2,0 Hz), 7,17-7,22 (2H, m), 7,53 (1H, dt, J = 7,9 y 2,1 Hz), 7,59-7,70 (2H, m), 7,99-8,02 (2H, m), 8,42 (1H, d, J = 1,7 Hz), 8,46 (1H, dd, J = 4,8 y 1,7 Hz).

Ejemplo 48

Síntesis de 1-etil-7-{3-[(1H-imidazol-2-ilmetil)-(2-piridin-3-iletil)amino]propoxi}-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,85 (3H, s), 1,15 (3H, t, J = 7,0 Hz), 1,52 (3H, s), 1,91-1,99 (2H, m), 2,68-2,90 (6H, m), 3,39 (3H, s), 3,60-3,78 (1H, m), 3,78-4,02 (4H, m), 4,07-4,22 (1H, m), 6,67 (1H, d, J = 2,5 Hz), 6,76 (1H, dd, J = 2,5 y 9,0 Hz), 6,85-6,94 (2H, m), 7,12-7,28 (2H, m), 7,46 (1H, d, J = 7,8 Hz), 8,44 (1H, d, J = 4,5 Hz), 8,47 (1H, s).

Ejemplo 49

Síntesis de diclorhidrato de 1-etil-7-{3-[(3H-imidazol-4-ilmetil)-(2-piridin-3-iletil)amino]propoxi}-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando materiales de partida apropiados y siguiendo los procedimientos de los Ejemplos 7 y 6, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-D_6) δppm:

0,76 (3H, s), 1,01 (3H, t, J = 6,9 Hz), 1,32 (3H, s), 2,18-2,38 (2H, m), 3,17-3,42 (6H, m), 3,33 (3H, s), 3,58-3,72 (1H, m), 4,00-4,19 (3H, m), 4,40-4,52 (2H, m), 6,88-6,98 (2H, m), 7,42 (1H, d, J = 8,8 Hz), 7,73 (1H, dd, J = 5,3 y 7,5 Hz), 7,87 (1H, s), 8,21 (1H, d, J = 7,5 Hz), 8,67 (1H, d, J = 5,3 Hz), 8,78 (1H, s), 8,91 (1H, s).

Ejemplo 50

Síntesis de diclorhidrato de 1,3,3,5-tetrametil-7-{3-[(2-metilbenzil)-(2-piridin-3-iletil)amino]propoxi}-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando materiales de partida apropiados y siguiendo los procedimientos de los Ejemplos 7 y 6, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-D_6) δppm:

0,76 (3H, s), 1,33 (3H, s), 2,20-2,42 (2H, m), 2,50 (3H, s),

3,08-3,40 (2H, m), 3,30 (3H, s), 3,33 (3H, s), 3,49-3,62 (4H, m), 4,08-4,21 (2H, m), 4,37-4,61 (2H, m), 6,82-6,96 (2H, m), 7,17-7,41 (4H, m), 7,78 (1H, d, J = 7,3 Hz), 7,99 (1H, dd, J = 5,7 y 7,6 Hz), 8,49 (1H, d, J = 8,0 Hz), 8,82 (1H, d, J = 5,3 Hz), 8,94 (1H, s).

Ejemplo 51

Síntesis de triclorhidrato de 1,3,3,5-tetrametil-7-{3-[(2-piridin-3-iletil)-(quinolin-4-ilmetil)amino]propoxi}-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando materiales de partida apropiados y siguiendo los procedimientos de los Ejemplos 7 y 6, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-D_6) δppm:

0,74 (3H, s), 1,32 (3H, s), 2,13-2,45 (2H, m), 3,14-3,78 (6H, m), 3,29 (3H, s), 3,31 (3H, s), 3,98-4,17 (4H, m), 6,73-6,89 (2H, m), 7,33 (1H, d, J = 8,8 Hz), 7,90 (1H, t, J = 7,7Hz), 7,98-8,12 (2H, m), 8,37 (1H, d, J = 8,4 Hz), 8,53 (1H, d, J = 8,2 Hz), 8,38-8,69 (2H, m), 8,83 (1H, d, J = 5,6 Hz), 8,95 (1H, s), 9,22 (1H, d, J = 4,9 Hz).

Ejemplo 52

Síntesis de triclorhidrato de 1,3,3,5-tetrametil-7-{3-[(2-metilpiridin-4-ilmetil)(2-piridin-3-iletil)amino]propoxi}-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando materiales de partida apropiados y siguiendo los procedimientos de los Ejemplos 7 y 6, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-D_6) δppm:

0,76 (3H, s), 1,33 (3H, s), 2,10-2,37(2H, m), 2,69 (3H, s), 3,00-3,98 (6H, m), 3,30 (3H, s), 3,33 (3H, s), 3,98-4,22 (2H,

m), 4,41-4,78 (2H, m), 6,82-6,95 (3H, m), 7,37 (1H, d, J = 8,6 Hz), 7,88-8,26 (3H, m), 8,68-8,82 (2H, m), 8,85 (1H, s).

Ejemplo 53

Síntesis de triclorhidrato de 7-{3-[(3,5-dichloropiridin-4-ilmetil)-(2-piridin-3-iletil)amino]propoxi}-1-etil-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando materiales de partida apropiados y siguiendo los procedimientos de los Ejemplos 7 y 6, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-D_6) δppm:

0,76 (3H, s), 1,02 (3H, t, J = 7,0 Hz), 1,33 (3H, s), 2,09-2,44 (2H, m), 2,98-3,60 (6H, m), 3,33 (3H, s), 3,60-3,77 (1H, m), 3,98-4,18 (3H, m), 4,20-4,62 (2H, m), 6,80-7,00 (2H, m), 7,41 (1H, d, J = 8,7 Hz), 7,97-8,10 (1H, m), 8,49-8,78 (3H, m), 8,84 (1H, d, J = 5,4 Hz), 8,96 (1H, s).

Ejemplo 54

Síntesis de triclorhidrato de 1-etil-3,3,5-trimetil-7-{3-[(3-metilpiridin-4-ilmetil)-(2-piridin-3-iletil)amino]-propoxi}-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando materiales de partida apropiados y siguiendo los procedimientos de los Ejemplos 7 y 6, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-D_6) δppm:

0,75 (3H, s), 1,01 (3H, t, J = 6,9 Hz), 1,32 (3H, s), 2,11-2,42 (2H, m), 2,56 (3H, s), 3,08-3,59 (8H, m), 3,59-3,77 (1H, m), 3,95-4,18 (2H, m), 4,41-4,90 (4H, m), 6,82-6,97 (2H, m), 7,41 (1H, d, J = 8,8 Hz), 8,03 (1H, dd, J = 5,7 y 7,8 Hz), 8,30-8,69 (1H, m), 8,56 (1H, d, J = 8,1 Hz), 8,72-8,88 (3H, m), 8,96 (1H, s).

Ejemplo 55

Síntesis de triclorhidrato de 1-etil-3,3,5-trimetil-7-{3-[(2-piridin-3-iletil)piridin-3-ilmetilamino]propoxi}-1,5-dihidrobenzo[b]-[1,4]diazepina-2,4-diona

Usando materiales de partida apropiados y siguiendo los procedimientos de los Ejemplos 7 y 6, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-D_6) δppm:

0,76 (3H, s), 1,01 (3H, t, J = 6,9 Hz), 1,32 (3H, s), 2,27-2,41 (2H, m), 3,20-3,36 (2H, m), 3,33 (3H, s), 3,38-3,57 (4H, m), 3,67-3,76 (1H, m), 4,00-4,18 (3H, m), 4,52-4,75 (2H, m), 6,87-6,97 (2H, m), 7,42 (1H, d, J = 8,8 Hz), 7,83 (1H, dd, J = 5,3 y 7,9 Hz), 7,99 (1H, dd, J = 5,7 y 8,0 Hz), 8,51 (1H, d, J = 8,1 Hz), 8,65 (1H, d, J = 7,9 Hz), 8,78-8,87 (2H, m), 8,95 (1H, s), 9,13 (1H, s).

Ejemplo 56

Síntesis de diclorhidrato de 1-etil-3,3,5-trimetil-7-(3-{[2-(1-oxo-1H-isoquinolin-2-il)etil]piridin-3-ilmetil-amino}proposi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando materiales de partida apropiados y siguiendo los procedimientos de los Ejemplos 7 y 6, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-D_6) δppm:

0,75 (3H, s), 1,01 (3H, t, J = 7,0 Hz), 1,32 (3H, s), 2,19-2,40 (2H, m), 3,20-3,57 (4H, m), 3,32 (3H, s), 3,61-3,72 (1H, m), 3,99-4,10 (3H, m), 4,35-4,85 (4H, m), 6,70 (1H, d, J = 7,4 Hz), 6,81-6,97 (2H, m), 7,39 (1H, d, J = 9,0 Hz), 7,50-7,57 (2H, m), 7,66-7,92 (3H, m), 8,22 (1H, d, J = 8,0 Hz), 8,50-8,71 (1H, m), 8,78-8,90 (1H, m), 9,02-9,18 (1H, m).

Ejemplo 57

Síntesis de 1-etil-3,3,5-trimetil-7-(3-{[2-(1-oxo-1H-isoquinolin-2-il)etil]thiazol-2-ilmetil-amino}propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,84 (s, 3H), 1,15 (t, J = 7,1 Hz, 3H), 1,53 (s, 3H), 1,88-2,00 (m, 2H), 2,82 (t, J = 6,3 Hz, 2H), 3,01 (t, J = 6,3 Hz, 2H), 3,36 (s, 3H), 3,61-3,74 (m, 1H), 3,88 (t, J = 6,1 Hz, 2H), 4,07 (s, 2H), 4,08-4,23 (m, 3H), 6,42 (d, J = 7,3 Hz, 1H), 6,60-6,68 (m, 2H), 7,06 (d, J = 7,3 Hz, 1H), 7,12-7,15 (m, 2H), 7,48-7,49 (m, 2H), 7,64 (d, J = 7,4 Hz, 1H), 7,67 (d, J = 3,3 Hz, 1H), 8,39 (d, J = 7,4 Hz, 1H).

Ejemplo 58

Síntesis de 1-etil-7-(3-{(3-fluorobenzil)-[2-(1-oxo-1H-isoquinolin-2-il)etil]amino}propoxi)-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,85 (s, 3H), 1,15 (t, J = 7,0 Hz, 3H), 1,53 (s, 3H), 1,80-1,96 (m, 2H), 2,70 (t, J = 6,4 Hz, 2H), 2,70 (t, J = 6,4 Hz, 2H), 3,35 (s, 3H), 3,67 (s, 2H), 3,66-3,76 (m, 1H), 3,83 (t, J = 6,0 Hz, 2H), 4,08 (t, J = 6,0 Hz, 2H), 4,00-4,21 (m, 1H), 6,40 (d, J = 7,4 Hz, 1H), 6,55-6,61 (m, 2H), 6,80-6,95 (m, 1H), 6,88-7,00 (m, 3H), 7,05-7,18 (m, 2H), 8,41-8,50 (m, 2H),

7,64 (t, J = 8,0 Hz, 1H), 8,39 (d, J = 8,0 Hz, 1H).

Ejemplo 59

Síntesis de 1-etil-7-(3-{(3-metoxibenzil)-[2-(1-oxo-1H-isoquinolin-2-il)etil]amino}propoxi)-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,84 (s, 3H), 1,15 (t, J = 7,1 Hz, 3H), 1,52 (s, 3H), 1,80-1,96 (m, 2H), 2,70 (t, J = 6,8 Hz, 2H), 2,90 (t, J = 6,2 Hz, 2H), 3,36 (s, 3H), 3,65 (s, 2H), 3,68 (s, 3H), 3,65-3,72 (m, 1H), 3,84 (t, J = 6,2 Hz, 2H), 4,06 (t, J = 6,2 Hz, 2H), 4,10-4,20 (m, 1H), 6,38 (d, J = 7,3 Hz, 1H), 6,55-6,60 (m, 2H), 6,67-6,73 (m, 1H), 6,79-6,81 (m, 2H), 6,95-7,30 (m, 3H), 7,39-7,50 (m, 2H), 7,60-7,67 (m, 1H), 8,40 (d, J = 1,2 Hz, 1H).

Ejemplo 60

Síntesis de 1-etil-3,3,5-trimetil-7-(3-{[2-(1-oxo-1H-isoquinolin-2-il)etil]tiogen-2-ilmetilamino}propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,85 (s, 3H), 1,14 (t, J = 7,1 Hz, 3H), 1,52 (s, 3H), 1,80-1,96 (m, 2H), 2,69 (t, J = 6,8 Hz, 2H), 2,91 (t, J = 6,2 Hz, 2H), 3,35 (s, 3H), 3,65-3,78 (m, 1H), 3,82 (t, J = 6,2 Hz, 2H), 3,89 (s, 2H), 4,07 (t, J = 6,2 Hz, 2H), 4,10-4,25 (m,

1H), 6,40 (d, J = 7,3 Hz, 1H), 6,38-6,49 (m, 2H), 6,87-6,89 (m, 2H), 7,02-7,28 (m, 3H), 7,42-7,50 (m, 2H), 7,60-7,64 (m, 1H), 8,40 (d, J = 1,2 Hz, 1H).

Ejemplo 61

Síntesis de 7-(3-{bis-[2-(1-oxo-1H-isoquinolin-2-il)etil]-amino}propoxi)-1-etil-3,3,5-trimetil-1,5-dihidrobenzo[b]-[1,4]-diazepina-2,4-diona

Se agregó (1-oxo-1H-isoquinolin-2-il)acetaldehído (207 mg, 1,1 mmoles) a una solución de 1,2-dicloroetano (4 ml) de 7-(3-aminopropoxi)-1-etil-3,3,5-trimetil-1,5-dihidro-benzo[b][1,4]diazepina-2,4-diona (329 mg, 1,0 mmol) y triacetoxihidroborato de sodio (381 mg, 1,8 mmoles), y se agitó a temperatura ambiente durante la noche. Se agregó agua a la mezcla de reacción y se realizó la extracción con acetato de etilo. La capa orgánica se lavó con agua y una solución acuosa de cloruro de sodio saturada, en ese orden, se secó sobre sulfato de magnesio anhidro y se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (diclorometano:metanol = 20:1). El producto purificado se concentró bajo presión reducida para obtener de este modo 7-(3-{bis-[2-(1-oxo-1H-isoquinolin-2-il)etil]amino}-propoxi)-1-etil-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]-diazepina-2,4-diona como un polvo amarillo pálido.

^{1}H-NMR ($CDCl_3$) δppm:

0,84 (s, 3H), 1,14 (t, J = 7,1 Hz, 3H), 1,52 (s, 3H), 1,74-1,82 (m, 2H), 2,75 (t, J = 7,3 Hz, 2H), 2,94 (t, J = 6,2 Hz, 4H), 3,34 (s, 3H), 3,62-3,75 (m, 3H), 4,02 (t, J = 6,2 Hz, 4H), 4,12-4,23 (m, 1H), 6,16 (d, J = 7,3 Hz, 2H), 6,50 (dd, J

= 8,9 y 2,7 Hz, 1H), 6,56 (d, J = 2,7 Hz, 1H), 6,91 (d, J = 7,3 Hz, 2H), 7,09 (d, J = 8,9 Hz, 1H), 7,39-7,62 (m, 4H), 7,59-7,68 (m, 2H), 8,41 (d, J = 7,9 Hz, 2H).

Ejemplo 62

Síntesis de 1-etil-7-(3-{[2-(7-metoxi-2-oxo-3,4-dihidro-2H-quinolin-1-il)etil]piridin-4-ilmetilamino}propoxi)-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,84 (s, 3H), 1,14 (t, J = 7,1 Hz, 3H), 1,51 (s, 3H), 1,90-2,00 (m, 4H), 2,58 (t, J = 6,8 Hz, 2H), 2,68 (t, J = 6,8 Hz, 2H), 3,38 (s, 3H), 3,61 (s, 2H), 3,62-3,72 (m, 1H), 3,95-4,00 (m, 4H), 4,08-4,22 (m, 1H), 6,44 (d, J = 7,3 Hz, 1H), 6,68 (d, J = 2,7 Hz, 1H), 6,75 (dd, J = 9,0 y 2,7 Hz, 1H), 6,95 (d, J = 7,3 Hz, 1H), 7,17 (d, J = 9,0 Hz, 1H), 7,25-7,27 (m, 2H), 7,45-7,52 (m, 2H), 7,60-7,70 (m, 1H), 8,40 (d, J = 7,9 Hz, 1H), 8,48 (d, J = 1,5 Hz, 2H).

Ejemplo 63

Síntesis de 1-etil-3,3,5-trimetil-7-(3-{[2-(2-oxo-2H-quinolin-1-il)etil]piridin-4-ilmetilamino}propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,87 (s, 3H), 1,17 (t, J = 7,0 Hz, 3H), 1,54 (s, 3H), 1,92-2,04 (m, 2H), 2,80-2,86 (m, 4H), 3,41 (s, 3H), 3,76 (s, 2H),

3,68-3,78 (m, 1H), 4,01 (t, J = 6,0 Hz, 2H), 4,10-4,22 (m, 1H), 4,44 (t, J = 7,0 Hz, 2H), 6,66-6,70 (m, 2H), 6,76 (dd, J = 8,9 y 2,9 Hz, 1H), 7,09 (d, J = 8,3 Hz, 1H), 7,07-7,11 (m, 4H), 7,38-7,46 (m, 1H), 7,57 (d, J = 6,5 Hz, 1H), 7,68 (d, J = 9,5 Hz, 1H), 8,44 (d, J = 5,9 Hz, 2H).

Ejemplo 64

Síntesis de 1-etil-7-{3-[(2-(6-metoxi-2-oxo-2H-quinolin-1-il)etil)piridin-4-ilmetilamino]propoxi}-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,85 (s, 3H), 1,15 (t, J = 7,1 Hz, 3H), 1,52 (s, 3H), 1,89-2,00 (m, 2H), 2,81 (m, 4H), 3,39 (s, 3H), 3,74 (s, 2H), 3,65-3,77 (m, 1H), 3,85 (s, 3H), 3,99 (t, J = 6,0 Hz, 2H), 4,11-4,28 (m, 1H), 4,40 (t, J = 6,9 Hz, 2H), 6,64-6,70 (m, 2H), 6,74 (dd, J = 8,9 y 2,9 Hz, 1H), 6,96-7,04 (m, 3H), 7,16-7,20 (m, 3H), 7,60 (d, J = 9,5 Hz, 1H), 8,43 (d, J = 5,9 Hz, 2H).

Ejemplo 65

Síntesis de 1-etil-7-(3-{[2-(6-metoxiquinolin-2-iloxi)-etil]piridin-4-ilmetilamino}propoxi)-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,82 (s, 3H), 1,12 (t, J = 7,1 Hz, 3H), 1,51 (s, 3H), 1,90-2,05 (m, 2H), 2,77 (t, J = 7,0 Hz, 2H), 2,97 (t, J = 7,0 Hz,

2H), 3,34 (s, 3H), 4,58-5,59 (m, 1H), 3,77 (s, 2H), 3,90 (s, 3H), 3,95-4,04 (m, 2H), 4,04-4,19 (m, 1H), 4,50-4,63 (m, 2H), 6,59-6,66 (m, 2H), 6,83 (d, J = 8,8 Hz, 1H), 7,04 (d, J = 2,8 Hz, 1H), 7,11 (d, J = 8,9 Hz, 1H), 7,24-7,27 (m, 3H), 7,67 (d, J = 9,1 Hz, 1H), 7,89 (d, J = 8,8 Hz, 1H), 8,42 (d, J = 5,9 Hz, 2H).

Ejemplo 66

Síntesis de 1-etil-3,3,5-trimetil-7-(3-{[2-(2-oxo-3,4-dihidro-2H-quinolin-1-il)etil]piridin-4-ilmetilamino}-propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,85 (s, 3H), 1,14 (t, J = 7,1 Hz, 3H), 1,52 (s, 3H), 1,89-1,97 (m, 2H), 2,53-2,64 (m, 2H), 2,68-2,77 (m, 4H), 2,86 (t, J = 8,0 Hz, 2H), 3,38 (s, 3H), 3,69 (s, 2H), 3,60-3,78 (m, 1H), 3,93-4,20 (m, 5H), 6,67 (d, J = 2,7 Hz, 1H), 6,72-6,84 (m, 2H), 6,79 (t, J = 8,2 Hz, 1H), 7,10-7,22 (m, 5H), 8,44 (d, J = 6,0 Hz, 2H).

Ejemplo 67

Síntesis de 1-etil-3,3,5-trimetil-7-{3-[(2-(4-oxo-4H-tieno[3,2-c]piridin-5-il)etil)piridin-4-ilmetilamino]-propoxi}-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,88 (s, 3H), 1,17 (t, J = 7,1 Hz, 3H), 1,54 (s, 3H), 1,89-

1,97 (m, 2H), 2,74 (t, J = 6,8 Hz, 2H), 2,83-2,95 (m, 2H), 3,39 (s, 3H), 3,69 (s, 2H), 3,68-3,74 (m, 1H), 3,89 (t, J = 6,0 Hz, 2H), 4,12 (t, J = 6,0 Hz, 2H), 4,11-4,21 (m, 1H), 6,53-6,70 (m, 3H), 7,05 (d, J = 7,2 Hz, 1H), 7,10 (d, J = 5,9 Hz, 2H), 7,20 (d, J = 8,9 Hz, 1H), 7,32 (d, J = 5,3 Hz, 1H), 7,63 (d, J = 5,3 Hz, 1H), 8,32 (d, J = 5,9 Hz, 2H).

Ejemplo 68

Síntesis de 1-etil-3,3,5-trimetil-7-(3-{[2-(7-oxo-7H-tieno[2,3-c]piridin-6-il)etil]piridin-4-ilmetilamino}-propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,88 (s, 3H), 1,17 (t, J = 7,1 Hz, 3H), 1,54 (s, 3H), 1,89-1,97 (m, 2H), 2,74 (t, J = 6,8 Hz, 2H), 2,83-2,95 (m, 2H), 3,39 (s, 3H), 3,68 (s, 2H), 3,68-3,74 (m, 1H), 3,90 (t, J = 6,0 Hz, 2H), 4,05-4,21 (m, 3H), 6,56 (d, J = 7,1 Hz, 1H), 6,60-6,70 (m, 2H), 7,03-7,10 (m, 3H), 7,16-7,23 (m, 2H), 7,73 (d, J = 5,2 Hz, 1H), 8,31 (d, J = 5,9 Hz, 2H).

Ejemplo 69

Síntesis de 1-etil-7-(3-{[2-(8-metoxi-2-oxo-2H-quinolin-1-il)etil]piridin-4-ilmetilamino}propoxi)-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,87 (s, 3H), 1,17 (t, J = 7,1 Hz, 3H), 1,54 (s, 3H), 1,89-

1,97 (m, 2H), 2,78 (t, J = 6,7 Hz, 2H), 2,88 (t, J = 7,2 Hz, 2H), 3,41 (s, 3H), 3,75 (s, 3H), 3,68-3,79 (m, 3H), 3,98 (t, J = 6,2 Hz, 2H), 4,05-4,21 (m, 1H), 4,80 (t, J = 7,7 Hz, 2H), 6,65-6,78 (m, 3H), 6,96-7,03 (m, 1H), 7,11-7,23 (m, 5H), 7,62 (d, J = 9,4 Hz, 1H), 8,41 (d, J = 6,0 Hz, 2H).

Ejemplo 70

Síntesis de 1-etil-7-(3-{[2-(8-metoxiquinolin-2-iloxi)-etil]piridin-4-ilmetilamino}propoxi)-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,83 (s, 3H), 1,14 (t, J = 7,1 Hz, 3H), 1,51 (s, 3H), 1,89-2,03 (m, 2H), 2,76 (t, J = 6,7 Hz, 2H), 3,00 (t, J = 7,2 Hz, 2H), 3,35 (s, 3H), 3,59-3,67 (m, 1H), 3,80 (s, 2H), 3,99 (s, 3H), 3,95-4,07 (m, 2H), 4,10-4,19 (m, 1H), 4,70 (t, J = 7,0 Hz, 2H), 6,58-6,70 (m, 2H), 6,89 (d, J = 8,8 Hz, 1H), 6,95-7,05 (m, 1H), 7,11 (d, J = 8,9 Hz, 1H), 7,23-7,38 (m, 4H), 7,97 (d, J = 8,8 Hz, 1H), 8,41 (d, J = 6,0 Hz, 2H).

Ejemplo 71

Síntesis de 1-etil-3,3,5-trimetil-7-(3-{[2-(4-oxo-4H-furo[3,2-c]piridin-5-il)etil]piridin-4-ilmetilamino}-propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,87 (s, 3H), 1,16 (t, J = 7,1 Hz, 3H), 1,53 (s, 3H), 1,82-

1,95 (m, 2H), 2,72 (t, J = 6,8 Hz, 2H), 2,76-2,89 (m, 2H), 3,38 (s, 3H), 3,68 (s, 2H), 3,63-3,78 (m, 1H), 3,87 (t, J = 6,0 Hz, 2H), 4,10 (t, J = 6,0 Hz, 2H), 4,11-4,20 (m, 1H), 6,43 (d, J = 7,4 Hz, 1H), 6,60 (d, J = 2,8 Hz, 1H), 6,67 (dd, J = 9,0 y 2,8 Hz, 1H), 6,96 (d, J = 2,9 Hz, 1H), 7,05-7,11 (m, 3H), 7,19 (d, J = 9,0 Hz, 1H), 7,50 (d, J = 2,9 Hz, 1H), 8,35 (d, J = 6,0 Hz, 2H).

Ejemplo 72

Síntesis de 1-etil-7-(3-{[2-(6-metoxi-2-oxo-3,4-dihidro-2H-quinolin-1-il)etil]piridin-4-ilmetilamino}propoxi)-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,87 (s, 3H), 1,16 (t, J = 7,1 Hz, 3H), 1,53 (s, 3H), 1,86-1,96 (m, 2H), 1,87-2,01 (m, 2H), 2,55-2,61 (m, 2H), 2,70-2,85 (m, 6H), 3,40 (s, 3H), 3,62-3,78 (m, 1H), 3,71 (s, 2H), 3,75 (s, 3H), 3,98-4,21 (m, 3H), 6,48 (d, J = 2,3 Hz, 1H), 6,49 (dd, J = 8,2 y 2,3 Hz, 1H), 6,69 (d, J = 2,7 Hz, 1H), 6,76 (dd, J = 8,0 y 2,7 Hz , 1H), 7,06 (d, J = 8,2 Hz, 1H), 7,18-7,23 (m, 3H), 8,44 (d, J = 6,0 Hz, 2H).

Ejemplo 73

Síntesis de 1-etil-7-(3-{[2-(7-metoxi-2-oxo-3,4-dihidro-2H-quinolin-1-il)etil]piridin-4-ilmetilamino}propoxi)-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,85 (s, 3H), 1,14 (t, J = 7,1 Hz, 3H), 1,52 (s, 3H), 1,84-1,96 (m, 2H), 2,55-2,63 (m, 2H), 2,62-2,71 (m, 4H), 2,75-2,84 (m, 2H), 3,38 (s, 3H), 3,68 (s, 2H), 3,77 (s, 3H), 3,64-3,76 (m, 1H), 3,96-4,23 (m, 5H), 6,61-6,75 (m, 5H), 7,16-7,22 (m, 3H), 8,45 (d, J = 6,0 Hz, 2H).

Ejemplo 74

Síntesis de N-(3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil)-N-(2-(7-metil-1-oxo-1H-isoquinolin-2-il)etil)-2-nitrobenceno-sulfonamida

Se agregaron N,N,N',N'-tetra metil azodicarboxamida (TMAD) (118 mg) y tri-n-butil fosfina (0,17 ml) a una solución de THF (5 ml) de N-[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)-propil]-2-nitrobencenosulfonamida (231 mg) y 2-(2-hidroxietil)-7-metil-2H-isoquinolin-1-ona (93 mg), y se agitó a temperatura ambiente durante la noche. Se agregó agua a la mezcla de reacción, y se realizó la extracción con diclorometano. La capa orgánica se secó sobre sulfato de sodio anhidro y se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:metanol = 20:1→10:1). El producto purificado se concentró a sequedad bajo presión reducida para obtener de este modo 205 mg (rendimiento: 65%) de N-(3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil)-N-(2-(7-metil-1-oxo-1H-isoquinolin-2-il)etil)-2-nitrobencenosulfonamida como un sólido amorfo blanco.

^{1}H-NMR ($CDCl_3$) δppm:

0,84 (3H, s), 1,14 (3H, t, J = 7,1 Hz), 1,52 (3H, s), 2,04-2,19 (2H, m), 2,49 (3H, s), 3,39 (3H, s), 3,62 (2H, t, J = 6,7 Hz), 3,60-3,78 (1H, m), 3,73 (2H, t, J = 6,7 Hz), 3,94 (2H, t, J = 5,7 Hz), 4,10-4,26 (1H, m), 4,23 (2H, t, J = 6,7 Hz), 6,43 (1H, d, J = 7,3 Hz), 6,68 (1H, d, J = 2,7 Hz), 6,72 (1H, dd, J = 2,7 y 8,9 Hz), 7,08 (1H, d, J = 7,3 Hz), 7,17 (1H, d, J = 8,9 Hz), 7,39 (1H, d, J = 8,1 Hz), 7,46-7,54 (1H, m), 7,54-7,62 (3H, m), 7,93-8,03 (1H, m), 8,16 (1H, s).

Ejemplo 75

Síntesis de 1-etil-3,3,5-trimetil-7-{3-[2-(7-metil-1-oxo-1H-isoquinolin-2-il)etilamino]propoxi}-1,5-dihidrobenzo[b]-[1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 18, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,84 (3H, s), 1,14 (3H, t, J = 7,0 Hz), 1,52 (3H, s), 1,89-2,05 (2H, m), 2,48 (3H, s), 2,87 (2H, t, J = 6,7 Hz), 3,06 (2H, t, J = 6,2 Hz), 3,38 (3H, s), 3,61-3,76 (1H, m), 4,02 (2H, t, J = 6,1 Hz), 4,14 (2H, t, J = 6,2 Hz), 4,10-4,22 (1H, m), 6,44 (1H, d, J = 7,3 Hz), 6,69 (1H, d, J = 2,7 Hz), 6,75 (1H, dd, J = 2,7 y 8,9 Hz), 7,06 (1H, d, J = 7,3 Hz), 7,15 (1H, d, J = 8,9 Hz), 7,40 (1H, d, J = 8,0 Hz), 7,45-7,50 (1H, m), 8,22 (1H, s).

Ejemplo 76

Síntesis de diclorhidrato de 1-etil-3,3,5-trimetil-7-(3-{[2-(7-metil-1-oxo-1H-isoquinolin-2-il)etil]piridin-4-il-metilamino}propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-

diona

Usando materiales de partida apropiados y siguiendo los procedimientos de los Ejemplos 7 y 6, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-D_6) δppm:

0,74 (3H, s), 1,01 (3H, t, J = 6,9Hz), 1,32 (3H, s), 2,00-2,24 (2H, m), 2,44 (3H, s), 2,89-4,60 (10H, m), 3,30 (3H, s), 4,81 (2H, s), 6,62 (1H, d, J = 7,1 Hz), 6,78 (1H, d, J = 9,1 Hz), 6,85 (1H, s), 7,36 (1H, d, J = 9,1 Hz), 7,45 (1H, d, J = 7,1 Hz), 7,95-8,13 (5H, m), 8,86 (2H, d, J = 6,0 Hz).

Ejemplo 77

Síntesis de 1-etil-3,3,5-trimetil-7-{3-[(piridin-4-ilmetil) amino]propoxi}-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Se agregó 4-piridinacarbaldehído (0,64 ml, 6,8 mmoles) a una solución de metanol (10 ml) de 7-(3-aminopropoxi)-1-etil-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona (2,18 g, 6,8 mmoles), y se agitó bajo una atmósfera de nitrógeno a temperatura ambiente durante 1,5 horas. La mezcla de reacción se enfrió en un baño de agua helada, y se agregó borohidruro de sodio (257 mg, 6,8 mmoles) a 0°C. La mezcla se agitó luego a temperatura ambiente durante la noche. Se agregó agua a la mezcla de reacción, y se realizó la extracción con acetato de etilo. La capa orgánica se lavó con agua y una solución acuosa de cloruro de sodio saturada, en ese orden, se secó sobre sulfato de magnesio anhidro, y se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:metanol = 9:1→3:2). El producto purificado se concentró bajo presión reducida para obtener de este modo 2,35 g

Industria y Comercio

SUPERINTENDENCIA

OK
EGF

DELEGATURA DE PROPIEDAD INDUSTRIAL

División de Nuevas Creaciones

SOLICITUD
PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 10-117060 3/3

54. **TÍTULO** _____

_____

_____

_____

51. **CLASIFICACIÓN INTERNACIONAL** _____

71. **SOLICITANTE** _____

DOMICILIO _____

74. **APODERADO** _____

22. **BOGOTÁ, D.C.,** _____

(FORMA P-10)

(rendimiento: 84%) de 1-etil-3,3,5-trimetil-7-{3-[(piridin-4-ilmetil)amino]propoxi}-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona como un aceite amarillo pálido.

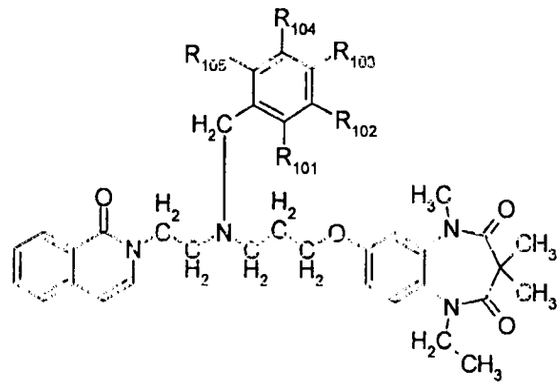
^{1}H-NMR ($CDCl_3$) δppm:

0,86 (s, 3H), 1,12 (t, J = 7,1 Hz, 3H), 1,52 (s, 3H), 1,97-2,09 (m, 2H), 2,84 (t, J = 6,8 Hz, 2H), 3,39 (s, 3H), 3,62-3,78 (m, 1H), 3,85 (s, 2H), 4,09 (t, J = 6,1 Hz, 2H), 4,06-4,24 (m, 1H), 6,71 (d, J = 2,8 Hz, 1H), 6,80 (dd, J = 9,0 y 2,8 Hz, 1H), 7,20 (d, J = 9,0 Hz, 1H), 7,26-7,27 (m, 2H), 8,53 (d, J = 6,0 Hz, 2H).

Ejemplos 78 a 456

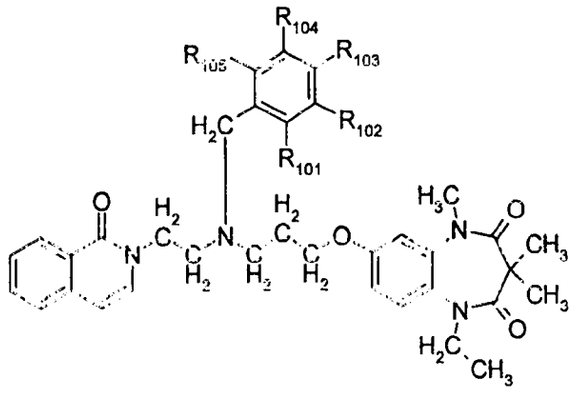
Usando materiales de partida apropiados y siguiendo los procedimientos de los Ejemplos arriba mencionados, se prepararon los compuestos mostrados en las Tablas 1 a 33.

Tabla 1



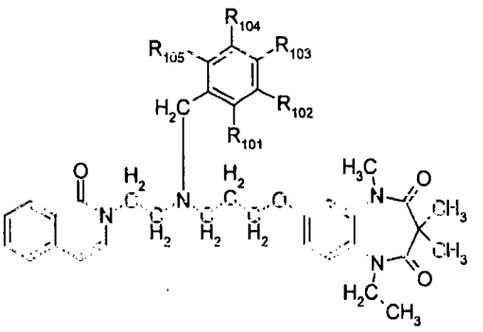
Ejemplo	R101	R102	R103	R104	R105	MS(M+1)
78	-H	-H	-H	-H	-H	581
79	-H	-H	$-CO_2H$	-H	-H	625
80	-H	-H	$-C_6H_5$	-H	-H	657
81	-H	-H	$-OCH_3$	-H	-H	611
82	-H	-H	-OH	-H	-H	597
83	-H	-H	$-CH_3$	-H	-H	595
84	-H	-H	$-CH(CH_3)_2$	-H	-H	623
85	-H	-H	-CN	-H	-H	606
86	-H	-H	$-OC_2H_5$	-H	-H	625
87	-H	-OH	-H	-H	-H	597
88	-H	-H	$-NHCOCH_3$	-H	-H	638
89	-Cl	-H	-H	-H	-H	615
90	-H	-Cl	-H	-H	-H	615
91	-H	-H	-Cl	-H	-H	615
92	-F	-H	-H	-H	-H	599
93	-CN	-H	-H	-H	-H	606
94	$-CF_3$	-H	-H	-H	-H	649
95	-H	$-CF_3$	-H	-H	-H	649
96	-H	$-CH_3$	-H	-H	-H	595
97	-H	-H	$-CF_3$	-H	-H	649
98	-H	-H	$-C_2H_5$	-H	-H	609
99	-H	-H	-F	-H	-H	599
100	$-CH_3$	-H	-H	-H	-H	595
101	-H	-CN	-H	-H	-H	606
102	$-OCH_3$	-H	-H	-H	-H	611
103	-H	-H	$-SCH_3$	-H	-H	627
104	-H	-H	$-OCH(CH_3)_2$	-H	-H	639

Tabla 2



Ejemplo	R101	R102	R103	R104	R105	MS(M+1)
105	-H	$-C_6H_5$	-H	-H	-H	657
106	-H	-H	-2-TIENILO	-H	-H	663
107	-OH	-H	-H	-H	-H	597
108	-H	-H	-3-PIRIDILO	-H	-H	658
109	-H	-3-PIRIDILO	-H	-H	-H	658
110	-3-PIRIDILO	-H	-H	-H	-H	658
111	-2-TIENILO	-H	-H	-H	-H	663
112	-H	-H	-2-FURILO	-H	-H	647

Tabla 3



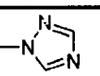
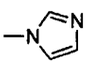
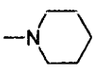
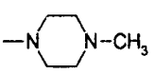
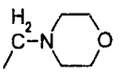
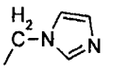
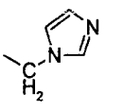
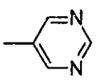
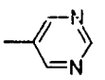
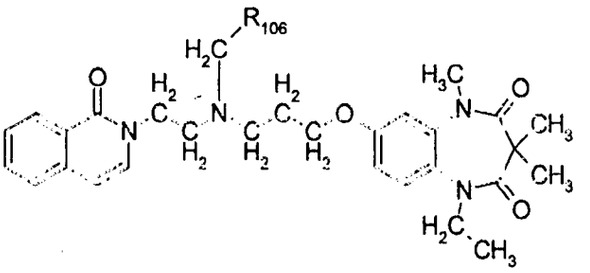
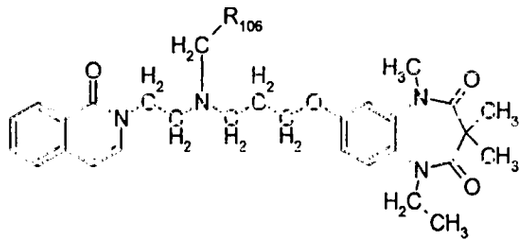
Ejemplo	R101	R102	R103	R104	R105	MS(M+1)
113	-H	-H		-H	-H	648
114	-H	-H		-H	-H	647
115	-H	-H		-H	-H	664
116		-H	-H	-H	-H	679
117	-H		-H	-H	-H	647
118	-H	-H		-H	-H	680
119	-H	-H		-H	-H	661
120	-H		-H	-H	-H	661
121	-H	-H		-H	-H	659
122	-H		-H	-H	-H	659

Tabla 4



Ejemplo	R106	MS(M+1)
123	-2-IMIDAZOLILO	571
124	-2-PIRIDILO	582
125	-3-TIENILO	587
126	-3-INDOLILO	620
127	-2-BENZOFURANILO	621
128	-4-QUINOLILO	632
129	-2-QUINOLILO	632
130	-CH=CHC$_6$H$_5$(trans)	607
131	-4-IMIDAZOLILO	571
132	-2-FURILO	571
133	-2-NAFTILO	631
134	-5-BENZOFURANILO	621
135	-3-QUINOLILO	632
136	-CH$_2$C$_6$H$_5$	595
137	-8-QUINOLILO	632
138	-CH(CH$_3$)C$_6$H$_5$	609
139	-(CH$_2$)$_2$C$_6$H$_5$	609

Tabla 5



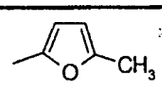
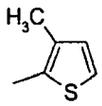
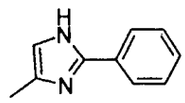
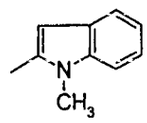
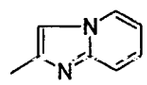
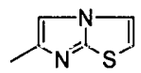
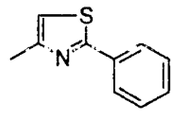
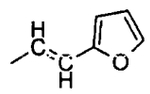
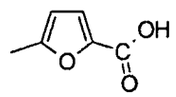
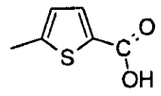
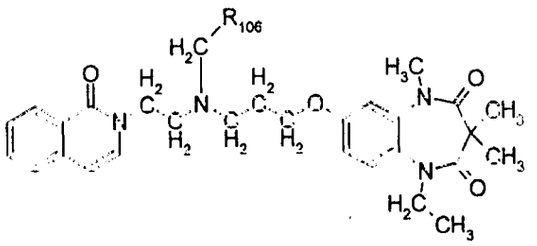
Ejemplo	R106	MS(M+1)
140		585
141		601
142		647
143		634
144		621
145		627
146		664
147		597
148		615
149		631

Tabla 6



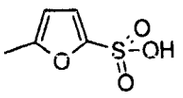
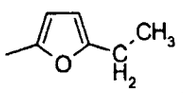
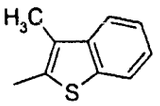
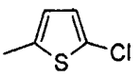
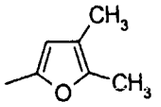
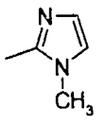
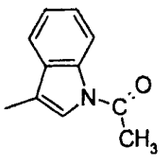
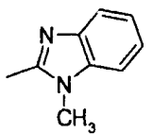
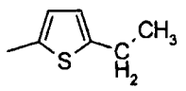
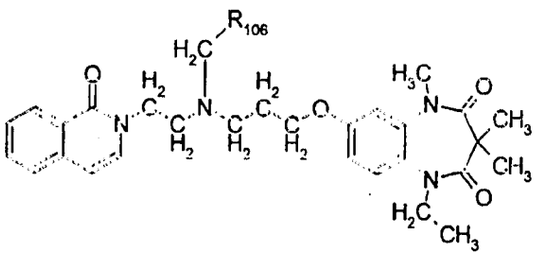
Ejemplo	R106	MS(M+1)
150		651
151		599
152		651
153		621
154		599
155		585
156		662
157		635
158		615

Tabla 7



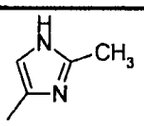
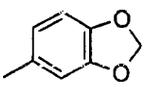
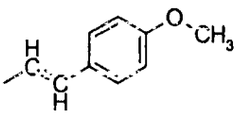
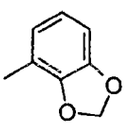
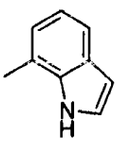
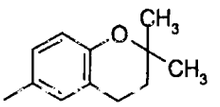
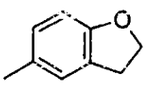
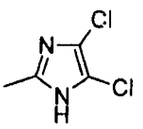
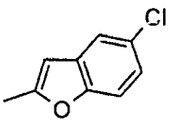
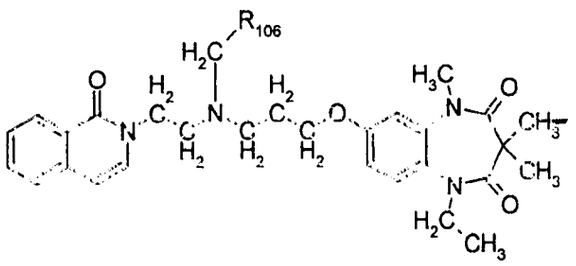
Ejemplo	R106	MS(M+1)
159		585
160		625
161		637
162		625
163		620
164		665
165		623
166		639
167		655

Tabla 8



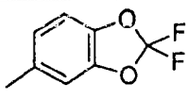
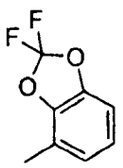
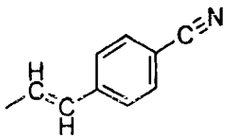
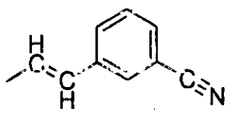
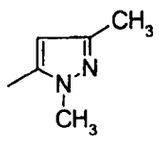
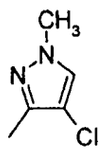
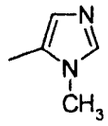
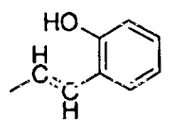
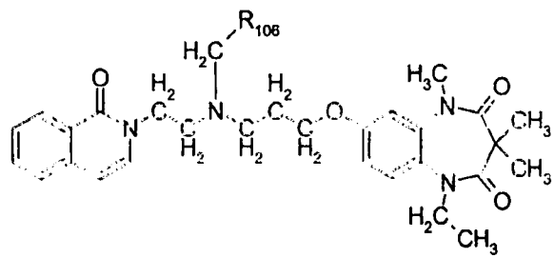
Ejemplo	R106	MS(M+1)
168		661
169		661
170		632
171		632
172		599
173		619
174		585
175		623

Tabla 9



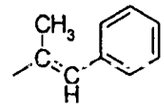
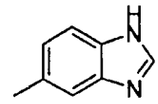
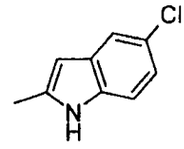
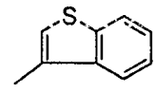
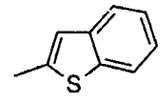
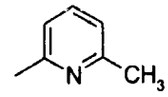
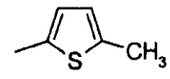
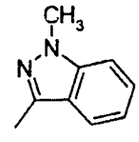
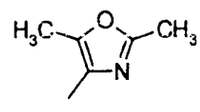
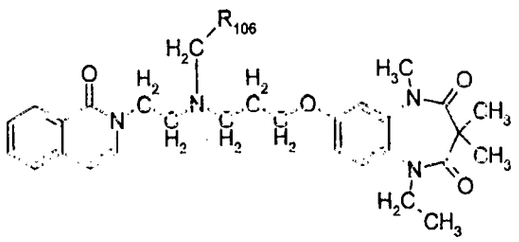
Ejemplo	R106	MS(M+1)
176		621
177		621
178		654
179		637
180		637
181		596
182		601
183		635
184		600

Tabla 10



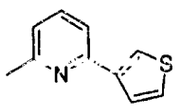
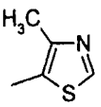
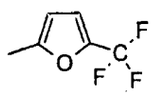
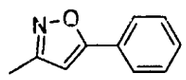
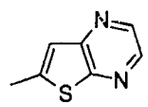
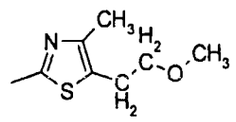
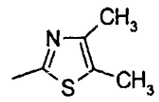
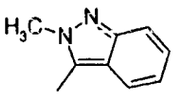
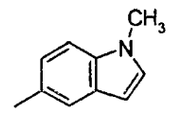
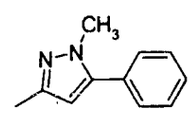
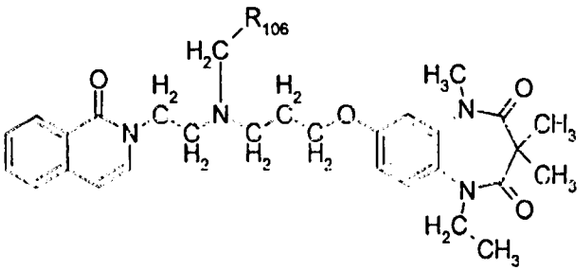
Ejemplo	R106	MS(M+1)
185		664
186		602
187		639
188		648
189		639
190		660
191		616
192		635
193		634
194		661

Tabla 11



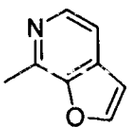
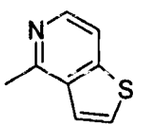
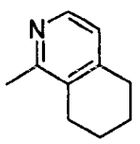
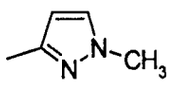
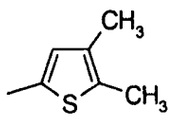
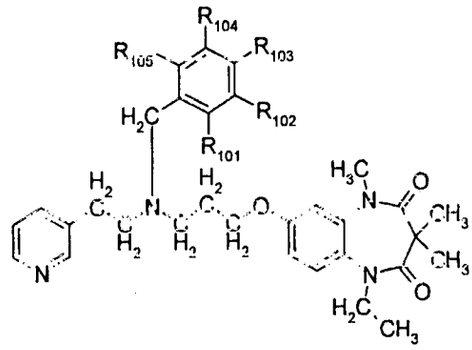
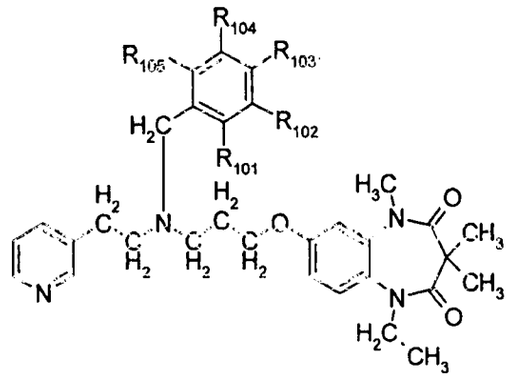
Ejemplo	R106	MS(M+1)
195		622
196		638
197		636
198		585
199		615

Tabla 12



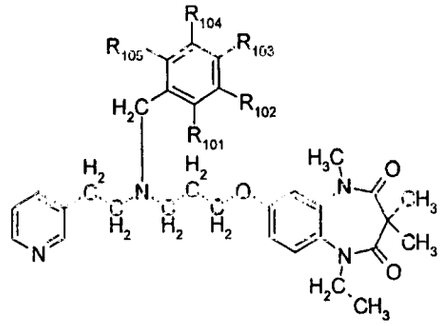
Ejemplo	R101	R102	R103	R104	R105	MS(M+1)
200	-H	-H	-H	-H	-H	515
201	-H	-H	$-CO_2H$	-H	-H	559
202	-H	-H	$-C_6H_5$	-H	-H	591
203	-H	-H	$-OCH_3$	-H	-H	545
204	-H	-H	-H	$-OCH_3$	-H	545
205	-H	-H	-OH	-H	-H	531
206	-H	-H	$-CH_3$	-H	-H	529
207	-H	-H	$-CH(CH_3)_2$	-H	-H	557
208	-H	-H	-CN	-H	-H	540
209	-H	-H	$-OC_2H_5$	-H	-H	559
210	-H	-H	-H	-OH	-H	531
211	-H	-H	-OH	-OH	-H	547
212	-H	-H	-H	-H	$-CO_2H$	559
213	-H	-H	$-NHCOCH_3$	-H	-H	572
214	-H	-H	$-O(CH_2)_3N(CH_3)_2$	-H	-H	616
215	-H	-H	-H	-H	-Cl	549
216	-H	-H	-H	-Cl	-H	549
217	-H	-H	-Cl	-H	-H	549
218	-H	-H	-H	-H	-F	533
219	-H	-H	-H	-H	-CN	540
220	-H	-H	-H	-H	$-CF_3$	583
221	-H	-H	-H	$-CF_3$	-H	583
222	-H	-H	-H	$-CH_3$	-H	529
223	-H	-H	$-CF_3$	-H	-H	583
224	-H	-H	$-C_2H_5$	-H	-H	543
225	-H	-H	-F	-H	-H	533
226	-H	-H	-H	-H	$-CH_3$	529
227	-H	-H	$-CO_2CH_3$	-H	-H	573

Tabla 13



Ejemplo	R101	R102	R103	R104	R105	MS(M+1)
228	-H	-H	-H	-F	-H	533
229	-H	-H	-H	-CN	-H	540
230	-H	-H	-H	-H	$-OCH_3$	545
231	-H	-H	$-SCH_3$	-H	-H	561
232	-H	-H	-H	-H	$-CO_2CH_3$	573
233	-H	-H	$-SO_2CH_3$	-H	-H	593
234	-H	-H	$-OCH(CH_3)_2$	-H	-H	573
235	-H	-H	-H	$-C_6H_5$	-H	591
236	-H	-H	-H	-H	$-NHSO_2CH_3$	608
237	-H	-H	-1-IMIDAZOLILO	-H	-H	581
238	-H	-H	-2-TIENILO	-H	-H	597
239	-H	-H	-H	-H	-OH	531
240	-H	-H	-3-PIRIDILO	-H	-H	592
241	-H	-H	-H	-3-PIRIDILO	-H	592
242	-H	-H	-H	-H	-3-PIRIDILO	592
243	-H	-H	-H	-H	-2-TIENILO	597
244	-H	-H	-2-FURILO	-H	-H	581

Tabla 14



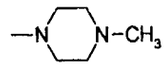
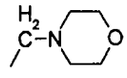
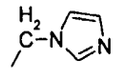
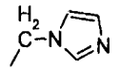
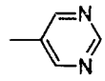
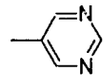
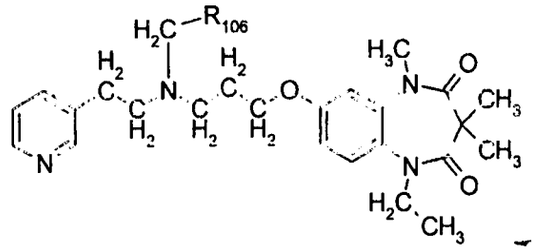
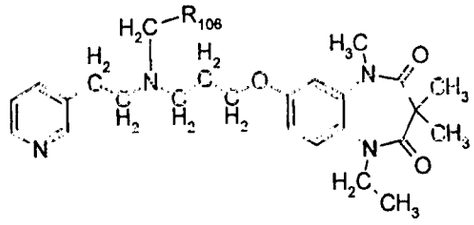
Ejemplo	R101	R102	R103	R104	R105	MS(M+1)
245	-H	-H		-H	-H	582
246	-H	-H	-H	-H		613
247	-H	-H	-H		-H	581
248	-H	-H		-H	-H	614
249	-H	-H		-H	-H	595
250	-H	-H	-H		-H	595
251	-H	-H		-H	-H	593
252	-H	-H	-H		-H	593
253	-H	-H		-H	-H	598

Tabla 15



Ejemplo	R106	MS(M+1)
254	-3-FURILO	505
255	-2-PIRIDILO	516
256	-2-TIENILO	521
257	-3-TIENILO	521
258	-2-BENZOFURANILO	555
259	-4-QUINOLILO	566
260	-2-QUINOLILO	566
261	-CH=CHC$_6$H$_5$(trans)	541
262	-2-TIAZOLILO	522
263	-1-NAFTILO	565
264	-2-FURILO	505
265	-2-NAFTILO	565
266	-5-BENZOFURANILO	555
267	-3-QUINOLILO	566
268	-CH$_2$C$_6$H$_5$	529
269	-8-QUINOLILO	566
270	-CH(CH$_3$)C$_6$H$_5$	543
271	-(CH$_2$)$_2$C$_6$H$_5$	543
272	-6-QUINOLILO	566
273	-2-BENZTIAZOLILO	572

Tabla 16



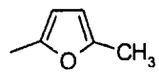
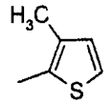
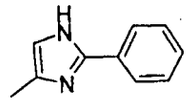
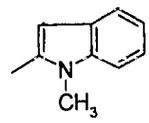
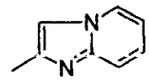
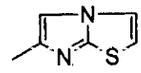
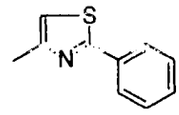
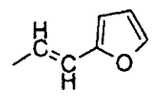
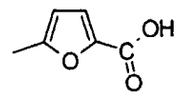
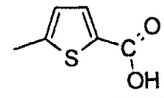
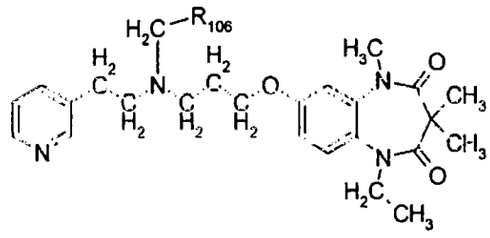
Ejemplo	R106	MS(M+1)
274		519
275		535
276		581
277		568
278		555
279		561
280		598
281		531
282		549
283		565

Tabla 17



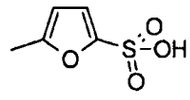
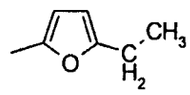
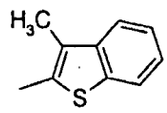
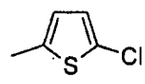
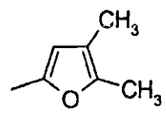
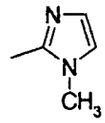
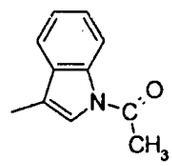
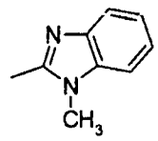
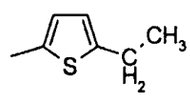
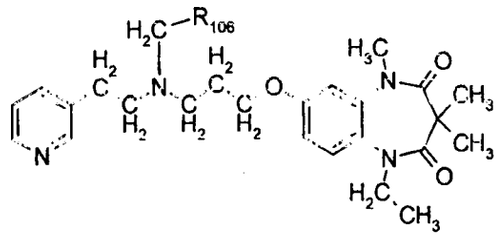
Ejemplo	R106	MS(M+1)
284		585
285		533
286		585
287		555
288		533
289		519
290		596
291		569
292		549

Tabla 18



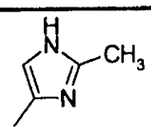
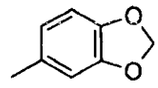
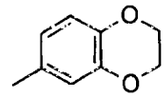
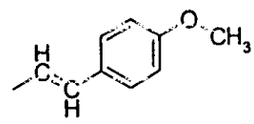
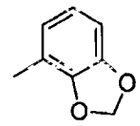
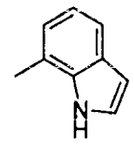
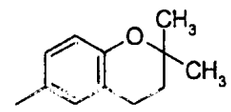
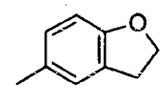
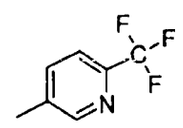
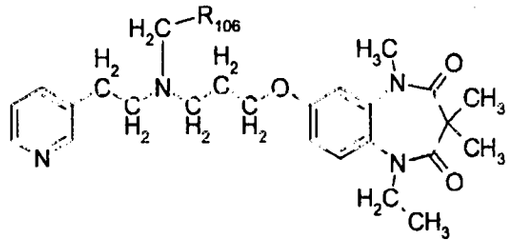
Ejemplo	R106	MS(M+1)
293		519
294		559
295		573
296		571
297		559
298		554
299		599
300		557
301		584

Tabla 19



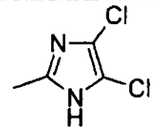
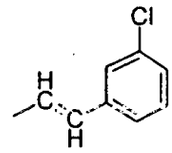
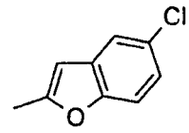
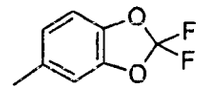
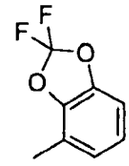
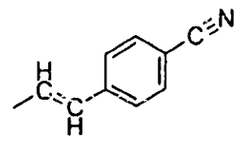
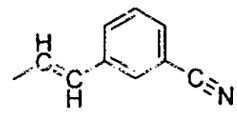
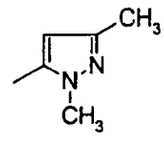
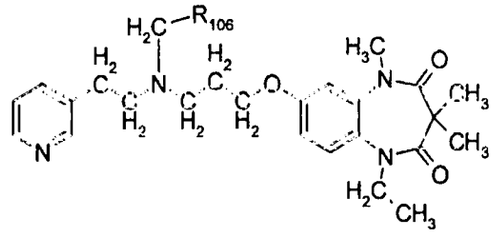
Ejemplo	R106	MS(M+1)
302		573
303		575
304		589
305		595
306		595
307		566
308		566
309		533

Tabla 20



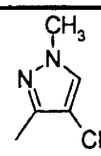
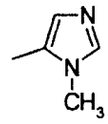
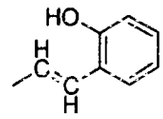
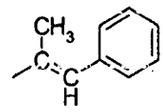
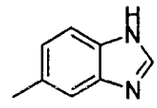
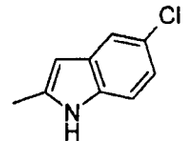
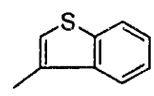
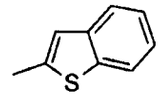
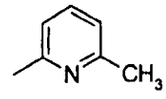
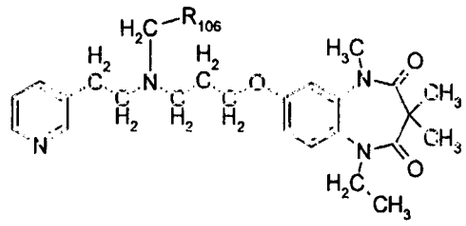
Ejemplo	R106	MS(M+1)
310		553
311		519
312		557
313		555
314		555
315		588
316		571
317		571
318		530

Tabla 21



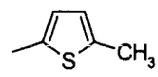
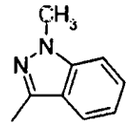
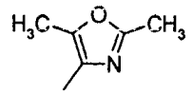
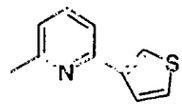
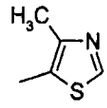
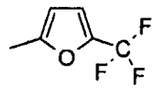
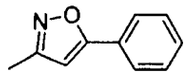
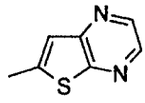
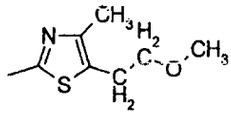
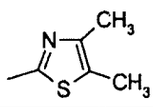
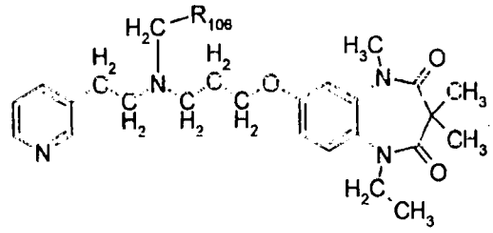
Ejemplo	R106	MS(M+1)
319		535
320		569
321		534
322		598
323		536
324		573
325		582
326		573
327		594
328		550

Tabla 22



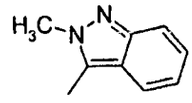
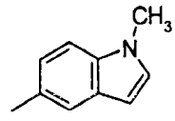
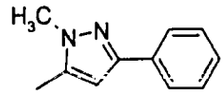
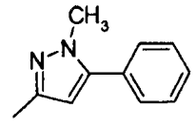
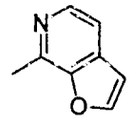
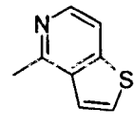
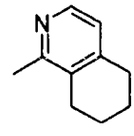
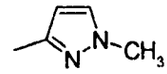
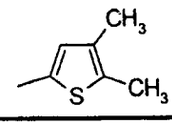
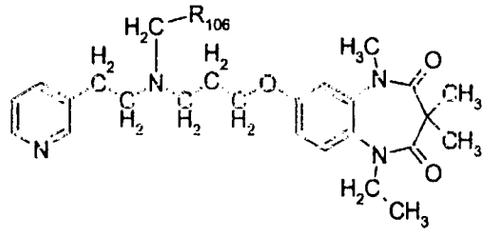
Ejemplo	R106	MS(M+1)
329		569
330		568
331		595
332		595
333		556
334		572
335		570
336		519
337		549

Tabla 23



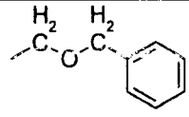
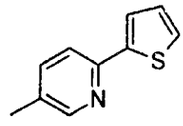
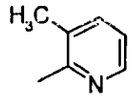
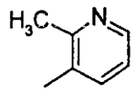
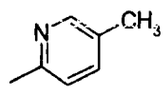
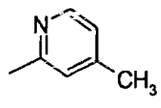
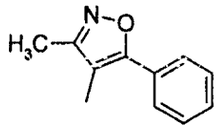
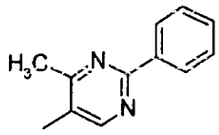
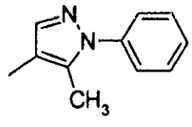
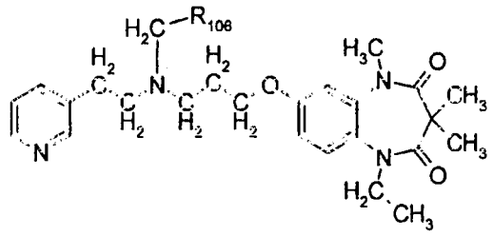
Ejemplo	R106	MS(M+1)
338		559
339		598
340		530
341		530
342		530
343		530
344		596
345		607
346		595

Tabla 24



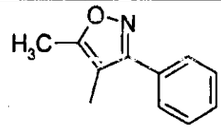
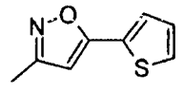
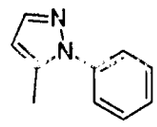
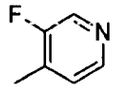
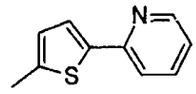
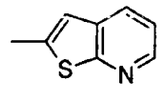
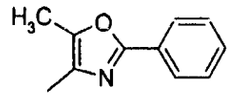
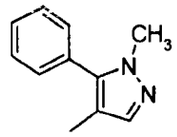
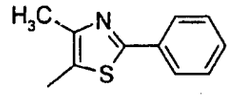
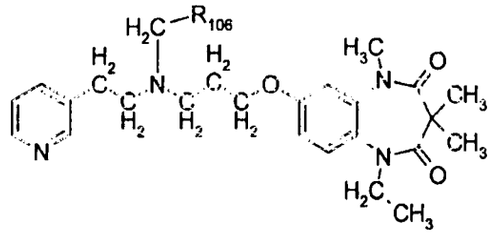
Ejemplo	R106	MS(M+1)
347		596
348		588
349		581
350		534
351		598
352		572
353		596
354		595
355		612

Tabla 25



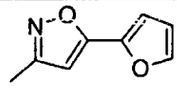
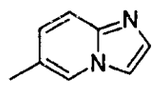
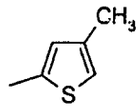
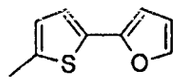
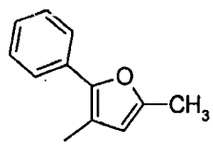
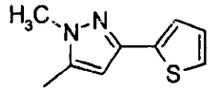
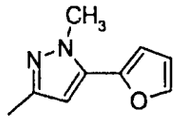
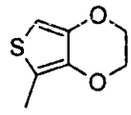
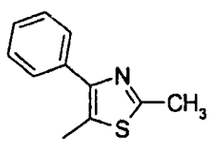
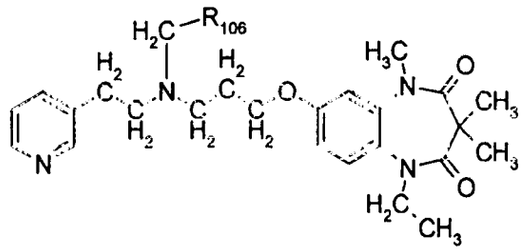
Ejemplo	R106	MS(M+1)
356		572
357		555
358		535
359		587
360		595
361		601
362		585
363		579
364		612

Tabla 26



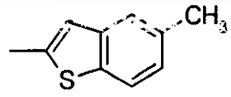
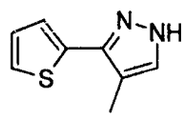
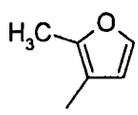
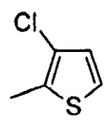
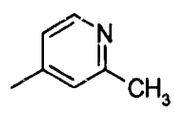
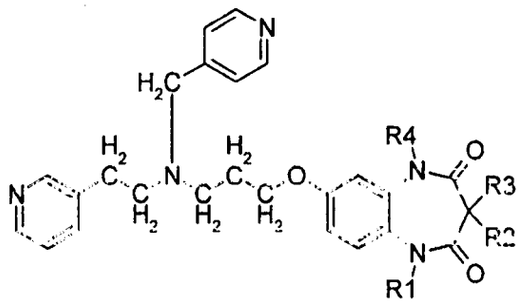
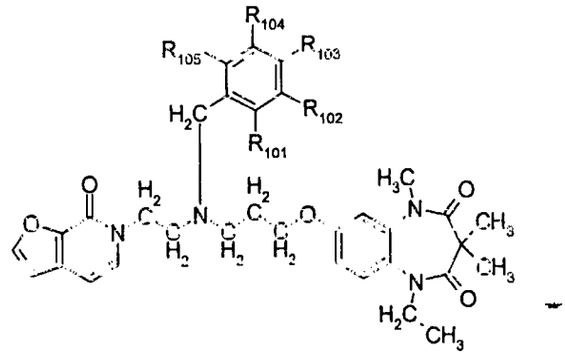
Ejemplo	R106	MS(M+1)
365		585
366		587
367		519
368		555
369		530

Tabla 27



Ejemplo	R1	R2	R3	R4	MS(M+1)
370	$-CH_3$	-H	-H	$-CH_3$	474
371	-H	-H	-H	-H	446

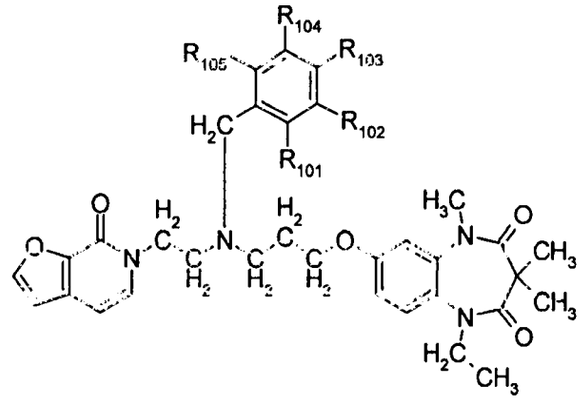
Tabla 28



Ejemplo	R101	R102	R103	R104	R105	MS(M+1)
372	-H	-H	-H	-H	-H	571
373	-H	-H	$-CO_2H$	-H	-H	615
374	-H	-H	$-C_6H_5$	-H	-H	647
375	-H	-H	$-OCH_3$	-H	-H	601
376	-H	-H	-H	$-OCH_3$	-H	601
377	-H	-H	-OH	-H	-H	587
378	-H	-H	$-CH_3$	-H	-H	585
379	-H	-H	$-CH(CH_3)_2$	-H	-H	613
380	-H	-H	-CN	-H	-H	596
381	-H	-H	$-OC_2H_5$	-H	-H	615
382	-H	-H	-H	-OH	-H	587
383	-H	-H	-OH	-OH	-H	603
384	-H	-H	-H	-H	$-CO_2H$	615
385	-H	-H	$-NHCOCH_3$	-H	-H	628
386	-H	-H	$-O(CH_2)_3N(CH_3)_2$	-H	-H	672
387	-H	-H	-H	-H	-Cl	605
388	-H	-H	-H	-Cl	-H	605
389	-H	-H	-Cl	-H	-H	605
390	-H	-H	-H	-H	-F	589
391	-H	-H	-H	-H	-CN	596
392	-H	-H	-H	-H	$-CF_3$	639
393	-H	-H	-H	$-CF_3$	-H	639
394	-H	-H	-H	$-CH_3$	-H	585
395	-H	-H	$-CF_3$	-H	-H	639
396	-H	-H	$-C_2H_5$	-H	-H	599
397	-H	-H	-F	-H	-H	589
398	-H	-H	-H	-H	$-CH_3$	585
399	-H	-H	$-CO_2CH_3$	-H	-H	629

514

Tabla 29



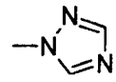
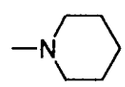
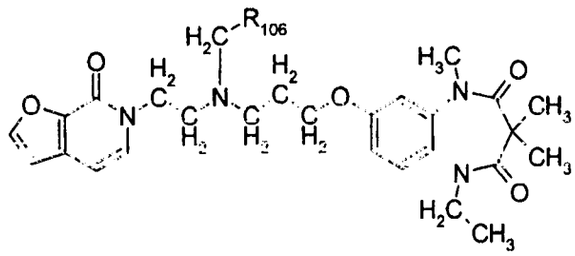
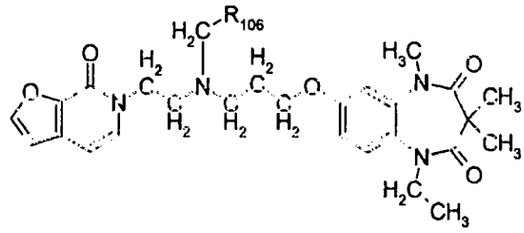
Ejemplo	R101	R102	R103	R104	R105	MS(M+1)
400	-H	-H	-H	-F	-H	589
401	-H	-H	-H	-CN	-H	596
402	-H	-H	-H	-H	$-OCH_3$	601
403	-H	-H	$-SCH_3$	-H	-H	617
404	-H	-H	-H	-H	$-CO_2CH_3$	629
405	-H	-H	$-SO_2CH_3$	-H	-H	649
406	-H	-H	$-OCH(CH_3)_2$	-H	-H	629
407	-H	-H	-H	$-C_6H_5$	-H	647
408	-H	-H	-H	-H	$-NHSO_2CH_3$	664
409	-H	-H	-1-IMIDAZOLILO	-H	-H	637
410	-H	-H	-2-TIENILO	-H	-H	653
411	-H	-H		-H	-H	638
412	-H	-H		-H	-H	654

Tabla 30



Ejemplo	R106	MS(M+1)
413	-3-FURILO	561
414	-2-IMIDAZOLILO	561
415	-2-PIRIDILO	572
416	-3-PIRIDILO	572
417	-2-TIENILO	577
418	-3-TIENILO	577
419	-2-BENZOFURANILO	611
420	-4-QUINOLILO	622
421	-2-QUINOLILO	622
422	-CH=CHC$_6$H$_5$(trans)	597
423	-2-TIAZOLILO	578
424	-4-IMIDAZOLILO	561
425	-1-NAFTILO	621
426	-2-FURILO	561
427	-2-NAFTILO	621
428	-5-BENZOFURANILO	611

Tabla 31



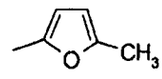
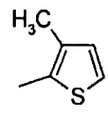
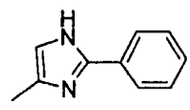
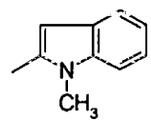
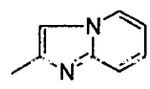
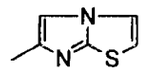
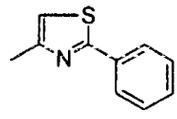
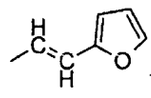
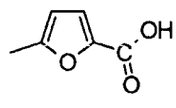
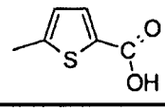
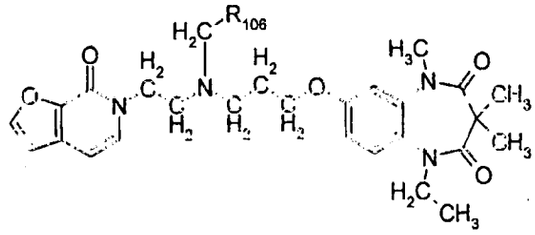
Ejemplo	R106	MS(M+1)
429		575
430		591
431		637
432		624
433		611
434		617
435		654
436		587
437		605
438		621

Tabla 32



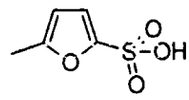
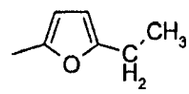
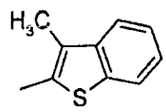
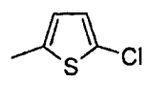
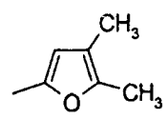
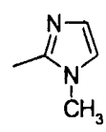
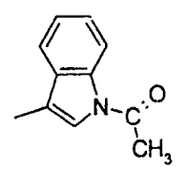
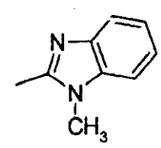
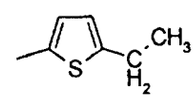
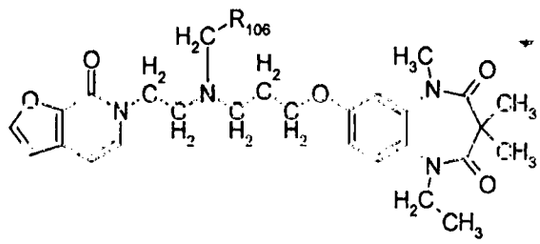
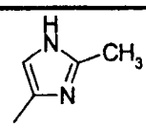
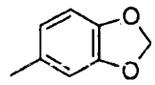
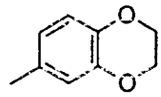
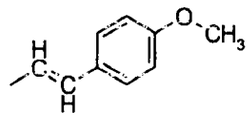
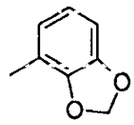
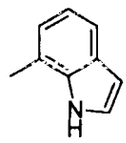
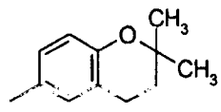
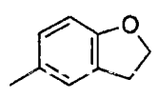
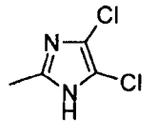
Ejemplo	R106	MS(M+1)
439		641
440		589
441		641
442		611
443		589
444		575
445		652
446		625
447		605

Tabla 33



Ejemplo	R106	MS(M+1)
448		575
449		615
450		629
451		627
452		615
453		610
454		655
455		613
456		629

Usando materiales de partida apropiados y siguiendo los procedimientos de los Ejemplos de referencia 1 a 62, se sintetizaron los siguientes compuestos objetivo.

Ejemplo de referencia 63

(1-Oxo-1H-isoquinolin-2-il)acetaldehído

^{1}H-NMR ($CDCl_3$) δppm:

4,78 (s, 2H), 6,59 (d, J = 7,3 Hz, 1H), 7.00 (d, J = 7,3 Hz, 1H), 7,52-7,59 (m, 2H), 7,68-7,73 (m, 1H), 8,44 (d, J = 8,9 Hz, 1H), 9,76 (s, 1H).

Ejemplo de referencia 64

(2-Oxo-2H-quinolin-1-il)acetaldehído

^{1}H-NMR ($CDCl_3$) δppm:

5,15 (s, 2H), 6,76 (d, J = 9,5 Hz, 1H), 7,05 (d, J = 8,5 Hz, 1H), 7,24-7,29 (m, 1H), 7,54-7,60 (m, 1H), 7,61 (dd, J= 7,7 y 1,5 Hz, 1H), 7,77 (d, J = 9,5 Hz, 1H), 9,70 (s, 1H).

Ejemplo de referencia 65

6-(2,2-Dihidroxietil)-6H-tieno[2,3-c]piridin-7-ona

1H-NMR (DMSO-d6) dppm:

3,98 (d, J = 5,3 Hz, 2H), 5,11-5,16 (m, 1H), 6,04 (d, J = 6,4 Hz, 1H), 6,66 (d, J = 7,1 Hz, 2H), 7,27 (d, J = 5,2 Hz, 1H), 7,41 (d, J = 7,1 Hz, 1H), 7,84 (d, J = 5,2 H, 1H).

Ejemplo de referencia 66

5-(2,2-Dihidroxietil)-5H-furo[3,2-c]piridin-4-ona

^{1}H-NMR (DMSO-d_6) δppm:

3,88 (d, J = 5,4 Hz, 2H), 4,95-5,03 (m, 1H), 6,08 (d, J = 6,4 Hz, 2H), 6,69 (dd, J = 7,4, 0,8 Hz, 1H), 6,94 (dd, J = 2,1 y 0,8 Hz, 1H), 7,50 (d, J = 7,4 Hz, 1H), 7,86 (d, J = 2,1 Hz, 1H).

Ejemplo de referencia 67

5-(2,2-Dihidroxietil)-5H-tieno[3,2-c]piridin-4-ona

^{1}H-NMR (DMSO-d_6) δppm:

3,90 (d, J = 6,3 Hz, 2H), 4,99-5,04 (m, 1H), 6,07 (d, J = 6,3 Hz, 2H), 6,86 (d, J = 7,2 Hz, 1H), 7,41-7,49 (m, 2H), 7,57-7,64 (m, 1H).

Ejemplo de referencia 68

2-Bromo-5-(2,2-dihidroxietil)-5H-furo[3,2-c]piridin-4-ona

^{1}H-NMR (DMSO-d_6) δppm:

3,86 (d, J = 5,4 Hz, 2H), 4,95-5,03 (m, 1H), 6,07 (d, J = 6,4 Hz, 2H), 6,69 (dd, J = 7,4 y 0,8 Hz, 1H), 7,08 (d, J = 0,8 Hz, 1H), 7,51 (d, J = 7,4 Hz, 1H).

Ejemplo de referencia 69

5-(2,2-Dihidroxietil)-2-metil-5H-furo[3,2-c]piridin-4-ona

^{1}H-NMR (DMSO-d_6) δppm:

2,36 (s, 3H), 3,86 (d, J = 5,4 Hz, 2H), 4,94-4,98 (m, 1H), 6,04 (d, J = 6,4 Hz, 2H), 6,52 (s, 1H), 6,59 (d, J = 7,4 Hz, 1H), 7,41 (d, J = 7,4 H, 1H).

Ejemplo de referencia 70

5-(2,2-Dihidroxietil)-2-etil-5H-tieno[3,2-c]piridin-4-ona

^{1}H-NMR (DMSO-d_6) δppm:

1,73 (t, J = 7,5z, 3H), 3,31 (q, J = 7,5 Hz, 2H), 4,32 (d, J = 6,8 Hz, 2H), 5,40-5,51 (m, 1H), 6,53 (d, J = 6,2 Hz, 2H), 7,22 (d, J = 7,2 Hz, 1H), 7,65 (s, 1H), 7,82 (d, J = 7,2 Hz, 1Hz).

Ejemplo de referencia 71

(7-Bromo-1-oxo-1H-isoquinolin-2-il)acetaldehído

^{1}H-NMR ($CDCl_3$) δppm:

4,77 (s, 2H), 6,52 (d, J = 7,4 Hz, 1H), 6,97 (d, J = 7,4 Hz, 1H), 7,43 (d, J = 8,5 Hz, 1H), 7,76 (dd, J = 8,5 y 2,1 Hz,

1H), 8,55 (d, J = 2,1 Hz, 1H), 9,73 (s, 1H).

Ejemplo de referencia 72

(1-Oxo-5,6,7,8-tetrahidro-1H-isoquinolin-2-il)acetaldehído

^{1}H-NMR ($CDCl_3$) δppm:

1,73-1,94 (4H, m), 2,64-2,81 (2H, m), 2,81-2,98 (2H, m), 5,04-5,17 (2H, m), 6,72-6,84 (1H, m), 7,08 (1H, d, J = 6,5 Hz), 8,31 (1H, d, J = 6,5 Hz).

Ejemplo de referencia 73

2-Butilpiridina-3-carbaldehído

^{1}H-NMR ($CDCl_3$) δppm:

0,96 (3H, t, J = 7,4 Hz), 1,41-1,48 (2H, m), 1,67-1,76 (2H, m), 3,21 (2H, t, J = 8,0 Hz), 7 31 (1H, dd, J = 7,8 y 4 8 Hz), 8,13 (1H, dd, J = 7,8 y 1,9 Hz), 8,72 (1H, dd, J = 4,8 y 1,9 Hz), 10,36 (1H, s).

Ejemplo de referencia 74

Ácido 1-(etoxicarbonil)ciclobutanocarboxílico

^{1}H-NMR ($CDCl_3$) δppm:

1,27 (t, J = 7,1 Hz, 3H), 2,00-2,07 (m, 2H), 2,60 (t, J = 8,2 Hz, 4H), 4,25 (q, J = 7,1 Hz, 1H).

Ejemplo de referencia 75

Etil 1-(2-aminofenilcarbamoil)ciclobutanocarboxilato

^{1}H-NMR ($CDCl_3$) δppm:

1,34 (t, J = 7,1 Hz, 3H), 1,97-2,08 (m, 2H), 2,60-2,68 (m, 2H), 2,71-2,82 (m, 2H), 3,80 (br, 2H), 4,29 (q, J = 7,1 Hz, 2H), 6,77-6,83 (m, 2H), 7,02-7,08 (m, 1H), 7,95 (br, 1H).

Ejemplo de referencia 76

Espiro[benzo[b][1,4]diazepina-3,1'-ciclobutano]-2,4(1H,5H)-diona

^{1}H-NMR (DMSO-d_6) δppm:

1,59-1,70 (m, 2H), 3,29-3,44 (m, 4H), 7,07-7,14 (m, 4H), 10,4 (br, 2H).

Ejemplo de referencia 77

1,5-Dimetilespiro[benzo[b][1,4]diazepina-3,1'-ciclobutano]-2,4-(1H,5H)diona

^{1}H-NMR ($CDCl_3$) δppm:

1,26-1,68 (m, 4H), 2,83-2,89 (m, 2H), 3,44 (s, 6H), 7,23-7,30 (m, 4H).

Ejemplo de referencia 78

1,5-Dimetil-7-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-espiro[benzo[b][1,4]diazepina-3,1'-ciclobutano]-2,4(1H,5H)-diona

^{1}H-NMR ($CDCl_3$) δppm:

1,26 (s, 6H), 1,60 (s, 6H), 1,62-1,69 (m, 4H), 2,06-2,89 (m, 2H), 3,45 (s, 3H), 3,48 (s, 3H), 7,26-7,28 (m, 1H), 7,65-7,70 (m, 2H).

Ejemplo de referencia 79

7-Hidroxi-1,5-dimetilespiro[benzo[b][1,4]diazepina-3,1'-ciclobutano]-2,4(1H,5H)-diona

^{1}H-NMR ($CDCl_3$) δppm:

1,58-1,62 (m, 4H), 2,83-2,88 (m, 2H), 3,41 (s, 3H), 3,44 (s, 3H), 7,14 (d, J = 8,7 Hz, 1H), 7,36 (dd, J = 8,7 y 2,1 Hz, 1H), 7,41 (d, J = 2,1 Hz, 1H).

Ejemplo 457

Síntesis de sulfato de 1-etil-3,3,5-trimetil-7-{3-[(piridin-4-il-metil)amino]propoxi}-1,5-dihidrobenzo[b]-[1,4]-diazepina-2,4-diona

Se agregó ácido sulfúrico (13 µl) a una solución de acetato de etilo (5 ml) de 1-etil-3,3,5-trimetil-7-{3-

[(piridin-4-ilmetil)amino]propoxi}-1,5-dihidrobenzo[b]-[1,4]-diazepina-2,4-diona (100 mg, 0,24 mmoles) y se agitó a temperatura ambiente durante 15 minutos. La mezcla resultante se concentró a sequedad bajo presión reducida para obtener de este modo sulfato de 1-etil-3,3,5-trimetil-7-{3-[(piridin-4-ilmetil)amino]propoxi}-1,5-dihidrobenzo-[b][1,4]diazepina-2,4-diona como un sólido amorfo blanco.

^{1}H-NMR (DMSO-d_6) δppm:

0,74 (s, 3H), 0,99 (t, J = 7,0 Hz, 3H), 1,31 (s, 3H), 2,14-2,18 (m, 2H), 3,14-3,18 (m, 2H), 3,31 (s, 3H), 3,61-3,69 (m, 1H), 4,00-4,09 (m, 1H), 4,10-4,14 (m, 2H), 4,27 (s, 2H), 6,94-6,95 (m, 2H), 7,40 (d, J = 9,0 Hz, 1H), 7,55-7,57 (m, 2H), 8,62-8,64 (m, 2H).

Ejemplo 458

Síntesis de 1,3,3,5-tetrametil-7-(3-{[2-(1-oxo-3,4-dihidro-1H-isoquinolin-2-il)etil]piridin-4-ilmetilamino}propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona tris-fosfato

Se agregó una solución acuosa de ácido fosfórico al 85% (0,34 ml) a una solución de etanol (19 ml) de 1,3,3,5-tetrametil-7-(3-{[2-(1-oxo-3,4-dihidro-1H-isoquinolin-2-il)etil]piridin-4-ilmetilamino}-propoxi)-1,5-dihidro-benzo[b][1,4]diazepina-2,4-diona (1,05 g, 1,84 mmoles), y se agitó a 50°C durante 15 minutos. La mezcla de reacción se enfrió a temperatura ambiente. La materia insoluble precipitada se recogió por filtración, se lavó con etanol y se secó para obtener de este modo 1,59 g (rendimiento: 73%) de 1,3,3,5-tetrametil-7-(3-{[2-(1-oxo-3,4-dihidro-1H-isoquinolin-2-il)etil]piridin-4-ilmetil-amino}-propoxi)-1,5-dihidro-benzo[b][1,4]diazepina-2,4-diona tris(fosfato) como

un sólido blanco.

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (3H, s), 1,32 (3H, s), 1,78-1,98 (2H, m), 2,55-2,77 (4H, m), 2,81-2,98 (2H, m), 3,28 (3H, s), 3,29 (3H, s), 3,51 (2H, t, 6,6 Hz), 3,62 (2H, m), 3,68 (s, 2 H), 3,99 (2H, t, J = 6,0 Hz), 6,75 (2H, dd, J = 2,6 y 9,0 Hz), 6,82 (2H, d, 2,6 Hz), 7,21-7,38 (5H, m), 7,41-7,51 (1H, m), 8,34 (2H, d, J = 5,8 Hz).

Ejemplo 459

Síntesis de N-[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil]-N-(2-piridin-3-iletil)isonicotinamida

Se agregó clorhidrato de N-(3-dimetilaminopropil)-N'-etil-carbodiimida (WSC) (0,16 g, 0,85 mmoles) a una solución de acetonitrilo (6 ml) de 1-etil-3,3,5-trimetil-7-[3-(2-piridin-3-iletilamino)propoxi]-1,5-dihidrobenzo[b]-[1,4]diazepina-2,4-diona (0,3 g, 0,71 mmoles), ácido isonicotínico (96 mg, 0,78 mmoles) y 1-hidroxibenzotriazol (HOBT) (0,138 g, 0,85 mmoles) y luego se agitó a temperatura ambiente durante 2 días. El solvente se concentró bajo presión reducida. Se agregaron acetato de etilo y una solución acuosa de hidrógeno carbonato de sodio a la mezcla de reacción, y se agitó durante 1 hora. Se agregó agua a la mezcla de reacción, y se realizó la extracción con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio anhidro y se concentró bajo presión reducida. El residuo así obtenido se purificó por cromatografía líquida de media presión (gel de sílice, diclorometano:metanol = 92:8). El producto purificado se concentró bajo presión reducida y se

cristalizó a partir de acetato de etilo, dietil éter y n-hexano. Los cristales precipitados se recogieron por filtración y se secaron para obtener de este modo 0,21 g (rendimiento: 56%) de N-[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo-[b][1,4]diazepin-7-iloxi)propil]-N-(2-piridin-3-iletil)-isonicotinamida como un polvo blanco. Punto de fusión 88,1 a 92,2°C

Ejemplo 460

Síntesis de 1-etil-3,3,5-trimetil-7-(3-{[2-(4-oxo-4H-tieno-[3,2-c]piridin-5-il)etil]piridin-4-ilmetilamino}-propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,88 (s, 3H), 1,17 (t, J = 7,1 Hz, 3H), 1,54 (s, 3H), 1,89-1,97 (m, 2H), 2,74 (t, J = 6,8 Hz, 2H), 2,83-2,95 (m, 2H), 3,39 (s, 3H), 3,69 (s, 2H), 3,68-3,74 (m, 1H), 3,89 (t, J = 6,0 Hz, 2H), 4,12 (t, J = 6,0 Hz, 2H), 4,11-4,21 (m, 1H), 6,53-6,70 (m, 3H), 7,05 (d, J = 7,2 Hz, 1H), 7,10 (d, J = 5,9 Hz, 2H), 7,20 (d, J = 8,9 Hz, 1H), 7,32 (d, J = 5,3 Hz, 1H), 7,63 (d, J = 5,3 Hz, 1H), 8,32 (d, J = 5,9 Hz, 2H).

Ejemplo 461

Síntesis de 1-etil-3,3,5-trimetil-7-(3-{[2-(7-oxo-7H-tieno[2,3-c]piridin-6-il)etil]piridin-4-ilmetilamino}-propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,88 (s, 3H), 1,17 (t, J = 7,1 Hz, 3H), 1,54 (s, 3H), 1,89-1,97 (m, 2H), 2,74 (t, J = 6,8 Hz, 2H), 2,83-2,95 (m, 2H), 3,39 (s, 3H), 3,68-3,74 (m, 3H), 3,90 (t, J = 6,0 Hz, 2H), 4,05-4,21 (m, 3H), 6,56 (d, J = 7,1 Hz, 1H), 6,60-6,70 (m, 2H), 7,03-7,10 (m, 3H), 7,16-7,23 (m, 2H), 7,73 (d, J = 5,2 Hz, 1H), 8,31 (d, J = 5,9 Hz, 2H).

Ejemplo 462

Síntesis de 1-etil-3,3,5-trimetil-7-(3-{[2-(4-oxo-4H-furo[3,2-c]piridin-5-il)etil]piridin-4-ilmetilamino}propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

Polvo blanco

Punto de fusión 93,8°C

^{1}H-NMR ($CDCl_3$) δppm:

0,87 (s, 3H), 1,16 (t, J = 7,1 Hz, 3H), 1,53 (s, 3H), 1,82-1,95 (m, 2H), 2,72 (t, J = 6,8 Hz, 2H), 2,76-2,89 (m, 2H), 3,38 (s, 3H), 3,68 (s, 2H), 3,63-3,78 (m, 1H), 3,87 (t, J = 6,0 Hz, 2H), 4,10 (t, J = 6,0 Hz, 2H), 4,11-4,20 (m, 1H), 6,43 (d, J = 7,4 Hz, 1H), 6,60 (d, J = 2,8 Hz, 1H), 6,67 (dd, J = 9,0 y 2,8 Hz, 1H), 6,96 (d, J = 2,9 Hz, 1H), 7,05-7,11 (m, 3H), 7,19 (d, J = 9,0 Hz, 1H), 7,50 (d, J = 2,9 Hz, 1H), 8,35 (d, J = 6,0 Hz, 2H).

Ejemplo 463

Síntesis de diclorhidrato de 7-(3-{[2-(2-bromo-4-oxo-4H-furo[3,2-c]piridina-5-il)etil]piridin-4-ilmetilamino}-propoxi)-1-etil-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]-

diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7 y del Ejemplo 6, se sintetizó el compuesto objetivo.

Amorfo

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (s, 3H), 1,01 (t, J = 7,1 Hz, 3H), 1,32 (s, 3H), 2,15 (br, 2H), 2,95-3,40 (m, 2H), 3,32 (s, 3H), 3,61-3,73 (m, 3H), 4,01-4,09 (m, 3H), 4,34 (br, 4H), 6,81 (br, 2H), 6,88 (br, 1H), 7,10 (s, 1H), 7,39 (d, J = 9,0 Hz, 1H), 7,74 (br, 1H), 8,13 (br, 2H), 8,86 (br, 2H).

Ejemplo 464

Síntesis de diclorhidrato de 1-etil-3,3,5-trimetil-7-(3-{[2-(2-metil-4-oxo-4H-furo[3,2-c]piridin-5-il)etil]piridin-4-ilmetil-amino}-propoxi)-1,5-ihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 6, se sintetizó el compuesto objetivo.

Amorfo

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (s, 3H), 1,01 (t, J = 7,1 Hz, 3H), 1,32 (s, 3H), 2,00-2,22 (m, 2H), 2,22 (s, 3H), 3,11-3,39 (m, 7H), 3,60-3,71 (m, 1H), 4,02-4,07 (m, 3H), 4,30-4,45 (m, 2H), 4,51-4,71(m, 2H), 6,55 (s, 1H), 6,72 (d, J = 7,3 Hz, 1H), 6,84-6,90 (m, 2H), 7,40 (d, J = 9,0 Hz, 1H), 7,64 (d, J = 7,3 Hz, 1H), 8,21 (br, 2H), 8,89 (br, 2H).

Ejemplo 465

Síntesis de 1-etil-3,3,5-trimetil-7-(3-{[2-(2-metil-4-oxo-4H-

furo[3,2-c]piridin-5-il)etil]piridin-4-ilmetil-amino}-propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,87 (s, 3H), 1,16 (t, J = 7,1 Hz, 3H), 1,53 (s, 3H), 1,83-1,96 (m, 2H), 2,42 (s, 3H), 2,72 (t, J = 6,2 Hz, 2H), 2,85 (t, J = 6,0 Hz, 2H), 3,39 (s, 3H), 3,68 (s, 2H), 3,66-3,79 (m, 1H), 3,89 (t, J = 6,1 Hz, 2H), 4,08-4,23 (m, 3H), 6,37 (d, J = 7,3 Hz, 1H), 6,49-6,54 (m, 1H), 6,63-6,69 (m, 2H), 7,01 (d, J = 7,3 Hz, 1H), 7,08-7,12 (m, 2H), 7,19 (d, J = 8,3 Hz, 1H), 8,35-8,37 (m, 2H).

Ejemplo 466

Síntesis de diclorhidrato de 1-etil-7-(3-{[2-(2-etil-4-oxo-4H-tieno[3,2-c]-piridin-5-il)-etil]-piridin-4-ilmetil-amino}-propoxi)-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]-diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7 y Ejemplo 6, se sintetizó el compuesto objetivo.

Amorfo

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (s, 3H), 1,01 (t, J = 7,0 Hz, 3H), 1,28 (t, J = 7,5 Hz, 3H), 1,32 (s, 3H), 2,09 (br, 2H), 2,87 (q, J = 7,5 Hz, 2H), 3,10-3,21 (m, 2H), 3,30 (s, 3H), 3,51-3,69 (m, 3H), 3,90-4,09 (m, 5H), 4,30 (br, 2H), 6,71-6,88 (m, 3H), 7,18-7,20 (m, 1H), 7,36-7,43 (m, 1H), 7,52 (br, 1H), 7,86 (br, 2H), 8,69 (br, 2H).

Ejemplo 467

Síntesis de diclorhidrato de 7-(3-{[2-(2,3-dimetil-4-oxo-4H-furo[3,2-c]piridin-5-il)etil]piridin-4-ilmetilamino}-propoxi)-1-etil-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]-diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7 y Ejemplo 6, se sintetizó el compuesto objetivo.

Amorfo amarillo pálido

^{1}H-NMR (DMSO-d_6) δppm:

0,74 (s, 3H), 1,01 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,05-2,20 (m, 2H), 2,17 (s, 3H), 2,29 (s, 3H), 3,05-3,20 (m, 2H), 3,31 (s, 3H), 3,61-3,73 (m, 3H), 3,95-4,05 (m, 3H), 4,31 (br, 4H), 6,63 (br, 1H), 6,81-6,88 (m, 2H), 7,39 (d, J= 9,0 Hz, 1H), 7,56 (d, J = 7,3 Hz, 1H), 8,04 (br, 2H), 8,79 (br, 2H).

Ejemplo 468

Síntesis de diclorhidrato de 1-etil-7-(3-{[2-(2-furan-3-il-4-oxo-4H-furo[3,2-c]piridin-5-il)etil]piridin-4-ilmetil-amino}propoxi)3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]-diazepina-2,4-diona

Se agregaron una solución de carbonato de sodio 2N (0,3 ml) y tetrakis(trifenilfosfina)paladio(0) (37,2 mg, 0,03 mmoles) a una solución de dimetoxietano (2 ml) de 7-(3-{[2-(2-bromo-4-oxo-4H-furo[3,2-c]piridin-5-il)etil]-piridin-4-ilmetilamino}propoxi)-1-etil-3,3,5-trimetil-1, 5-dihidrobenzo[b][1,4]diazepina-2,4-diona (0,20 g, 0,31 mmoles) y ácido furan-3-borónico (39,2 mg, 0,035 mmoles), y se agitó bajo atmósfera de argón a 80°C durante 6,5 horas. La mezcla de reacción se enfrió a temperatura ambiente, y se purificó

por cromatografía en columna de gel de sílice (acetato de etilo:metanol = 100:0→93:7). El producto purificado se concentró bajo presión reducida y el residuo resultante se disolvió en acetato de etilo (10 ml). Se agregó una solucion de 4N HCl acetato de etilo (0,5 ml) a la solución y se concentró a sequedad bajo presión reducida para obtener de este modo 0,10 g (rendimiento: 51%) de diclorhidrato de 1-etil-7-(3-{[2-(2-furan-3-il-4-oxo-4H-furo[3,2-c]piridin-5-il)etil]piridin-4-ilmetilamino}-propoxi)-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona como un sólido amorfo amarillo pálido.

^{1}H-NMR (DMSO-d_6) δppm:

0,73 (s, 3H), 1,00 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,09 (br, 2H), 3,21-3,40 (m, 2H), 3,29 (s, 3H), 3,51-3,64 (m, 3H), 3,81-4,01 (m, 5H), 4,30 (br, 2H), 6,78 (br, 2H), 6,84 (br, 1H), 6,98 (d, J = 0,74 Hz, 1H), 7,16 (s, 1H), 7,33 (d, J = 8,5 Hz, 1H), 7,69 (d, J = 5,9 Hz, 1H), 7,82 (s, 1H), 7,93 (br, 2H), 8,19 (s, 1H), 8,74 (br, 2H).

Ejemplo 469

Síntesis de triclorhidrato de 1-etil-3,3,5-trimetil-7-(3-{[2-(4-oxo-2-piridin-3-il-4H-furo[3,2-c]piridin-5-il)etil]-piridin-4-ilmetilamino}-propoxi)-1,5-dihidrobenzo[b][1,4]-diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 468, se sintetizó el compuesto objetivo.

Amorfo amarillo pálido

^{1}H-NMR (DMSO-d_6) δppm:

0,73 (s, 3H), 0,99 (t, J = 7,0 Hz, 3H), 1,31 (s, 3H), 2,13

(br, 2H), 3,10-3,30 (m, 2H), 3,30 (s, 3H), 3,70-3,85 (m, 1H), 3,92-4,03 (m, 5H), 4,38 (br, 4H), 6,80-6,87 (m, 3H), 7,35 (d, J = 9,0 Hz, 1H), 7,79-7,84 (m, 3H), 8,07 (br, 2H), 8,55 (d, J = 8,0 Hz, 1H), 8,72 (dd, J = 1,3, 5,2 Hz, 1H), 8,82 (br, 2H), 9,23 (d, J = 1,8 Hz, 1H).

Ejemplo 470

Síntesis de triclorhidrato de 1-etil-3,3,5-trimetil-7-(3-{[2-(4-oxo-2-piridin-4-il-4H-furo[3,2-c]piridin-5-il)etil]-piridin-4-ilmetilamino}propoxi)-1,5-dihidrobenzo[b][1,4]-diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 468, se sintetizó el compuesto objetivo.

Polvo amarillo

^{1}H-NMR (DMSO-d_6) δppm:

0,74 (s, 3H), 0,99 (t, J = 7,0 Hz, 3H), 1,31 (s, 3H), 2,11 (br, 2H), 3,12-3,30 (m, 2H), 3,29 (s, 3H), 3,55-3,69 (m, 1H), 3,91-4,08 (m, 5H), 4,36 (br, 4H), 6,77-6,90 (m, 3H), 7,35 (d, J = 8,9 Hz, 1H), 7,93 (br, 3H), 8,30 (br, 3H), 8,76 (br, 2H), 8,91 (d, J = 5,6 Hz, 2H).

Ejemplo 471

Síntesis de triclorhidrato de 7-[3-({2-[2-(3-amino-henil)-4-oxo-4H-furo[3,2-c]-piridin-5-il]etil}piridin-4-ilmetil-amino)propoxi]1-etil-3,3,5-trimetil-1,5-dihidrobenzo[b]-[1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 468, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,73 (s, 3H), 0,9 (t, J = 7,0 Hz, 3H), 1,31 (s, 3H), 2,10 (br, 2H), 3,02-3,20 (m, 2H), 3,30 (s, 3H), 3,55-3,70 (m, 1H), 3,95-4,03 (m, 5H), 4,39 (br, 4H), 6,78-6,88 (m, 3H), 7,15-7,80 (m, 2H), 7,53 (br, 2H), 7,62-7,81 (m, 3H), 8,06 (br, 2H), 8,82 (br, 2H).

Ejemplo 472

Síntesis de 1-etil-3,3,5-trimetil-7-(3-{[2-(7-oxo-7H-furo-[2,3-c]piridin-6-il)etil]piridin-3-ilmetilamino}-propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

Polvo blanco

Punto de fusión 125°C

Ejemplo 473

Síntesis de diclorhidrato de 1-etil-3,3,5-trimetil-7-(3-{[2-(7-oxo-7H-furo[2,3-c]piridin-6-il)etil]quinolin-4-ilmetilamino}-propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7 y Ejemplo 6, se sintetizó el compuesto objetivo.

Polvo blanco

^{1}H-NMR (DMSO-d_6) δppm:

0,74 (3H, s), 1,01 (3H, t, J = 7,0 Hz), 1,32 (3H, s), 2,00-2,28 (2H, m), 2,70-5,31 (15H, m), 6,45-6,59 (1H, m), 6,76-6,80 (1H, m), 6,83-6,87 (2H, m), 7,37 (1H, d, J = 9,0 Hz) 7,42-7,58 (1H, m), 7,72-7,88 (1H, m), 7,95-8,19 (3H, m), 8,31 (1H, d, J = 8,6 Hz), 8,43-8,50 (1H, m), 9,03-9,19 (1H, m).

Ejemplo 474

Síntesis de clorhidrato de 1-etil-7-(3-{(3-hidroxibenzil)-[2-(7-oxo-7H-furo[2,3-c]piridin-6-il)etil]amino}propoxi)-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7 y Ejemplo 6, se sintetizó el compuesto objetivo.

Polvo blanco

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (3H, s), 1,01 (3H, t, J = 7,0 Hz), 1,32 (3H, s), 2,12-2,27 (2H, m), 3,20-3,44 (7H, m) 3,45-3,43 (2H, m), 3,63-3,70 (1H, m), 3,99-4,09 (3H, m), 4,35-4,37 (1H, m), 4,43-4,53 (1H, m) 6,68-6,71 (1H, m), 6,84-6,93 (4H, m), 6,99-7,10 (2H, m), 7,20-7,26 (1H, m), 7,40 (1H, d, J = 7,7 Hz), 7,54-7,58 (1H, m), 8,17 (1H, s), 9,72-9,80(1H, m).

Ejemplo 475

Síntesis of diclorhidrato de 1-etil-3,3,5-trimetil-7-(3-{[2-(7-oxo-7H-furo[2,3-c]piridin-6-il)etil]tiazol-2-il-metilamino}-propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7 y Ejemplo 6, se sintetizó el compuesto objetivo.

Polvo blanco

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (3H, s), 1,00 (3H, t, J = 7,1 Hz), 1,32 (3H, s), 2,05-2,28 (2H, m), 3,10-3,84 (8H, m), 3,99-4,09 (3H, m), 4,40-4,50 (2H, m), 4,72-4,88 (2H, m), 6,64-6,67 (1H, m), 6,84-6,92 (3H, m), 7,39 (1H, d, J = 9,0 Hz) 7,52-7,59 (1H, m), 7,65-7,91

(2H, m), 8,14 (1H, d, J = 1,9 Hz).

Ejemplo 476

Síntesis de diclorhidrato de 1-etil-3,3,5-trimetil-7-(3-{[2-(4-oxo-2-fenil-4H-furo[3,2-c]piridin-5-il)etil]piridin-4-ilmetilamino}propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 468, se sintetizó el compuesto objetivo.

Amorfo

^{1}H-NMR (DMSO-d_6) δppm:

0,72 (s, 3H), 0,99 (t, J = 7,0 Hz, 3H), 1,31 (s, 3H), 2,09 (br, 2H), 3,11-3,30 (m, 2H), 3,29 (s, 3H), 3,61-3,72 (m, 1H), 3,60-4,04 (m, 5H), 4,38 (br, 4H), 6,71-6,88 (m, 3H), 7,32 (d, J = 8,6 Hz, 1H), 7,37-7,41 (m, 1H), 7,46-7,51 (m, 3H), 7,74 (br, 1H), 7,86 (d, J = 7,4 Hz, 2H), 8,03 (br, 2H), 8,81 (br, 2H).

Ejemplo 477

Síntesis de diclorhidrato de 1-etil-7-[3-({2-[2-(4-metoxifenil)-4-oxo-4H-furo[3,2-c]piridin-5-il]etil}-piridin-4-ilmetilamino)-propoxi]-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 468, se sintetizó el compuesto objetivo.

Amorfo

^{1}H-NMR (DMSO-d_6) δppm:

0,71 (s, 3H), 0,98 (t, J = 7,0 Hz, 3H), 1,31 (s, 3H), 2,00 (br, 2H), 3,28 (s, 3H), 3,20-3,38 (m, 2H), 3,50-3,70 (m, 1H),

3,82 (s, 3H), 3,90-4,02 (m, 5H), 4,40 (br, 4H), 6,82 (br, 3H), 7,05 (d, J = 8,8 Hz, 2H), 7,30 (br, 2H), 7,66 (br, 1H), 7,79 (d, J = 8,8 Hz, 2H), 7,92 (br, 2H), 8,68 (br, 2H).

Ejemplo 478

Síntesis de 1-etil-3,3,5-trimetil-7-[3-(piridin-4-ilmetil-piridin-2-ilmetilamino)propoxi]-1,5-dihidrobenzo[b][1,4]-diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

Aceite incoloro

^{1}H-NMR ($CDCl_3$) δppm:

0,86 (s, 3H), 1,15 (t, J = 7,1 Hz, 3H), 1,53 (s, 3H), 1,91-2,08 (m, 2H), 2,66 (t, J = 6,9 Hz, 2H), 3,39 (s, 3H), 3,61 (s, 2H), 3,63 (s, 2H), 3,61-3,78 (m, 1H), 3,97 (t, J = 6,1 Hz, 2H), 4,03-4,20 (m, 1H), 6,60 (d, J = 2,7 Hz, 1H), 6,70 (dd, J = 2,7 y 9,0 Hz, 1H), 7,16-7,26 (m, 4H), 7,64-7,68 (m, 1H), 8,46-8,52 (m, 3H), 8,60 (br, 1H).

Ejemplo 479

Síntesis de triclorhidrato de 1-etil-3,3,5-trimetil-7-[3-(piridin-4-ilmetil-piridin-2-ilmetilamino)propoxi]-1,5-dihidrobenzo[b][1,4]-diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 6, se sintetizó el compuesto objetivo.

Sólido blanco

^{1}H-NMR (DMSO-d_6) δppm:

0,76 (s, 3H), 1,05 (t, J = 7,0 Hz, 3H), 1,33 (s, 3H), 2,09 (br, 2H), 2,75 (br, 2H), 3,31 (s, 3H), 3,61-3,73 (m, 1H),

4,03-4,30 (m, 5H), 4,53 (br, 2H), 6,81-6,82 (m, 2H), 7,34-7,37 (m, 1H), 7,94 (br, 1H), 8,15 (br, 2H), 8,64 (br, 1H), 8,80-8,87 (m, 3H), 9,01 (Br, 1H).

Ejemplo 480

Síntesis of 1-etil-3,3,5-trimetil-7-[3-(piridin-4-ilmetil-piridin-3-ilmetilamino)propoxi]-1,5-dihidrobenzo[b][1,4]-diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

Aceite incoloro

^{1}H-NMR ($CDCl_3$) δppm:

0,86 (s, 3H), 1,15 (t, J = 7,1 Hz, 3H), 1,53 (s, 3H), 1,91-2,04 (m, 2H), 2,71 (t, J = 6,9 Hz, 2H), 3,38 (s, 3H), 3,67 (s, 2H), 3,61-3,72 (m, 1H), 3,80 (s, 2H), 3,99 (t, J = 6,1 Hz, 2H), 4,05-4,20 (m, 1H), 6,61 (d, J = 2,8 Hz, 1H), 6,71 (dd, J = 2,8 y 9,0 Hz, 1H), 7,14-7,19 (m, 2H), 7,26-7,31 (m, 2H), 7,46 (d, J = 7,8 Hz, 1H), 7,57-7,68 (m, 1H), 8,47-8,54 (m, 3H).

Ejemplo 481

Síntesis de triclorhidrato de 1-etil-3,3,5-trimetil-7-[3-(piridin-4-ilmetil-piridin-3-ilmetilamino)propoxi]-1,5-dihidrobenzo[b][1,4]-diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 6, se sintetizó el compuesto objetivo.

Amorfo blanco

^{1}H-NMR (DMSO-d_6) δppm:

0,76 (s, 3H), 1,01 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,14

(br, 2H), 2,96 (br, 2H), 3,30 (s, 3H), 3,61-3,73 (m, 1H), 4,03-4,10 (m, 3H), 4,27-4,32 (m, 4H), 6,81-6,85 (m, 2H), 7,38 (d, J = 9,0 Hz, 1H), 7,64 (br, 1H), 7,81 (br, 1H), 8,07 (br, 3H), 8,81 (br, 3H).

Ejemplo 482

Síntesis de 7-[3-(bis-piridin-4-ilmetilamino)propoxi]-1-etil-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

Aceite incoloro

^{1}H-NMR ($CDCl_3$) δppm:

0,86 (s, 3H), 1,15 (t, J = 7,1 Hz, 3H), 1,53 (s, 3H), 1,91-2,02 (m, 2H), 2,66 (t, J = 6,6 Hz, 2H), 3,38 (s, 3H), 3,62 (s, 4H), 3,61-3,78 (m, 1H), 3,92-3,99 (m, 2H), 4,01-4,20 (m, 1H), 6,61 (d, J = 2,8 Hz, 1H), 6,70 (dd, J = 2,8 y 9,0 Hz, 1H), 7,20 (d, J = 9,0 Hz, 1H), 7,28-7,30 (m, 4H), 8,50-8,53 (m, 4H).

Ejemplo 483

Síntesis de triclorhidrato de 7-[3-(bis-piridin-4-ilmetilamino)propoxi]-1-etil-3,3,5-trimetil-1,5-dihidro-benzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 6, se sintetizó el compuesto objetivo.

Amorfo blanco

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (s, 3H), 1,02 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,01 (br, 2H), 2,67 (br, 2H), 3,30 (s, 3H), 3,63-3,72 (m, 1H),

4,03-4,10 (m, 7H), 6,81-6,85 (m, 2H), 7,37 (d, J = 9,0 Hz, 1H), 8,10 (br, 4H), 8,84 (br, 4H).

Ejemplo 484

Síntesis of 1-etil-3,3,5-trimetil-7-{3-[(5-metilfuran-2-ilmetil)piridin-4-ilmetilamino]propoxi}-1,5-dihidro-benzo-[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

Aceite amarillo pálido

^{1}H-NMR ($CDCl_3$) δppm:

0,86 (s, 3H), 1,15 (t, J = 7,1 Hz, 3H), 1,53 (s, 3H), 1,91-2,05 (m, 2H), 2,27 (s, 3H), 2,67 (t, J = 6,6 Hz, 2H), 3,39 (s, 3H), 3,63 (s, 2H), 3,64 (s, 2H), 3,62-3,79 (m, 1H), 4,02 (t, J = 6,2 Hz, 2H), 4,07-4,22 (m, 1H), 5,87 (br, 1H), 6,04 (br, 1H), 6,66 (d, J = 2,8 Hz, 1H), 6,75 (dd, J = 2,8 y 9,0 Hz, 1H), 7,20 (d, J = 9,0 Hz, 1H), 7,24-7,26 (m, 2H), 8,46-8,50 (m, 2H).

Ejemplo 485

Síntesis de diclorhidrato de 1-etil-3,3,5-trimetil-7-{3-[(5-metilfuran-2-ilmetil)piridin-4-ilmetilamino]propoxi}-1,5-dihidro-benzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 6, se sintetizó el compuesto objetivo.

Amorfo amarillo pálido

^{1}H-NMR (DMSO-d_6) δppm:

0,76 (s, 3H), 1,01 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,21-2,30 (m, 5H), 3,05 (br, 2H), 3,32 (s, 3H), 3,62-3,72 (m, 1H),

4,02-4,11 (m, 3H), 4,23-4,58 (m, 4H), 6,10 (br, 1H), 6,57 (br, 1H), 6,87-6,91 (m, 2H), 7,40 (d, J = 9,0 Hz, 1H), 8,20 (br, 2H), 8,90 (br, 2H).

Ejemplo 486

Síntesis de triclorhidrato de 1-etil-3,3,5-trimetil-7-{3-[(2-metilamino-etil)-piridin-4-ilmetilamino]propoxi}-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 44, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,76 (s, 3H), 1,01 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,21 (br, 2H), 2,51 (s, 3H), 3,10 (br, 2H), 3,33 (s, 3H), 3,35 (br, 2H), 3,61-3,72 (m, 1H), 4,00-4,12 (m, 5H), 4,55 (br, 2H), 6,90 (dd, J = 2,6, 9,0 Hz, 1H), 6,94 (d, J = 2,6 Hz, 1H), 7,40 (d, J = 9,0 Hz, 1H), 8,35 (br, 2H), 8,95 (br, 2H), 9,50 (br, 2H).

Ejemplo 487

Síntesis de N-(2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil]piridin-4-ilmetilamino}etil)-N-metilbenzamida

Se agregó fosforocianidato de dietilo (0,15 g, 1,0 mmoles) a una solución de THF (5 ml) de 1-etil-3,3,5-trimetil-7-{3-[(2-metilaminoetil)piridin-4-ilmetilamino]-propoxi}-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona (0,39 g, 0,83 mmoles), ácido benzoico (0,14 g, 1,1 mmoles), y trietilamina (0,15 ml, 1,1 mmoles), y la mezcla se agitó a temperatura ambiente durante la noche. La mezcla de reacción se purificó por cromatografía en columna de gel de sílice

(acetato de etilo:metanol = 100:0→80:20). El producto purificado se concentró bajo presión reducida para obtener de este modo 0,41 g (rendimiento: 86%) de N-(2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil]piridin-4-ilmetil-amino}etil)-N-metil-benzamida como un aceite incoloro.

^{1}H-NMR ($CDCl_3$) δppm:

0,84 (s, 3H), 1,15 (t, J = 7,1 Hz, 3H), 1,52 (s, 3H), 1,86-1,98 (m, 2H), 2,72 (br, 4H), 2,93 (br, 3H), 3,36 (s, 3H), 3,40-3,69 (m, 5H), 3,98 (br, 2H), 4,13-4,23 (m, 1H), 6,66 (d, J = 2,8 Hz, 1H), 6,70 (dd, J = 2,8 y 9,0 Hz, 1H), 7,15 (d, J = 9,0 Hz, 1H), 7,17-7,27 (m, 2H), 7,30-7,39 (m, 5H), 8,47-8,50 (m, 2H).

Ejemplo 488

Síntesis de diclorhidrato de N-(2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]-diazepin-7-iloxi)propil]piridin-4-ilmetilamino}etil)-N-metilbenzamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 6, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (s, 3H), 1,01 (t, J = 7,0 Hz, 3H), 1,33 (s, 3H), 2,38 (br, 2H), 2,97 (s, 3H), 3,32 (br, 5H), 3,40-3,49 (m, 2H), 3,61-3,70 (m, 1H), 3,97 (br, 2H), 4,01-4,10 (m, 1H), 4,15 (br, 2H), 4,87 (br, 2H), 6,90-6,95 (m, 2H), 7,40-7,49 (m, 6H), 8,50 (br, 2H), 9,05 (br, 2H).

Ejemplo 489

Síntesis de N-(2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil]

piridin-4-ilmetilamino}etil)-3-metoxi-N-metilbenzamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 487, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,84 (s, 3H), 1,13 (t, J = 7,1 Hz, 3H), 1,52 (s, 3H), 1,92 (br, 2H), 2,71 (br, 4H), 2,93 (br, 3H), 3,36 (s, 3H), 3,40-3,80 (m, 5H), 3,79 (s, 3H), 3,99 (br, 2H), 4,08-4,25 (m, 1H), 6,67 (d, J = 2,8 Hz, 1H), 6,72 (dd, J = 2,8 y 9,0 Hz, 1H), 6,85-6,94 (m, 3H), 7,16 (d, J = 9,0 Hz, 1H), 7,12-7,30 (m, 3H), 8,47-8,50 (m, 2H).

Ejemplo 490

Síntesis de diclorhidrato de N-(2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]-diazepin-7-iloxi)propil]piridin-4-ilmetilamino}etil)-3-metoxi-N-metilbenzamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 6, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (br, 3H), 1,00 (br, 3H), 1,32 (s, 3H), 2,33 (br, 2H), 2,94 (s, 3H), 3,30 (br, 7H), 3,61-3,70 (m, 1H), 3,77 (s, 3H), 4,01-4,15 (m, 5H), 4,71 (br, 2H), 6,91 (br, 2H), 7,02 (br, 3H), 7,32-7,41 (m, 2H), 8,17 (br, 2H), 8,89 (br, 2H).

Ejemplo 491

Síntesis de N-(2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil]piridin-4-ilmetilamino}etil)-4-metoxi-N-metilbenzamida

Usando un material de partida apropiado y siguiendo el

procedimiento del Ejemplo 487, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,84 (s, 3H), 1,13 (t, J = 7,1 Hz, 3H), 1,51 (s, 3H), 1,84-1,97 (m, 2H), 2,60-2,78 (m, 4H), 2,95 (s, 3H), 3,37 (s, 3H), 3,50-3,75 (m, 5H), 3,82 (s, 3H), 4,00 (t, J = 6,2 Hz, 2H), 4,08-4,21 (m, 1H), 6,67 (d, J = 2,8 Hz, 1H), 6,86 (dd, J = 2,8 y 9,0 Hz, 1H), 6,85-6,88 (m, 2H), 7,16 (d, J = 9,0 Hz, 1H), 7,17-7,21 (m, 2H), 7,32-7,33 (m, 2H), 8,47-8,50 (m, 2H).

Ejemplo 492

Síntesis de diclorhidrato de N-(2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]-diazepin-7-iloxi)propil]piridin-4-ilmetilamino}etil)-4-methxi-N-metilbenzamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 6, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (br, 3H), 1,00 (br, 3H), 1,32 (s, 3H), 2,32 (br, 2H), 2,99 (s, 3H), 3,30 (br, 5H), 3,66 (br, 2H), 3,78 (s, 3H), 3,88 (br, 3H), 4,10 (br, 3H), 4,64 (br, 2H), 6,87-6,97 (m, 4H), 7,38-7,45 (m, 3H), 8,12 (br, 2H), 8,95 (br, 2H).

Ejemplo 493

Síntesis de N-(2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil]piridin-4-ilmetilamino}etil)-2-fluoro-N-metilbenzamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 487, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,84 (s, 3H), 1,13 (t, J = 7,1 Hz, 3H), 1,51 (s, 3H), 1,95-2,04 (m, 2H), 2,43-2,59 (m, 2H), 2,81-2,95 (m, 2H), 2,83 (s, 3H), 3,35 (s, 3H), 3,62-3,79 (m, 5H), 4,02-4,21 (m, 3H), 6,61-6,79 (m, 3H), 7,00-7,39 (m, 6H), 8,46-8,49 (m, 2H).

Ejemplo 494

Síntesis de N-(2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil]piridin-4-ilmetilamino}etil)-2-fluoro-N-metilbenzamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 6, se sintetizó el compuesto objetivo.

^{1}H-NMR ($DMSO-d_6$) δppm:

0,75 (br, 3H), 1,00 (br, 3H), 1,32 (s, 3H), 2,32 (br, 2H), 2,88 (s, 3H), 3,30 (br, 5H), 3,68 (br, 3H), 4,12 (br, 5H), 4,72 (br, 2H), 6,89-6,93 (m, 2H), 7,29 (br, 2H), 7,38-7,42 (m, 1H), 7,51 (br, 2H), 8,29 (br, 2H), 8,96 (br, 2H).

Ejemplo 495

Síntesis de N-(2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil]piridin-4-ilmetilamino}etil)-2,N-dimetilbenzamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 487, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,84 (s, 3H), 1,13 (t, J = 7,1 Hz, 3H), 1,49 (s, 3H), 1,95-2,04 (m, 2H), 2,26 (s, 3H), 2,43-2,59 (m, 2H), 2,73 (s, 3H), 2,72-2,81 (m, 2H), 3,35 (s, 3H), 3,62-3,79 (m, 5H), 4,02-4,27 (m, 3H), 6,60-6,79 (m, 2H), 7,00-7,35 (m, 7H), 8,46-8,52 (m,

2H).

Ejemplo 496

Síntesis de diclorhidrato de N-(2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]-diazepin-7-iloxi)propil]piridin-4-ilmetilamino}etil)-2,N-dimetilbenzamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 6, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (s, 3H), 1,00 (br, 3H), 1,32 (s, 3H), 2,18 (s, 3H), 2,33 (br, 2H), 2,78 (s, 3H), 3,30 (br, 5H), 3,60 - 3,75 (m, 3H), 4,04-4,08 (m, 3H), 4,13(br, 2H), 4,71 (br, 2H), 6,87-6,93 (m, 2H), 7,15-7,31 (m, 4H), 7,40-7,42 (m, 1H), 8,23 (br, 2H), 8,92 (br, 2H).

Ejemplo 497

Síntesis de N-(2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil]piridin-4-ilmetilamino}etil)-4,N-dimetilbenzamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 487, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,84 (s, 3H), 1,13 (t, J = 7,1 Hz, 3H), 1,51 (s, 3H), 1,84-1,98 (m, 2H), 2,35 (s, 3H), 2,60-2,78 (m, 4H), 2,93 (s, 3H), 3,36 (s, 3H), 3,53-3,78 (m, 5H), 4,00 (br, 2H), 4,07-4,22 (m, 1H), 6,67(d, J = 2,8 Hz, 1H), 6,70 (dd, J = 2,8 y 9,0 Hz, 1H), 7,10-7,17 (m, 3H), 7,20-7,27 (m, 4H), 8,47-8,50 (m, 2H).

Ejemplo 498

Síntesis de diclorhidrato de N-(2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]-diazepin-7-iloxi)propil]piridin-4-ilmetilamino}etil)-4,N-dimetilbenzamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 6, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,74 (s, 3H), 1,00 (br, 3H), 1,32 (s, 3H), 2,32 (br, 5H), 2,95 (s, 3H), 3,30 (br, 5H), 3,60-3,75 (m, 3H), 3,80-4,15 (m, 5H), 4,68 (br, 2H), 6,91(br, 2H), 7,23 (br, 2H), 7,40-7,42 (m, 3H), 8,23 (br, 2H), 8,91 (br, 2H).

Ejemplo 499

Síntesis de N-(2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil]piridin-4-ilmetilamino}etil)-2-(2-metoxifenil)-N-metil-acetamide

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 487, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,84 (s, 3H), 1,13 (t, J = 7,1 Hz, 3H), 1,52 (s, 3H), 1,84-1,99 (m, 2H), 2,60-2,73 (m, 4H), 3,04 (s, 3H), 3,37 (s, 3H), 3,41-3,53 (m, 2H), 3,65 (br, 2H), 3,61-3,70 (m, 1H), 3,83 (s, 3H), 3,93-4,00 (m, 2H), 4,06-4,21 (m, 1H), 4,68 (s, 2H), 6,63-6,73 (m, 2H), 6,80-6,97(m, 4H), 7,10-7,24 (m, 3H), 8,47-8,49 (m, 2H).

Ejemplo 500

Síntesis de diclorhidrato de N-(2-{[3-(1-etil-3,3,5-trimetil-

2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]-diazepin-7-iloxi)propil]piridin-4-ilmetilamino}etil)-2-(2-metoxifhenil)-N-metilacetamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 6, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,74 (s, 3H), 1,01 (t, J = 7,0 Hz, 3H), 1,31 (s, 3H), 2,25 (br, 2H), 3,04 (s, 3H), 3,30 (br, 5H), 3,40-3,49 (m, 2H), 3,75 (s, 3H), 3,75 (br, 1H), 3,94-4,08 (m, 5H), 4,67 (br, 2H), 4,83 (s, 2H), 6,79-6,99 (m, 6H), 3,78 (d, J = 9,0 Hz, 1H), 8,05 (br, 2H), 8,83 (br, 2H).

Ejemplo 501

Síntesis de N-(2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil]piridin-4-ilmetilamino}etil)-2-(3-metoxifenil)-N-metil-acetamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 487, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,84 (s, 3H), 1,13 (t, J = 7,1 Hz, 3H), 1,52 (s, 3H), 1,82-1,93 (m, 2H), 2,60-2,73 (m, 4H), 2,91 (s, 3H), 3,37 (s, 3H), 3,41-3,54 (m, 2H), 3,59-3,70 (m, 5H), 3,76 (s, 3H), 3,97 (t, J = 6,1 Hz, 2H), 4,06-4,21 (m, 1H), 6,65-6,81 (m, 5H), 7,13-7,25 (m, 4H), 8,44-8,50 (m, 2H).

Ejemplo 502

Síntesis de diclorhidrato de N-(2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]-diazepin-7-

iloxi)propil]piridin-4-ilmetilamino}etil)-2-(3-metoxifenil)-N-metilacetamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 6, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,74 (s, 3H), 1,00 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,24 (br, 2H), 3,03 (s, 3H), 3,23 (br, 2H), 3,30 (s, 3H), 3,63-3,72 (m, 6H), 4,01-4,08 (m, 5H), 4,62 (br, 4H), 6,78-6,91 (m, 5H), 7,20 (t, J = 7,8 Hz, 1H), 7,39 (d, J = 8,9 Hz, 1H), 8,22 (br, 2H), 8,90 (br, 2H).

Ejemplo 503

Síntesis de N-(2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil]piridin-4-ilmetilamino}etil)-2-(4-metoxifenil)-N-metil-acetamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 487, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,84 (s, 3H), 1,3 (t, J = 7,1 Hz, 3H), 1,52 (s, 3H), 1,82-1,93 (m, 2H), 2,57-2,73 (m, 4H), 2,91 (s, 3H), 3,37 (s, 3H), 3,43-3,54 (m, 2H), 3,59 (s, 2H), 3,60-3,75 (m, 3H), 3,76 (s, 3H), 3,97 (t, J = 6,1 Hz, 2H), 4,06-4,21 (m, 1H), 6,65 (br, 1H), 6,73 (dd, J = 8,9 y 2,8 Hz, 1H), 6,83 (d, J = 8,4 Hz, 2H), 7,05-7,21 (m, 5H), 8,44-8,50 (m, 2H).

Ejemplo 504

Síntesis de diclorhidrato de N-(2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]-diazepin-7-

548

iloxi)propil]piridin-4-ilmetilamino}etil)-2-(4-metoxifenil)-N-metilacetamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 6, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,74 (s, 3H), 1,00 (t, J = 7,0 Hz, 3H), 1,31 (s, 3H), 2,27 (br, 2H), 3,04 (s, 3H), 3,23 (br, 2H), 3,30 (s, 3H), 3,63-3,72 (m, 6H), 4,01-4,08 (m, 5H), 4,62 (br, 4H), 6,78-6,89 (m, 4H), 7,12-7,14 (m, 2H), 7,39 (d, J = 9,0 Hz, 1H), 7,96 (br, 2H), 8,81 (br, 2H).

Ejemplo 505

Síntesis de 2-benzo[1,3]dioxol-5-il-N-(2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]-diazepin-7-iloxi)propil]piridin-4-ilmetilamino}etil)-N-metilacetamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 487, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,84 (s, 3H), 1,13 (t, J = 7,1 Hz, 3H), 1,52 (s, 3H), 1,82-1,93 (m, 2H), 2,57-2,73 (m, 4H), 2,92 (s, 3H), 3,37 (s, 3H), 3,41-3,50 (m, 2H), 3,57 (s, 2H), 3,59-3,73 (m, 3H), 3,98 (t, J = 6,1 Hz, 2H), 4,07-4,20 (m, 1H), 5,89 (s, 2H), 6,64-6,77 (m, 5H), 7,07-7,25 (m, 3H), 8,44-8,49 (m, 2H).

Ejemplo 506

Síntesis de diclorhidrato de 2-benzo[1,3]dioxol-5-il-N-(2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil]piridin-4-ilmetil-

amino}-etil)-N-metilacetamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 6, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,74 (s, 3H), 1,00 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,25 (br, 2H), 3,03 (s, 3H), 3,23 (br, 2H), 3,30 (s, 3H), 3,63-3,71 (m, 3H), 4,01-4,08 (m, 5H), 4,58 (br, 2H), 4,69 (br, 2H), 5,97 (s, 2H), 6,67-6,69 (m, 1H), 6,80-6,83 (m, 2H), 6,89-6,91 (m, 2H), 7,39 (d, J = 8,9 Hz, 1H), 8,14 (br, 2H), 8,87 (br, 2H).

Ejemplo 507

Síntesis de dichlorhidrato de 1-etil-3,3,5-trimetil-7-(3-{(3-metilpiridin-4-ilmetil)-[2-(7-oxo-7H-furo[2,3-c]-piridin-6-il)etil]-amino}-propoxi)-1,5-dihidrobenzo[b]-[1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7 y del Ejemplo 6, se sintetizó el compuesto objetivo.

Polvo blanco

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (3H, s), 1,02 (3H, t, J = 7,1 Hz), 1,32 (3H, s), 1,90-2,01 (2H, m), 2,35-2,45 (3H, m), 2,61-3,95 (8H, m), 3,96-4,32 (7H, m), 6,49-6,61 (1H, m), 6,81-6,89 (3H, m), 7,39 (1H, d, J = 9,0 Hz), 7,41-7,51 (1H, m), 7,52-8,02 (1H, m), 8,11 (1H, s), 8,41-8,49 (1H, m), 8,65 (1H, s)

Ejemplo 508

Síntesis de diclorhidrato de 1-etil-3,3,5-trimetil-7-(3-{(2-metilpiridin-4-ilmetil)-[2-(7-oxo-7H-furo[2,3-c]-piridin-6-

il)etil]-amino}propoxi)-1,5-dihidrobenzo[b][1,4]-diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7 y del Ejemplo 6, se sintetizó el compuesto objetivo.

Polvo blanco

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (3H, s), 1,01 (3H, t, J = 7,1 Hz), 1,32 (3H, s), 1,82-2,11 (2H, m), 2,61-3,81 (8H, m), 3,89-4,41 (10H, m), 6,54-6,59 (1H, m), 6,78-6,91 (3H, m), 7,39 (1H, d, J = 9,0 Hz), 7,48-7,53 (1H, m), 7,52-7,99 (2H, m), 8,12 (1H, s), 8,52-8,68 (1H, m).

Ejemplo 509

Síntesis de diclorhidrato de 1-etil-7-(3-{(3-fluoropiridin-4-ilmetil)-[2-(7-oxo-7H-furo[2,3-c]piridin-6-il)etil]-amino}propoxi)-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]-diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7 y del Ejemplo 6, se sintetizó el compuesto objetivo.

Polvo blanco

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (3H, s), 1,01 (3H, t, J = 7,1 Hz), 1,32 (3H, s), 1,99-2,27 (2H, m), 3,31 (3H, s), 3,33-3,81 (5H, m), 3,96-4,20 (3H, m), 4,25-4,45 (4H, m), 6,60-6,64 (1H, m), 6,80-6,92 (3H, m), 7,39 (1H, d, J = 9,0 Hz), 7,52-7,56 (1H, m), 7,57-8,12 (1H, m), 8,14 (1H, s), 8,15-8,57 (1H, m), 8,60-8,66 (1H, m).

Ejemplo 510

Síntesis de diclorhidrato de 1-etil-3,3,5-trimetil-7-(3-{(2-

metilpiridin-3-ilmetil)-[2-(7-oxo-7H-furo[2,3-c]-piridin-6-il)etil]-amino}propoxi)-1,5-dihidrobenzo[b][1,4]-diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7 y del Ejemplo 6, se sintetizó el compuesto objetivo.

Polvo blanco

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (3H, s), 1,01 (3H, t, J = 7,1 Hz), 1,32 (3H, s), 1,90-2,17 (2H, m), 2,52-3,00 (4H, m), 3,25-3,94 (9H, m), 4,01-4,35 (5H, m), 6,52-6,60 (1H, m), 6,82-6,91 (3H, m), 6,93-7,38 (1H, m), 7,40 (1H, d, J = 9,0 Hz), 7,47-7,94 (2H, m), 8,12 (1H, s), 8,60-8,68 (1H, m).

Ejemplo 511

Síntesis de 1-etil-3,3,5-trimetil-7-{3-[[2-(7-oxo-7H-furo-[2,3-c]piridin-6-il)etil]-(4-trifluorometilpiridin-3-ilmetil)amino]propoxi}-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

Polvo blanco

Punto de fusión 137 a 138°C.

Ejemplo 512

Síntesis de triclorhidrato de 1-etil-3,3,5-trimetil-7-{3-[[2-(7-oxo-7H-furo[2,3-c]piridin-6-il)etil]-(2-pirrolidin-1-ilpiridin-4-ilmetil)amino]propoxi}-1,5-dihidrobenzo[b]-[1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el

procedimiento del Ejemplo 7 y del Ejemplo 6, se sintetizó el compuesto objetivo.

Polvo blanco

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (3H, s), 1,01 (3H, t, J = 7,1 Hz), 1,32 (3H, s), 1,91-2,03 (5H, m), 3,27-3,76 (13H, m), 3,99-4,61 (7H, m), 6,58-6,62 (1H, m), 6,91-7,24 (4H, m), 7,40 (1H, d, J = 9,1 Hz), 7,43-8,09 (3H, m), 8,13 (1H, s).

Ejemplo 513

Síntesis de fosfato de 2-({[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)-propil]-[2-(7-oxo-7H-furo[2,3-c]piridin-6-il)etil]amino}-metil)-benzonitrilo

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7 y del Ejemplo 458, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (3H, s), 1,02 (3H, t, J = 7,0 Hz), 1,32 (3H, s), 1,78-1,90 (2H, m), 2,65 (2H, t, J = 6,5 Hz), 2,77 (2H, t, J = 5,7 Hz), 3,30 (3H, s), 3,34-4,13 (8H, m), 6,46 (1H, d, J = 6,7 Hz), 6,74 (1H, dd, J = 2,7 y 9,0 Hz), 6,81 (1H, d, J = 2,7 Hz), 6,85 (1H, d, J = 2,0 Hz), 7,21-7,32 (3H, m), 7,35-7,40 (2H, m), 7,63 (1H, m), 8,07 (1H, d, J = 2,0 Hz).

Ejemplo 514

Síntesis de clorhidrato de 7-(3-{(3,5-dihidroxibenzil)-[2-(7-oxo-7H-furo[2,3-c]piridin-6-il)etil]amino}propoxi)-1-etil-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7 y del Ejemplo 6, se sintetizó el

compuesto objetivo.

Polvo blanco

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (3H, s), 1,00 (3H, t, J = 7,0 Hz), 1,32 (3H, s), 2,20-2,35 (2H, m), 3,08-3,62 (7H, m), 3,63-3,72 (1H, m), 3,99-4,17(3H, m), 4,18-4,28 (1H, m), 4,30-4,72 (3H, m), 6,34 (1H, s), 6,45 (2H, s), 6,70 (1H, d, J = 7,0 Hz), 6,86-6,96 (3H, m), 7,39 (1H, d, J = 8,9 Hz), 7,56 (1H, d, J = 7,1 Hz), 8,16 (1H, s), 9,47 (2H, br s).

Ejemplo 515

Síntesis de clorhidrato de 1-etil-7-(3-{(5-fluoropiridin-3-ilmetil)-[2-(7-oxo-7H-furo[2,3-c]piridin-6-il)etil]amino}-propoxi)-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7 y del Ejemplo 6, se sintetizó el compuesto objetivo.

Polvo blanco

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (3H, s), 1,00 (3H, t, J = 7,1 Hz), 1,32 (3H, s), 2,17-2,32 (2H, m), 3,22-3,73 (8H, m), 3,99-4,10 (3H, m), 4,44-4,66(4H, m), 6,68 (1H, d, J = 7,0 Hz), 6,85-6,93 (3H, m), 7,41 (1H, d, J = 9,0 Hz), 7,58 (1H, d, J = 7,0 Hz), 8,05-8,21 (2H, m), 8,64-8,71 (2H, m).

Ejemplo 516

Síntesis de 1-etil-7-(2-hidroxi-3-{[2-(1-oxo-1H-isoquinolin-2-il)etil]piridin-4-ilmetilamino}propoxi)-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el

procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

Sólido incoloro

Punto de fusión 67 a 74°C.

Ejemplo 517

Síntesis de 1-etil-7-(2-hidroxi-3-{[2-(1-oxo-1H-isoquinolin-2-il)etil]piridin-3-ilmetilamino}propoxi)-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

Sólido incoloro

^{1}H-NMR (DMSO-d_6) δppm:

0,74 (3H, s), 1,03 (3H, t, J = 7,0 Hz), 1,32 (3H, s), 2,54-3,08 (3H, m), 3,23-3,30 (3H, m), 3,49-3,92 (6H, m), 3,92-4,27 (3H, m), 4,84-4,99 (1H, m), 6,45-6,56 (1H, m), 6,56-6,79 (2H, m), 6,88-7,06 (1H, m), 7,22-7,38 (1H, m), 7,38-7,73 (5H, m), 8,16 (1H, d, J = 8,1 Hz), 8,23-8,35 (1H, m), 8,42 (1H, s).

Ejemplo 518

Síntesis de N-(2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil]piridin-4-ilmetilamino}etil)-3-fluoro-N-metilbenzamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 487, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,84 (s, 3H), 1,13 (t, J = 7,1 Hz, 3H), 1,52 (s, 3H), 2,02 (br, 2H), 2,73 (br, 4H), 2,92 (s, 3H), 3,36 (s, 3H), 3,41-3,73 (m, 5H), 3,99 (br, 2H), 4,07-4,20 (m, 1H), 6,67 (d, J =

2,8 Hz, 1H), 6,72 (dd, J = 2,8 y 9,0 Hz, 1H), 7,03-7,40 (m, 7H), 8,48-8,51 (m, 2H).

Ejemplo 519

Síntesis de diclorhidrato de N-(2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]-diazepin-7-iloxi)propil]piridin-4-ilmetilamino}-etil)-3-fluoro-N-metilbenzamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 6, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (s, 3H), 1,00 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,33 (br, 2H), 2,93 (s, 3H), 3,30 (br, 5H), 3,61-3,71 (m, 3H), 4,01-4,11 (m, 5H), 4,66 (br, 2H), 6,88-6,91 (m, 2H), 7,28-7,33 (m, 2H), 7,39-7,40 (m, 2H), 7,46-7,52 (m, 1H), 8,14 (br, 2H), 8,91 (br, 2H).

Ejemplo 520

Síntesis de N-(2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil]piridin-4-ilmetilamino}etil)-4-fluoro-N-metilbenzamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 487, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,84 (s, 3H), 1,13 (t, J = 7,1 Hz, 3H), 1,52 (s, 3H), 1,95 (br, 2H), 2,73 (br, 4H), 2,94 (s, 3H), 3,37 (s, 3H), 3,42-3,77 (m, 5H), 3,98 (br, 2H), 4,07-4,20 (m, 1H), 6,67 (d, J= 2,8 Hz, 1H), 6,72 (dd, J = 2,8 y 9,0 Hz, 1H), 7,05 (t, J = 8,6 Hz, 2H), 7,16 (d, J = 9,0 Hz, 1H), 7,26 (br, 2H), 7,32-

7,38 (m, 2H), 8,48-8,51 (m, 2H).

Ejemplo 521

Síntesis de diclorhidrato de N-(2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]-diazepin-7-iloxi)propil]piridin-4-ilmetilamino}etil)-4-fluoro-N-metilbenzamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 6, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,74 (s, 3H), 1,00 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,27 (br, 2H), 2,94 (s, 3H), 3,30 (br, 5H), 3,61-3,91 (m, 5H), 4,03-4,10 (m, 3H), 4,62 (br, 2H), 6,86-6,90 (m, 2H), 7,24-7,26 (m, 2H), 7,39 (d, J = 8,9 Hz, 1H), 7,56 (br, 2H), 8,00 (br, 2H), 8,82 (br, 2H).

Ejemplo 522

Síntesis de N-(2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil]piridin-4-ilmetilamino}etil)-3,N-dimetilbenzamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 487, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,84 (s, 3H), 1,13 (t, J = 7,1 Hz, 3H), 1,52 (s, 3H), 1,97 (br, 2H), 2,34 (s, 3H), 2,78 (br, 4H), 2,94 (s, 3H), 3,36 (s, 3H), 3,43-3,81 (m, 5H), 4,04 (br, 2H), 4,07-4,20 (m, 1H), 6,67 (d, J = 2,8 Hz, 1H), 6,73 (dd, J = 2,8 y 9,0 Hz, 1H), 7,09-7,26 (m, 5H), 7,32 (br, 2H), 8,48-8,51 (m, 2H).

Ejemplo 523

Síntesis de diclorhidrato de N-(2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]-diazepin-7-iloxi)propil]piridin-4-ilmetilamino}etil)-3,N-dimetilbenzamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 6, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (s, 3H), 1,00 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,32 (br, 5H), 2,94 (s, 3H), 3,30 (br, 5H), 3,61-3,91 (m, 5H), 4,02-4,11 (m, 3H), 4,62 (br, 2H), 6,89-6,90 (m, 2H), 7,20-7,31 (m, 4H), 7,39 (d, J = 8,9 Hz, 1H), 8,05 (br, 2H), 8,83 (br, 2H).

Ejemplo 524

Síntesis de 2-dimetilamino-N-(2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil]piridin-4-ilmetilamino}etil)-N-metilbenzamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 487, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,84 (s, 3H), 1,13 (t, J = 7,1 Hz, 3H), 1,52 (s, 3H), 1,99 (br, 2H), 2,76 (s, 6H), 2,74-2,89 (m, 4H), 3,06 (s, 3H), 3,36 (s, 3H), 3,53-3,83 (m, 5H), 3,95-4,21 (m, 3H), 6,67-6,75 (m, 2H), 6,85-6,97 (m, 2H), 7,10-7,24 (m, 3H), 7,40-7,42 (m, 2H), 8,53-8,55 (m, 2H).

Ejemplo 525

Síntesis de triclorhidrato de 2-dimetilamino-N-(2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo-

[b][1,4]diazepin-7-iloxi)propil]piridin-4-ilmetilamino}-etil)-N-metilbenzamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 6, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,74 (s, 3H), 1,00 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,32 (br, 2H), 2,84 (s, 6H), 2,94 (s, 3H), 3,01 (br, 7H), 3,64-3,70 (m, 1H), 3,93 (br, 2H), 4,03-4,14 (m, 3H), 4,69 (br, 2H), 6,85-6,93 (m, 2H), 7,12 (br, 1H), 7,23 (br, 2H), 7,39-7,42 (m, 2H), 8,22 (br, 2H), 8,92 (br, 2H).

Ejemplo 526

Síntesis de triclorhidrato de 3-dimetilamino-N-(2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil]piridin-4-ilmetil-amino}etil)-N-metilbenzamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 487, se sintetizó el compuesto objetivo.

Polvo blanco

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (s, 3H), 1,00 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,34 (br, 2H), 2,96 (s, 3H), 3,05 (s, 6H), 3,31 (s, 3H), 3,43 (br, 2H), 3,58-3,69 (m, 1H), 3,94 (br, 2H), 4,01-4,10 (m, 1H), 4,13 (br, 2H), 4,68 (br, 2H), 4,81 (br, 2H), 6,88-6,93 (m, 2H), 7,18 (br, 1H), 7,40 (d, J = 9,0 Hz, 1H), 7,47 (br, 3H), 8,47 (br, 2H), 9,03 (br, 2H).

Ejemplo 527

Síntesis de triclorhidrato de 4-dimetilamino-N-(2-{[3-(1-

etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo-[b][1,4]diazepin-7-iloxi)propil]piridin-4-ilmetilamino}-etil)-N-metilbenzamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 487, se sintetizó el compuesto objetivo.

Sólido blanco

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (s, 3H), 1,00 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,31 (br, 2H), 3,00 (br, 9H), 3,22-3,48 (m, 4H), 3,31 (s, 3H), 3,61-3,70 (m, 1H), 3,89 (br, 2H), 3,99-4,14 (m, 3H), 4,80 (br, 2H), 6,87-6,93 (m, 2H), 7,12 (br, 2H), 7,40 (d, J = 9,0 Hz, 1H), 7,48 (br, 2H), 8,46 (br, 2H), 9,03 (br, 2H).

Ejemplo 528

Síntesis de (2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]-diazepin-7-iloxi)-propil]-piridin-4-ilmetilamino}etil)-metilamida del ácido furan-2-carboxílico

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 487, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,86 (s, 3H), 1,15 (t, J = 7,1 Hz, 3H), 1,54 (s, 3H), 1,88-1,96 (m, 2H), 2,65-2,80 (m, 4H), 3,14 (s, 3H), 3,39 (s, 3H), 3,61-3,75 (m, 5H), 4,01 (t, J = 6,2 Hz, 2H), 4,04-4,22 (m, 1H), 6,45-6,48 (m, 1H), 6,67-6,69 (m, 1H), 6,73 (dd, J = 2,8 y 9,0 Hz, 1H), 6,99 (d, J = 3,5 Hz, 1H), 7,18 (d, J = 9,0 Hz, 1H), 7,24-7,26 (m, 2H), 7,60 (br, 1H), 8,49-8,50 (m, 2H).

Ejemplo 529

Síntesis diclorhidrato de la (2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil]piridin-4-ilmetilamino}etil)metilamida del ácido furan-2-carboxílico

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 6, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (s, 3H), 1,00 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,29 (br, 2H), 3,10-3,40 (m, 2H), 3,32 (s, 3H), 3,59-3,70 (m, 1H), 3,80-4,11 (m, 7H), 4,70 (br, 2H), 6,63 (d, J = 1,6 Hz, 1H), 6,88 (dd, J = 2,7, 9,0 Hz, 1H), 6,92 (d, J = 2,7 Hz, 1H), 6,96 (d, J = 3,3 Hz, 1H), 7,40 (d, J = 9,0 Hz, 1H), 7,86 (br, 1H), 8,38 (br, 2H), 8,94 (br, 2H).

Ejemplo 530

Síntesis de la (2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)-propil]piridin-4-ilmetilamino}etil)metilamida del ácido tiofen-2-carboxílico

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 487, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,86 (s, 3H), 1,15 (t, J = 7,1 Hz, 3H), 1,54 (s, 3H), 1,86-1,96 (m, 2H), 2,63-2,80 (m, 4H), 3,14 (s, 3H), 3,38 (s, 3H), 3,62-3,77 (m, 5H), 4,01 (t, J = 6,2 Hz, 2H), 4,03-4,20 (m, 1H), 6,67 (d, J = 2,8 Hz, 1H), 6,73 (dd, J = 2,8 y 9,0 Hz, 1H), 7,01-7,03 (m, 1H), 7,16 (d, J = 9,0 Hz, 1H), 7,24-7,26 (m, 2H), 7,30-7,32 (m, 1H), 7,59-7,61 (m, 1H), 8,48-8,50 (m,

2H).

Ejemplo 531

Síntesis de diclorhidrato de la (2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]-diazepin-7-iloxi)propil]piridin-4-ilmetilamino}etil)-metilamida del ácido tiofen-2-carboxílico

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 6, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (s, 3H), 1,00 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,26 (br, 3H), 3,23 (br, 2H), 3,31 (s, 3H), 3,64-3,70 (m, 3H), 3,80-3,93 (m, 2H), 4,02-4,08 (m, 3H), 4,59 (br, 2H), 6,85-6,89 (m, 2H), 7,14 (br, 1H), 7,39 (d, J = 8,9 Hz, 1H), 7,58 (br, 1H), 7,79 (br, 1H), 7,95 (br, 2H), 8,80 (br, 2H).

Ejemplo 532

Síntesis de la (2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)-propil]piridin-4-ilmetilamino}etil)metilamida del ácido furan-3-carboxílico

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 487, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,84 (s, 3H), 1,13 (t, J = 7,1 Hz, 3H), 1,52 (s, 3H), 1,87-1,98 (m, 2H), 2,63-2,80 (m, 4H), 3,05 (s, 3H), 3,37 (s, 3H), 3,53-3,70 (m, 5H), 3,99 (t, J = 6,2 Hz, 2H), 4,01-4,21 (m, 1H), 6,56 (s, 1H), 6,66 (d, J = 2,8 Hz, 1H), 6,72 (dd, J = 2,8 y 9,0 Hz, 1H), 7,16 (d, J = 9,0 Hz, 1H), 7,24-7,26 (m,

2H), 7,39 (br, 1H), 7,66 (br, 1H), 8,47-8,50 (m, 2H).

Ejemplo 533

Síntesis de diclorhidrato de la (2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]-diazepin-7-iloxi)propil]piridin-4-ilmetilamino}etil)-metilamida del ácido furan-3-carboxílico

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 6, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (s, 3H), 1,00 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,26 (br, 2H), 3,14 (br, 3H), 3,31 (s, 5H), 3,62-3,70 (m, 3H), 3,87 (br, 2H), 4,03-4,09 (m, 3H), 4,61 (br, 2H), 6,74 (br, 1H), 6,85-6,90 (m, 2H), 7,39 (d, J = 8,9 Hz, 1H), 7,74 (s, 1H), 8,09 (br, 2H), 8,14 (br, 1H), 8,85 (br, 2H).

Ejemplo 534

Síntesis de la (2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)-propil]piridin-4-ilmetilamino}etil)metilamida del ácido tiofen-3-carboxílico

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 487, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,84 (s, 3H), 1,13 (t, J = 7,1 Hz, 3H), 1,52 (s, 3H), 1,88-1,97 (m, 2H), 2,62-2,78 (m, 4H), 3,00 (s, 3H), 3,37 (s, 3H), 3,51-3,73 (m, 5H), 3,99 (t, J = 6,2 Hz, 2H), 4,01-4,21 (m, 1H), 6,66 (d, J = 2,8 Hz, 1H), 6,71 (dd, J = 2,8 y 9,0 Hz, 1H), 7,13-7,26 (m, 4H), 7,26-7,29 (m, 1H), 7,43-7,44 (m, 1H),

8,48-8,50 (m, 2H).

Ejemplo 535

Síntesis de diclorhidrato de la (2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]-diazepin-7-iloxi)propil]piridin-4-ilmetilamino}etil) metilamida del ácido tiofen-3-carboxílico

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 6, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (s, 3H), 1,00 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,28 (br, 2H), 3,06 (br, 5H), 3,31 (s, 3H), 3,61-3,70 (m, 3H), 3,87 (br, 2H), 4,03-4,09 (m, 3H), 4,61 (br, 2H), 6,86-6,90 (m, 2H), 7,28 (br, 1H), 7,39 (d, J = 8,9 Hz, 1H), 7,58-7,60 (m, 1H), 7,91 (br, 1H), 8,06 (br, 2H), 8,84 (br, 2H).

Ejemplo 536

Síntesis de la (2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)-propil]piridin-4-ilmetilamino}etil)metilamida del ácido ciclohexanocarboxílico

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 487, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,83 (s, 3H), 1,13 (t, J = 7,1 Hz, 3H), 1,52 (s, 3H), 1,50-1,81 (m, 10H), 1,88-2,00 (m, 2H), 2,39 (br, 1H), 2,60-2,78 (m, 4H), 2,93 (s, 3H), 3,37 (s, 3H), 3,43 (br, 2H), 3,61-3,74 (m, 3H), 3,91-4,21 (m, 3H), 6,67 (d, J = 2,8 Hz, 1H), 6,73 (dd, J = 2,8 y 9,0 Hz, 1H), 7,15 (d, J = 9,0 Hz, 1H), 7,24-

7,26 (m, 2H), 8,48 (br, 2H).

Ejemplo 537

Síntesis de diclorhidrato de la (2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]-diazepin-7-iloxi)propil]piridin-4-ilmetilamino}etil)-metilamida del ácido ciclohexanocarboxílico

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 6, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (s, 3H), 1,00 (t, J = 7,0 Hz, 3H), 1,08-1,28 (m, 6H), 1,32 (s, 3H), 1,66 (br, 4H), 2,26 (br, 2H), 2,55 (br, 1H), 3,03 (s, 3H), 3,21 (br, 2H), 3,32 (s, 3H), 3,64-3,71 (m, 3H), 4,02-4,10 (m, 5H), 4,59 (br, 2H), 6,87-6,92 (m, 2H), 7,40 (d, J = 8,9 Hz, 1H), 8,09 (br, 2H), 8,86 (br, 2H).

Ejemplo 538

Síntesis de la (2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-loxi)propil]-piridin-4-ilmetilamino}etil)metilamida del ácido benzo-[1,3]dioxol-5-carboxílico

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 487, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,84 (s, 3H), 1,13 (t, J = 7,1 Hz, 3H), 1,52 (s, 3H), 1,88-1,94 (m, 2H), 2,62-2,75 (m, 4H), 2,94 (s, 3H), 3,36 (s, 3H), 3,51 (br, 2H), 3,63 (s, 2H), 3,61-3,77 (m, 1H), 3,98(t, J = 6,2 Hz, 2H), 3,95-4,20 (m, 1H), 5,96 (s, 2H), 6,67 (d, J = 2,8 Hz, 1H), 6,72-6,79 (m, 2H), 6,83-6,88 (m, 2H), 7,15 (d, J

= 9,0 Hz, 1H), 7,24-7,26 (m, 2H), 8,47-8,50 (m, 2H).

Ejemplo 539

Síntesis de diclorhidrato de la (2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]-diazepin-7-iloxi)propil]piridin-4-ilmetilamino}etil)-matilamida del ácido benzo[1,3]dioxol-5-carboxílico

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 6, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (s, 3H), 1,00 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,32 (br, 2H), 2,95 (s, 3H), 3,31 (br, 5H), 3,62-3,71 (m, 3H), 4,02-4,09 (m, 5H), 4,71 (br, 2H), 6,06 (s, 2H), 6,86-7,06 (m, 5H), 7,39 (d, J = 8,9 Hz, 1H), 8,29 (br, 2H), 8,94 (br, 2H).

Ejemplo 540

Síntesis del diclorhidrato de 1-etil-3,3,5-trimetil-7-(3-{[2-(2-oxo-2H-piridin-1-il)etil]piridin-4-ilmetilamino}-propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

Amorfo marrón claro

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (s, 3H), 1,01 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,26 (br, 2H), 3,24 (br, 2H), 3,32 (s, 3H), 3,64-3,73 (m, 1H), 4,01-4,09 (m, 5H), 4,37 (br, 2H), 4,70 (br, 2H), 6,28 (t, J = 6,5 Hz, 1H), 6,41 (d, J = 9,0 Hz, 1H), 6,89 (dd, J = 2,5, 9,0 Hz, 1H), 6,93 (d, J = 2,5 Hz, 1H), 7,41 (d, J = 9,0 Hz, 1H), 7,42-7,47 (m, 1H), 7,78 (d, J = 6,5 Hz, 1H), 8,34 (br, 2H),

8,98 (br, 2H).

Ejemplo 541

Síntesis del diclorhidrato de la N-(2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]-diazepin-7-iloxi)propil]piridin-4-ilmetilamino}etil)-2-metoxi-N-metilbenzamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 487, se sintetizó el compuesto objetivo.

Polvo blanco

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (s, 3H), 1,01 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,33 (br, 2H), 2,79 (s, 3H), 3,21-3,44 (m, 2H), 3,30 (s, 3H), 3,53-3,64 (m, 1H), 3,94 (s, 3H), 3,90-4,15 (m, 7H), 4,76 (br, 2H), 6,84-7,14 (m, 4H), 7,22 (d, J = 7,4 Hz, 1H), 7,38-7,44 (m, 2H), 8,36 (br, 2H), 8,99 (br, 2H).

Ejemplo 542

Síntesis de diclorhidrato de N-(2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]-diazepin-7-iloxi)propil]piridin-4-ilmetilamino}-etil)-N-metil-2-trifluorometil-benzamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 487, se sintetizó el compuesto objetivo.

Polvo amarillo pálido

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (s, 3H), 1,00 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,36 (br, 2H), 2,78 (s, 3H), 3,30-3,43 (m, 5H), 3,61-3,70 (m, 1H), 3,85 (br, 2H), 4,00-4,19 (m, 5H), 4,81 (br, 2H), 6,84-6,95

(m, 2H), 7,40 (d, J = 9,0 Hz, 1H), 7,62-7,69 (m, 2H), 7,76 (t, J = 7,7 Hz, 1H), 7,82 (d, J = 7,7 Hz, 1H), 8,44 (br, 2H), 9,01 (br, 2H).

Ejemplo 543

Síntesis de diclorhidrato de N-(2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]-diazepin-7-iloxi)propil]piridin-4-ilmetilamino}etil)-N-metil-3-trifluorometil-benzamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 487, se sintetizó el compuesto objetivo.

Amorfo amarillo pálido

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (s, 3H), 1,00 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,36 (br, 2H), 2,95 (s, 3H), 3,25-3,33 (m, 2H), 3,31 (s, 3H), 3,37-3,45 (m, 2H), 3,61-3,73 (m, 1H), 3,97 (br, 2H), 4,00-4,13 (m, 1H), 4,13 (br, 2H), 4,82 (br, 2H), 6,89-6,94 (m, 2H), 7,40 (d, J = 9,0 Hz, 1H), 7,69 (t, J = 7,6 Hz, 1H), 7,82-7,86 (m, 2H), 7,91 (s, 1H), 8,47 (br, 2H), 9,02 (br, 2H).

Ejemplo 544

Síntesis de diclorhidrato de 2-ciano-N-(2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b]-[1,4]-diazepin-7-iloxi)propil]piridin-4-ilmetilamino}etil)-N-metil-benzamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 487, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (s, 3H), 1,00 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,31 (br, 2H), 2,89 (s, 3H), 3,16-3,45 (m, 2H), 3,30 (s, 3H), 3,50-3,75 (m, 3H), 3,90-4,15 (m, 5H), 4,71 (br, 2H), 6,82-6,94 (m, 2H), 7,40 (d, J = 9,0 Hz, 1H), 7,62-7,67 (m, 1H), 7,74 (br, 1H), 7,78-7,80 (m, 1H), 7,95 (d, J = 7,7 Hz, 1H), 8,29 (br, 2H), 8,94 (br, 2H).

Ejemplo 545

Síntesis de diclorhidrato de 4-ciano-N-(2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b]-[1,4]-diazepin-7-iloxi)propil]piridin-4-ilmetilamino}etil)-N-metil-benzamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 487, se sintetizó el compuesto objetivo.

Sólido blanco

^{1}H-NMR (DMSO-d_6) δppm:

0,74 (s, 3H), 1,00 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,31 (br, 2H), 2,91 (s, 3H), 3,21-3,40 (m, 4H), 3,30 (s, 3H), 3,50-3,75 (m, 1H), 3,93 (br, 2H), 4,00-4,13 (m, 3H), 4,69 (br, 2H), 6,87-6,92 (m, 2H), 7,39 (d, J = 9,0 Hz, 1H), 7,71 (d, J = 7,8 Hz, 2H), 7,92 (d, J = 7,8 Hz, 1H), 8,28 (br, 2H), 8,94 (br, 2H).

Ejemplo 546

Síntesis de diclorhidrato de N-(2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]-diazepin-7-iloxi)propil]piridin-4-ilmetilamino}etil)-N-metil-2-tiofen-2-il-acetamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 487, se sintetizó el compuesto

S69

objetivo.

Sólido blanco

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (s, 3H), 1,00 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,26 (br, 2H), 3,08 (s, 3H), 3,22 (br, 2H), 3,31 (s, 3H), 3,45-3,63 (m, 3H), 3,67-3,86 (m, 2H), 3,97 (s, 2H), 3,98-4,10 (m, 3H), 4,62 (br, 2H), 6,87-6,97 (m, 4H), 7,36-7,39 (m, 2H), 8,20 (br, 2H), 8,90 (br, 2H).

Ejemplo 547

Síntesis de diclorhidrato de N-(2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]-diazepin-7-iloxi)propil]piridin-4-ilmetilamino}etil)-N-metil-2-thiofen-3-ilacetamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 487, se sintetizó el compuesto objetivo.

Sólido blanco

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (s, 3H), 1,00 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,25 (br, 2H), 3,05 (s, 3H), 3,22 (br, 2H), 3,31 (s, 3H), 3,49-3,80 (m, 7H), 3,95-4,10 (m, 3H), 4,62 (br, 2H), 6,86-6,92 (m, 2H), 6,99-7,01 (m, 1H), 7,25 (br, 1H), 7,40 (d, J = 9,0 Hz, 1H), 7,44-7,46 (m, 1H), 8,21 (br, 2H), 8,91 (br, 2H).

Ejemplo 548

Síntesis de triclorhidrato de la (2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]-diazepin-7-iloxi)propil]piridin-4-ilmetilamino}etil)metil-amida del ácido tiazol-4-carboxílico

Usando un material de partida apropiado y siguiendo el

procedimiento del Ejemplo 487, se sintetizó el compuesto objetivo.

Sólido blanco

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (s, 3H), 1,00 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,31 (br, 2H), 3,17 (s, 3H), 3,23-3.40 (m, 2H), 3,31 (s, 3H), 3,61-3,80 (m, 3H), 3,95-4,11 (m, 5H), 4,66 (br, 2H), 6,89-6,92 (m, 2H), 7,40 (d, J = 9,0 Hz, 1H), 8,23-8,32 (m, 3H), 8,96 (br, 2H), 9,15-9,17 (m, 1H).

Ejemplo 549

Síntesis de triclorhidrato de la (2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]-diazepin-7-iloxi)propil]piridin-4-ilmetilamino}etil)metil-amida del ácido isoxazol-5-carboxílico

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 487, se sintetizó el compuesto objetivo.

Sólido blanco

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (s, 3H), 1,00 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,29 (br, 2H), 3,17 (s, 3H), 3,25 (br, 2H), 3,31 (s, 3H), 3,55-3,77 (m, 3H), 3,81-4,10 (m, 5H), 4,69 (br, 2H), 6,87-6,93 (m, 2H), 7,04 (d, J = 1,8 Hz, 1H), 7,40 (d, J = 9,0 Hz, 1H), 8,30 (br, 2H), 8,75-8,76 (m, 1H), 8,95 (br, 2H).

Ejemplo 550

Síntesis de triclorhidrato de la (2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]-diazepin-7-iloxi)propil]piridin-4-ilmetil-amino}etil)metil-amida del ácido 5-metil-isoxazol-3-carboxílico

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 487, se sintetizó el compuesto objetivo.

Sólido blanco

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (s, 3H), 1,00 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,27 (br, 2H), 2,46 (s, 3H), 3,11 (s, 3H), 3,21-3,47 (m, 2H), 3,32 (s, 3H), 3,50-3,95 (m, 5H), 4,00-4,13 (m, 3H), 4,67 (br, 2H), 6,50 (s, 1H), 6,87-6,93 (m, 2H), 7,40 (d, J = 9,0 Hz, 1H), 8,24 (br, 2H), 8,93 (br, 2H).

Ejemplo 551

Síntesis de 1-etil-3,3,5-trimetil-7-(3-{[2-(4-oxo-4H-furo-[3,2-c]piridin-5-il)etil]piridin-3-ilmetilamino}-propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

Polvo blanco

Punto de fusión 118 a 119°C

Ejemplo 552

Síntesis de diclorhidrato de 1-etil-3,3,5-trimetil-7-(3-{[2-(4-oxo-4H-furo[3,2-c]piridin-5-il)etil]piridin-3-ilmetilamino}-propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 6, se sintetizó el compuesto objetivo.

Amorfo blanco

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (3H, s), 1,01 (3H, t, J = 7,1 Hz), 1,32 (3H, s), 2,20-2,43 (2H, m), 3,08-3,40 (5H, m), 3,43-4,68 (10H, m), 6,82-6,94 (4H, m), 7,41 (1H, d, J = 8,9 Hz), 7,70-7,75 (2H, m), 7,92 (1H, d, J = 1,9 Hz), 8,36-8,48 (1H, m), 8,74-8,80 (1H, m), 8,94-9,02 (1H, m).

Ejemplo 553

Síntesis de 1-etil-3,3,5-trimetil-7-(3-{[2-(2-metil-4-oxo-4H-furo[3,2-c]piridin-5-il)etil]piridin-3-ilmetil-amino}-propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

Polvo blanco

^{1}H-NMR ($CDCl_3$) δppm:

0,86 (3H, s), 1,16 (3H, t, J = 7,1 Hz), 1,53 (3H, s), 1,88-1,93 (2H, m), 2,41 (3H, s), 2,70 (2H, t, J = 6,8 Hz), 2,86 (2H, t, J = 6,2 Hz), 3,39 (3H, s), 3,68-3,75 (3H, m), 3,86 (2H, t, J = 6,1 Hz), 4,07 (2H, t, J = 6,1 Hz) 4,14-4,21 (1H, m), 6,36 (1H, d, J = 7,3 Hz), 6,52 (1H, s), 6,62 (1H, s), 6,67 (1H, dd, J = 9,0, 2,8 Hz), 7,00 (1H, d, J = 7,4 Hz), 7,07 (1H, dd, J = 7,7, 4,9 Hz), 7,17 (1H, d, J = 9,0 Hz), 7,50 (1H, d, J = 7,8 Hz), 8,42 (1H, d, J = 4,8 Hz), 8,48 (1H, s).

Ejemplo 554

Síntesis de diclorhidrato de 1-etil-3,3,5-trimetil-7-(3-{[2-(2-oxo-2H-quinolin-1-il)etil]piridin-3-ilmetilamino}-propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7 y del Ejemplo 6, se sintetizó el

compuesto objetivo.

Amorfo blanco

^{1}H-NMR (DMSO-d_6) δppm:

0,74 (3H, s), 1,00 (3H, t, J = 7,0 Hz), 1,32 (3H, s), 2,18-2,39 (2H, m), 3,04-3,79 (7H, m), 3,99-4,28 (3H, m), 4,42-4,94 (5H, m), 6,66 (1H, d, J = 9,5 Hz), 6,78-6,97 (2H, m), 7,32 (1H, t, J = 7,4 Hz), 7,40 (1H, d, J = 8,9 Hz), 7,63 (1H, t, J = 7,2 Hz), 7,70-7,84 (3H, m), 8,00 (1H, d, J = 9,5 Hz), 8,39-8,52 (1H, m), 8,73-8,82 (1H, m), 8,99 (1H, s)

Ejemplo 555

Síntesis de diclorhidrato de 1-etil-3,3,5-trimetil-7-(3-{[2-(2-oxo-3,4-dihidro-2H-quinolin-1-il)etil]piridin-3-il-metilamino}-propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7 y del Ejemplo 6, se sintetizó el compuesto objetivo.

Amorfo blanco

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (3H, s), 1,00 (3H, t, J = 7,1 Hz), 1,32 (3H, s), 2,15-2,40 (2H, m), 2,57 (2H, t, J = 8,2 Hz), 2,89 (2H, t, J = 7,7 Hz), 3,08-3,96 (8H, m), 3,99-4,22 (3H, m), 4,29-4,51 (2H, m), 4,51-4,80 (2H, m), 6,86-6,94 (2H, m), 7,00-7,06 (1H, m), 7,20-7,32 (3H, m), 7,41 (1H, d, J = 8,9 Hz), 7,72-7,85 (1H, m), 8,46-8,60 (1H, m), 8,79-8,84 (1H, m), 9,04 (1H, s).

Ejemplo 556

Síntesis de 7-(3-{[2-(7-bromo-1-oxo-1H-isoquinolin-2-il)-etil]piridin-4-ilmetilamino}propoxi)-1-etil-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

Polvo amarillo pálido

Punto de fusión 146 a 147°C

Ejemplo 557

Síntesis de 1-etil-7-(3-{(2-hidroxi-piridin-4-ilmetil)-[2-(7-oxo-7H-furo[2,3-c]piridin-6-il)etil]amino}propoxi)3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

Polvo blanco

Punto de fusión 160,5 a 161,5°C

Ejemplo 558

Síntesis de triclorhidrato de 1-etil-3,3,5-trimetil-7-{3-[(2-metilpiridin-4-ilmetil)-(2-piridin-3-il-etil)amino]-propoxi}-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7 y del Ejemplo 6, se sintetizó el compuesto objetivo.

Amorfo blanco

^{1}H-NMR (DMSO-d_6) δppm:

0,74 (3H, s), 1,00 (3H, t, J = 7,0 Hz), 1,31 (3H, s), 1,68-2,48(2H,m), 2,64 (3H, s), 2,70-4,25 (6H, m), 3,30 (3H, s), 3,43 (2H, t, J = 7,0 Hz), 3,66 (1H, dq, J = 7,0 ,7,0Hz), 4,05 (1H, dq, J = 7,0, 7,0 Hz), 4,23-4,99 (2H, bs), 6,80-7,00 (2H, m), 7,40 (1H, d, J = 9,0 Hz), 7,48-8,23 (3H, m), 8,32 (1H, bs), 8,50-9,00 (1H, m), 8,74 (1H, d, J = 5,7 Hz), 8,80 (1H,

s), 12,00 (1H, bs).

Ejemplo 559

Síntesis de diclorhidrato de N-(2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]-diazepin-7-iloxi)propil]piridin-4-ilmetilamino}etil)-N-metil-4-trifluorometil-benzamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 487, se sintetizó el compuesto objetivo.

Amorfo incoloro

^{1}H-NMR (DMSO-d_6) δppm:

0,74 (s, 3H), 1,00 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,30 (br, 2H), 2,91 (s, 3H), 3,11-3,30 (m, 2H), 3,29 (s, 3H), 3,59-3,69 (m, 3H), 4,02 (br, 2H), 4,01-4,15 (m, 3H), 4,63 (br, 2H), 6,82-6,90 (m, 2H), 7,39 (d, J = 8,9 Hz, 1H), 7,55-8,02 (m, 6H), 8,81 (br, 2H).

Ejemplo 560

Síntesis de diclorhidrato de 3-ciano-N-(2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b]-[1,4]diazepin-7-iloxi)propil]piridin-4-ilmetilamino}etil)-N-metilbenzamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 487, se sintetizó el compuesto objetivo.

Amorfo incoloro

^{1}H-NMR (DMSO-d_6) δppm:

0,74 (s, 3H), 1,00 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,32 (br, 2H), 2,92 (s, 3H), 3,15-3,28 (m, 2H), 3,29 (s, 3H), 3,55-3,70 (m, 3H), 3,87 (br, 2H), 4,00-4,12 (m, 3H), 4,58

(br, 2H), 6,86-6,90 (m, 2H), 7,39 (d, J = 8,9 Hz, 1H), 7,63-7,68 (m, 1H), 7,73-8,14 (m, 5H), 8,84 (br, 2H).

Ejemplo 561

Síntesis de triclorhidrato de la (2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]-diazepin-7-iloxi)propil]piridin-4-ilmetilamino}etil)-metil-amida del ácido 1H-indazol-3-carboxílico

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 487, se sintetizó el compuesto objetivo.

Amorfo incoloro

^{1}H-NMR (DMSO-d_6) δppm:

0,73 (s, 3H), 0,99 (t, J = 7,0 Hz, 3H), 1,31 (s, 3H), 2,32 (br, 2H), 3,06 (br, 3H), 3,28 (br, 3H), 3,43 (br, 2H), 3,61-3,69 (m, 3H), 4,01-4,11 (m, 5H), 4,67 (br, 2H), 6,84-6,89 (m, 2H), 7,20-7,24 (m, 1H), 7,33-7,36 (m, 1H), 7,40-7,44 (m, 1H), 7,61-7,63 (m, 1H), 8,04 (br, 3H), 8,83 (br, 2H), 13,7 (br, 1H).

Ejemplo 562

Síntesis de diclorhidrato de la (2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetra-hidro-1H-benzo[b][1,4]-diazepin-7-iloxi)propil]piridin-4-ilmetilamino}etil)-metil-amida del ácido 1H-pirrol-3-carboxílico

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 487, se sintetizó el compuesto objetivo.

Amorfo incoloro

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (s, 3H), 1,00 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,26

(br, 2H), 3,10-3,25 (m, 5H), 3,31 (s, 3H), 3,57-3,69 (m, 3H), 3,87 (br, 2H), 4,02-4,08 (m, 3H), 4,60 (br, 2H), 6,15 (s, 1H), 6,63 (br, 1H), 6,83-6,94 (m, 3H), 7,39 (d, J = 8,9 Hz, 1H), 7,99 (br, 2H), 8,81 (br, 2H).

Ejemplo 563

Síntesis de triclorhidrato de la N-(2-{[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]-diazepin-7-iloxi)propil]piridin-4-ilmetilamino}etil)-N-metilnicotinamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 487, se sintetizó el compuesto objetivo.

Amorfo incoloro

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (s, 3H), 1,00 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,33 (br, 2H), 2,98 (s, 3H), 3,30 (s, 3H), 3,43 (br, 2H), 3,53-3,70 (m, 3H), 3,93-4,20 (m, 5H), 4,84 (br, 2H), 6,87-6,92 (m, 2H), 7,40 (d, J = 8,9 Hz, 1H), 7,78 (br, 1H), 8,28 (br, 3H), 8,80 (br, 1H), 8,94 (br, 3H).

Ejemplo 564

Síntesis de 1-etil-7-(3-{(2-hidroxipiridin-4-ilmetil)-[2-(1-oxo-1H-isoquinolin-2-il)etil]amino}propoxi)-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

Polvo blanco

Punto de fusión 155 a 156°C

Ejemplo 565

Síntesis de diclorhidrato de 1,3,3,5-Tetrametil-7-(3-{[2-(4-oxo-4H-furo[3,2-c]piridin-5-il)etil]piridin-4-ilmetil-amino}propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7 y del Ejemplo 6, se sintetizó el compuesto objetivo.

Sólido incoloro

Punto de fusión 149 a 153°C

^{1}H-NMR (DMSO-d_6) δppm:

0,76 (3H, s), 1,32 (3H, s), 1,73-2,42 (2H, m), 3,30 (3H, s), 3,32 (3H, s), 2,80-3,50 (4H, m), 3,83-4,81 (6H, m), 6,65-6,90 (3H, m), 6,94 (1H, d, J = 1,6 Hz), 7,35 (1H, d, J = 8,9 Hz), 7,71 (1H, d, J = 7,5 Hz), 7,91 (1H, d, J = 2,1 Hz), 7,95-8,35 (2H, m), 8,60-9,03 (2H, m).

Ejemplo 566

Síntesis de 1-etil-3,3,5-trimetil-7-(3-{[2-(2-metil-4-oxo-4H-furo[3,2-c]piridin-5-il)etil]pyrimidin-5-ilmetil-amino}-propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

Polvo blanco

Punto de fusión 154°C

Ejemplo 567

Síntesis de 1-etil-3,3,5-trimetil-7-{3-[[2-(2-metil-4-oxo-4H-furo[3,2-c]piridin-5-il)etil]-(2-metilpiridin-3-il-metil)amino]propoxi}-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el

procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

Polvo blanco

Punto de fusión 128 a 129°C

Ejemplo 568

Síntesis de 1-etil-3,3,5-trimetil-7-(3-{[2-(4-oxo-4H-tieno-[3,2-c]piridin-5-il)etil]piridin-3-ilmetilamino}-propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

Polvo blanco marfil

Punto de fusión 114°C

Ejemplo 569

Síntesis de diclorhidrato de 1-etil-3,3,5-trimetil-7-{3-[[2-(2-metil-4-oxo-4H-furo[3,2-c]piridin-5-il)etil]-(3-metilpiridin-4-ilmetil)amino]propoxi}-1,5-dihidrobenzo[b]-[1,4]-diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7 y del Ejemplo 6, se sintetizó el compuesto objetivo.

Amorfo blanco

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (3H, s), 1,02 (3H, t, J = 7,0 Hz), 1,32 (3H, s), 1,78-2,08 (2H, m), 2,27-2,46 (5H, m), 2,60-3,07 (3H, m), 3,31 (3H, s), 3,62-3,77 (2H, m), 3,79-5,39 (8H, m), 6,39-6,58 (1H, m), 6,58-6,74 (1H, m), 6,80-6,90 (2H, m), 7,39 (1H, d, J = 9,0 Hz), 7,45-7,59 (1H, m), 7,61-7,95 (1H, m), 8,30-8,61 (1H, m), 8,64-8,81 (1H, m).

Ejemplo 570

Síntesis de diclorhidrato de 1-etil-3,3,5-trimetil-7-{3-[[2-(2-metil-4-oxo-4H-furo[3,2-c]piridin-5-il)etil]-(2-metilpiridin-4-il-metil)amino]propoxi}-1,5-dihidrobenzo[b]-[1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7 y del Ejemplo 6, se sintetizó el compuesto objetivo.

Amorfo blanco

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (3H, s), 1,01 (3H, t, J = 7,0 Hz), 1,33 (3H, s), 2,03-2,38 (2H, m), 2,39 (3H, s), 2,55-2,78 (3H, m), 3,00-3,54 (5H, m), 3,62-3,71 (1H, m), 3,89-4,18 (5H, m), 4,26-4,64 (4H, m), 6,55 (1H, s), 6,67-6,76 (1H, m), 6,77-6,93 (2H, m), 7,39 (1H, d, J = 9,0 Hz), 7,58-7,64 (1H, m), 7,79-8,25 (2H, m), 8,60-8,78 (1H, m).

Ejemplo 571

Síntesis de diclorhidrato de 7-(3-{(5-chloro-piridin-2-ilmetil)-[2-(2-metil-4-oxo-4H-furo[3,2-c]piridin-5-il)-etil]amino}-propoxi)-1-etil-3,3,5-trimetil-1,5-dihidro-benzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7 y del Ejemplo 6, se sintetizó el compuesto objetivo.

Amorfo blanco

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (3H, s), 1,01 (3H, t, J = 7,1 Hz), 1,32 (3H, s), 2,20-2,32 (2H, m), 2,40 (3H, s), 3,31 (3H, s) 3,37-3,46 (2H, m), 3,49-3,58 (2H, m), 3,60-3,71 (1H, m), 3,99-4,69 (7H, m), 6,56

(1H, s), 6,78 (1H, d, J = 7,4 Hz), 6,86-6,90 (2H, m), 7,38-7,43 (1H, m), 7,64 (1H, d, J = 7,3 Hz), 7,68-7,73 (1H, m) 8,04-8,09 (1H, m), 8,54 (1H, s).

Ejemplo 572

Síntesis de 1-etil-7-(3-{(6-methoxi-piridin-3-ilmetil)-[2-(2-metil-4-oxo-4H-furo[3,2-c]piridin-5-il)etil]amino}-propoxi)-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

Polvo blanco

Punto de fusión 114 a 116°C

Ejemplo 573

Síntesis de 1-etil-3,3,5-trimetil-7-{3-[[2-(2-metil-4-oxo-4H-furo[3,2-c]piridin-5-il)etil]-(4-metilpiridin-3-il-metil)amino]propoxi}-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

Polvo blanco

Punto de fusión 147 a 148°C

Ejemplo 574

Síntesis de 1-etil-7-(3-{(6-methoxi-piridin-3-ilmetil)-[2-(4-oxo-4H-furo[3,2-c]piridin-5-il)etil]amino}propoxi)-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, el se sintetizó el compuesto objetivo.

Polvo blanco

Punto de fusión 111 a 113°C

Ejemplo 575

Síntesis de 1-etil-3,3,5-trimetil-7-(3-{(2-metilpiridin-3-ilmetil)-[2-(4-oxo-4H-furo[3,2-c]piridin-5-il)etil]-amino}-propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

Polvo blanco

Punto de fusión 111 a 114°C

Ejemplo 576

Síntesis de 1-etil-3,3,5-trimetil-7-(3-{[2-(1-oxo-1H-isoquinolin-2-il)etil]piridin-2-ilmetilamino}propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

Sólido blanco

Punto de fusión 94,6 a 95,4°C

Ejemplo 577

Síntesis de triclorhidrato de 1-etil-3,3,5-trimetil-7-{3-[(2-piridin-3-il-etil)-quinolin-4-ilmetilamino]propoxi}-1,5-dihidrobenzo[b]-[1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7 y del Ejemplo 6, se sintetizó el compuesto objetivo.

Polvo blanco

Punto de fusión 139 a 143°C

Ejemplo 578

Síntesis de 1-etil-3,3,5-trimetil-7-(3-{(4-metilpiridin-3-ilmetil)-[2-(7-oxo-7H-furo[2,3-c]piridin-6-il)etil]-amino}propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

Polvo blanco

Punto de fusión 123 a 124°C

Ejemplo 579

Síntesis de diclorhidrato de 1-etil-3,3,5-trimetil-7-{3-[[2-(4-oxo-4H-furo-[3,2-c]piridin-5-il)etil]-(2-piridin-3-il-etil)amino]-propoxi}-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7 y del Ejemplo 6, se sintetizó el compuesto objetivo.

Amorfo blanco

^{1}H-NMR (D_2O) δppm:

0,64 (3H, s), 0,96 (3H, t, J = 7,0 Hz), 1,29 (3H, s), 2,21 (2H, quin, J = 2,8 Hz), 3,25 (3H, s), 3,27-3,35 (2H, m), 3,55 (2H, t, J = 7,0 Hz), 3,57-3,69 (3H, m), 3,71 (2H, t, J = 5,4 Hz), 4,02 (1H, dq, J = 7,0, 7,0 Hz), 4,12 (2H, t, J = 5,4 Hz), 4,38-4,53 (2H,m), 6,75 (1H, s), 6,81-6,93(3H, m), 7,33 (1H, d, J = 9,0 Hz), 7,50 (1H, d, 7,5Hz), 7,58-7,65 (1H, m), 7,77-7,90 (1H, m), 8,30-8,40 (1H, m), 8,57 (1H, d, J = 5,6 Hz), 8,61 (1H, s).

Ejemplo 580

Síntesis de clorhidrato de 1-etil-7-(3-{(4-methoxi-benzil)-

[2-(4-oxo-4H-furo[3,2-c]piridin-5-il)etil]amino}propoxi)-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7 y del Ejemplo 6, se sintetizó el compuesto objetivo.

Polvo blanco

Punto de fusión 116,3 a 120°C (desc.)

Ejemplo 581

Síntesis de 1-etil-3,3,5-trimetil-7-(3-{(6-metilpiridin-3-ilmetil)-[2-(7-oxo-7H-furo[2,3-c]piridin-6-il)etil]amino}-propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

Polvo blanco

Punto de fusión 120 a 122°C

Ejemplo 582

Síntesis de 1-etil-3,3,5-trimetil-7-{3-[[2-(2-metil-4-oxo-4H-furo[3,2-c]piridin-5-il)etil]-(6-metilpiridin-3-il-metil)-amino]propoxi}-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

Polvo blanco

Punto de fusión 136 a 138°C

Ejemplo 583

Síntesis de 1-etil-3,3,5-trimetil-7-(3-{(6-metilpiridin-3-ilmetil)-[2-(4-oxo-4H-furo[3,2-c]piridin-5-il)etil]-amino}-propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

Polvo blanco

^{1}H-NMR ($CDCl_3$) δppm:

0,86 (3H, s), 1,15 (3H, t, J = 7,1 Hz), 1,53 (3H, s), 1,86-1,95 (2H, m), 2,48 (3H, s), 2,70 (2H, t, J = 6,8 Hz), 2,85 (2H, t, J = 6,2 Hz), 3,39 (3H, s), 3,63 (2H, s), 3,65-3,75 (1H, m), 3,86 (2H, t, J = 6,1 Hz), 4,06 (2H, t, J = 6,1 Hz), 4,14-4,22 (1H, m), 6,41 (1H, dd, J = 7,4, 0,8 Hz), 6,62 (1H, d, J = 2,7 Hz), 6,67 (1H, dd, J = 9,0, 2,4 Hz), 6,90-6,95 (2H, m), 7,07 (1H, d, J = 7,4 Hz), 7,18 (1H, d, J = 8,9 Hz), 7,35-7,42 (1H, m), 7,47 (1H, d, J = 2,1 Hz), 8,31 (1H, d, J = 1,8Hz).

Ejemplo 584

Síntesis de triclorhidrato de 1-etil-3,3,5-trimetil-7-{3-[(2-piridin-3-il-etil)-quinolin-5-ilmetilamino]propoxi}-1,5-dihidrobenzo-[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7 y del Ejemplo 6, se sintetizó el compuesto objetivo.

Amorfo blanco amarillo pálido

^{1}H-NMR (D_2O) δppm:

0,66 (3H, s), 0,97 (3H, t, J = 7,1 Hz), 1,30 (3H, s), 2,12-2,37 (2H,m), 3,25 (3H, s), 3,36-3,57 (4H, m), 3,57-3,74 (3H, m), 3,93-4,10 (3H, m), 5,08 (2H, s), 6,69 (1H, dd, J = 9,0 y 2,8 Hz), 6,71 (1H, d, J = 2,8 Hz), 7,30 (1H, d, J = 9,0Hz), 7,93 (1H, dd, J = 8,0 y 5,8 Hz), 7,98-8,13(3H, m), 8,23 (1H, d, J = 8,3 Hz), 8,43(1H, d, J = 8,3 Hz), 8,63 (1H, d, J = 5,7

Hz), 8,67 (1H, s), 9,04-9,13 (1H, m), 9,23 (1H, d, J = 8,7 Hz).

Ejemplo 585

Síntesis de diclorhidrato de 5-etil-1,3,3-trimetil-7-(3-{[2-(1-oxo-5,6,7,8-tetrahidro-1H-isoquinolin-2-il)etil]-piridin-4-ilmetil-amino}propoxi)-1,5-dihidrobenzo[b][1,4]-diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

Polvo blanco

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (3H, s), 1,01 (3H, t, J = 7,0 Hz), 1,32 (3H, s), 1,49-1,74 (4H, m), 2,03-2,40 (4H, m), 2,90-3,41(4H, m), 3,32 (3H, s), 3,56-4,84 (10H, m), 6,02 (1H, d, J = 6,8 Hz), 6,79-7,00 (2H, m), 7,31-7,57 (2H, m), 7,93-8,25 (2H, m), 8,68-9,08 (2H, m).

Ejemplo 586

Síntesis de 1-etil-3,3,5-trimetil-7-(3-{(2-metil-2H-pirazol-3-ilmetil)-[2-(1-oxo-1H-isoquinolin-2-il)etil]-amino}propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

Polvo blanco

Punto de fusión 96 a 99°C

Ejemplo 587

Síntesis de diclorhidrato de 7-{3-[benzotiazol-2-ilmetil-(2-piridin-3-il-etil)amino]propoxi}-1-etil-3,3,5-trimetil-1,5-

dihidro-benzo-[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7 y del Ejemplo 6, se sintetizó el compuesto objetivo.

Amorfo blanco

^{1}H-NMR (D_2O) δppm:

0,60 (3H, s), 0,95 (3H, t, J = 7,1 Hz), 1,28 (3H, s), 2,06-2,37 (2H,m), 3,07 (3H, s), 3,34-3,43 (2H, m), 3,47-3,56 (2H, m), 3,59 (1H, dq, J = 7,0, 7,0 Hz), 3,63-3,73 (2H, m), 3,98 (1H, dq, J = 7,0, 7,0 Hz), 4,03-4,16 (2H,m), 4,85 (1H, d, J = 15,2 Hz), 4,89 (1H, d, J = 15,2 Hz), 6,51 (1H, d, J = 2,8 Hz), 6,71 (1H, dd, J = 9,1 y 2,8 Hz), 7,20 (1H, d, J = 9,1 Hz), 7,38-7,53 (2H,m), 7,83(1H, d, J = 8,0 Hz), 7,87 (1H, dd, J = 8,0 y 5 8 Hz), 7,91 (1H, d, J = 8,0 Hz), 8,43 (1H, d, J = 8,0 Hz), 8,56 (1H, d, J = 5,8 Hz), 8 66 (1H, s).

Ejemplo 588

Síntesis de 1-etil-3,3,5-trimetil-7-(3-{(5-metilpiridin-3-ilmetil)-[2-(7-oxo-7H-furo[2,3-c]piridin-6-il)etil]-amino}-propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

Polvo blanco

Punto de fusión 130 a 131°C

Ejemplo 589

Síntesis de 1-etil-3,3,5-trimetil-7-{3-[[2-(2-metil-4-oxo-4H-furo[3,2-c]piridin-5-il)etil]-(5-metilpiridin-3-il-metil)amino]propoxi}-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

Polvo blanco

Punto de fusión 125 a 127°C

Ejemplo 590

Síntesis de 1-etil-3,3,5-trimetil-7-(3-{(4-metilpiridin-3-ilmetil)-[2-(4-oxo-4H-furo[3,2-c]piridin-5-il)etil]-amino}-propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

Polvo blanco

^{1}H-NMR ($CDCl_3$) δppm:

0,86 (3H, s), 1,15 (3H, t, J = 7,0 Hz), 1,53 (3H, s), 1,91-2,01 (2H, m), 2,25 (3H, s), 2,76 (2H, t, J = 6,8 Hz), 2,87 (2H, t, J = 6,5 Hz), 3,39 (3H, s), 3,65-3,74 (3H, m), 3,91 (2H, t, J = 6,2 Hz), 4,02 (2H, t, J = 6,4 Hz) 4,11-4,22 (1H, m), 6,41 (1H, d, J = 7,3 Hz), 6,65 (1H, d, J = 2,6 Hz), 6,70 (1H, dd, J = 8,9, 2,7 Hz), 6,91-6,97 (3H, m), 7,17 (1H, d, J = 9,0 Hz), 7,47 (1H, d, J = 2,0 Hz), 8,32 (1H, d, J = 4,8 Hz), 8,40 (1H, s).

Ejemplo 591

Síntesis de 1-etil-3,3,5-trimetil-7-(3-{(2-metilpiridin-3-ilmetil)-[2-(7-oxo-7H-tieno[2,3-c]piridin-6-il)etil]-amino}propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

Polvo blanco

Punto de fusión 115 a 117°C

Ejemplo 592

Síntesis de triclorhidrato de 7-{3-[(2,5-dimetil-2H-pirazol-3-ilmetil)-(2-piridin-3-iletil)amino]propoxi}-1-etil-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7 y del Ejemplo 6, se sintetizó el compuesto objetivo.

Amorfo blanco

^{1}H-NMR (D_2O) δppm:

0,70 (3H, s), 0,97 (3H, t, J = 7,0 Hz), 1,30 (3H, s), 2,06 (3H, s), 2,13-2,30 (2H, m), 3,29 (3H, s), 3,30-3,37 (2H, m), 3,37-3,48 (2H, m), 3,48-3,68 (3H, m), 3,73 (3H, s), 4,03 (1H, dq, J = 7,0, 7,0 Hz), 4,09 (2H, t, J = 5,4 Hz), 4,53 (2H, s), 6,30 (1H, s), 6,84 (1H, d, J = 2,7 Hz), 6,87 (1H, dd, J = 9,0 y 2,7 Hz), 7,36 (1H, d, J = 9,0 Hz), 7,95 (1H, dd, J = 8,0 y 5,9 Hz)), 8,44 (1H, d, J = 8,0 Hz), 8,64 (1H, d, J = 5,9 Hz), 8,66 (1H, s).

Ejemplo 593

Síntesis de diclorhidrato de 1-etil-3,3,5-trimetil-7-{3-[(4-metil-tiazol-5-ilmetil)-(2-piridin-3-il-etil)amino]-propoxi}-1,5-dihidro-benzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7 y del Ejemplo 6, se sintetizó el compuesto objetivo.

Polvo blanco

Punto de fusión 175 a 185°C

Ejemplo 594

590

Síntesis de 1-etil-3,3,5-trimetil-7-(3-{(5-metilpiridin-3-ilmetil)-[2-(4-oxo-4H-furo[3,2-c]piridin-5-il)etil]-amino}-propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

Polvo blanco

Punto de fusión 128 a 129°C

Ejemplo 595

Síntesis de 1-etil-3,3,5-trimetil-7-(3-{(2-metilpiridin-3-ilmetil)-[2-(4-oxo-4H-tieno[3,2-c]piridin-5-il)etil]-amino}-propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

Polvo blanco

Punto de fusión 95 a 98°C

Ejemplo 596

Síntesis de 1-etil-3,3,5-trimetil-7-{3-[[2-(2-metil-4-oxo-4H-furo[3,2-c]piridin-5-il)etil]-(2-metil-2H-pirazol-3-il-metil)amino]propoxi}-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

Polvo blanco

Punto de fusión 119 a 121°C

Ejemplo 597

Síntesis de diclorhidrato de 7-(3-{(1,5-dimetil-1H-pirazol-4-

ilmetil)-[2-(1-oxo-1H-isoquinolin-2-il)etil]amino}-propoxi)-1-etil-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]-diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7 y del Ejemplo 6, se sintetizó el compuesto objetivo.

Amorfo blanco

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (3H, s), 1,01 (3H, t, J = 7,2 Hz), 1,32 (3H, s), 2,22-2,38 (5H, m), 3,20-3,41 (5H, m), 3,41-3,49 (2H, m), 3,72 (3H, s), 4,04-4,17 (4H, m), 4,26-4,38 (2H, m), 4,40-4,47 (2H, m), 6,74 (1H, d, J = 7,4 Hz), 6,88-6,95 (2H, m), 7,42 (1H, d, J = 8,9 Hz), 7,51-7,56 (2H, m), 7,62 (1H, s), 7,66-7,78 (2H, m), 8,24 (1H, d, J = 8,0 Hz).

Ejemplo 598

Síntesis de 1-etil-3,3,5-trimetil-7-(3-{(6-metilpiridin-3-ilmetil)-[2-(1-oxo-1H-isoquinolin-2-il)etil]amino}propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

Polvo blanco

Punto de fusión 140 a 142°C

Ejemplo 599

Síntesis de 1-etil-3,3,5-trimetil-7-(3-{(6-metilpiridin-3-ilmetil)-[2-(4-oxo-4H-tieno[3,2-c]piridin-5-il)etil]amino}-propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto

objetivo.

Polvo blanco

Punto de fusión 126 a 129°C

Ejemplo 600

Síntesis de 1-etil-3,3,5-trimetil-7-(3-{(6-metilpiridin-3-ilmetil)-[2-(7-oxo-7H-tieno[2,3-c]piridin-6-il)etil]amino}propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

Polvo blanco

Punto de fusión 120 a 122°C

Ejemplo 601

Síntesis de 1-etil-3,3,5-trimetil-7-(3-{(2-metilpiridin-3-ilmetil)-[2-(1-oxo-1H-isoquinolin-2-il)etil]amino}propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

Polvo blanco

Punto de fusión 98 a 102°C

Ejemplo 602

Síntesis de 1-etil-3,3,5-trimetil-7-(3-{[2-(2-metil-4-oxo-4H-furo[3,2-c]piridin-5-il)etil]tiazol-2-ilmetil-amino}-propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

Polvo blanco

Punto de fusión 175 a 176°C

Ejemplo 603

Síntesis de 1-etil-3,3,5-trimetil-7-(3-{[2-(2-metil-4-oxo-4H-furo[3,2-c]piridin-5-il)etil]oxazol-2-ilmetil-amino}-propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

Polvo blanco

Punto de fusión 130 a 131°C

Ejemplo 604

Síntesis de 1-etil-3,3,5-trimetil-7-(3-{[2-(2-metil-4-oxo-4H-furo[3,2-c]piridin-5-il)etil]tiazol-5-ilmetil-amino}-propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

Polvo blanco

Punto de fusión 181 a 183°C

Ejemplo 605

Síntesis de 1-etil-3,3,5-trimetil-7-(3-{[2-(2-metil-4-oxo-4H-furo[3,2-c]piridin-5-il)etil]oxazol-5-ilmetil-amino}-propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

Polvo blanco

^{1}H-NMR ($CDCl_3$) δppm:

0,86 (3H, s), 1,15 (3H, t, J = 7,0 Hz), 1,53 (3H, s), 1,83-

1,90 (2H, m), 2,40 (3H, s), 2,65-2,75 (2H, m), 2,83-2,92 (2H, m), 3,40 (3H, s), 3,65-3,72 (1H, m), 3,79 (2H, s), 3,82-3,88 (2H, m) 4,03-4,08 (2H, m), 4,10-4,22 (1H, m), 6,35 (1H, d, J = 7.3 Hz), 6,54 (1H, s), 6,63-6,73 (2H, m), 6,92 (1H, s), 7,09 (1H, d, J = 7,4 Hz), 7,18 (1H, d, J = 8,9 Hz), 7,74 (1H, s).

Ejemplo 606

Síntesis de 1-etil-3,3,5-trimetil-7-(3-{[2-(2-metil-4-oxo-4H-furo[3,2-c]piridin-5-il)etil]thiazol-4-ilmetil-amino}-propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

Polvo blanco

Punto de fusión 136 a 137°C

Ejemplo 607

Síntesis de 1-etil-3,3,5-trimetil-7-(3-{[2-(2-metil-4-oxo-4H-furo[3,2-c]piridin-5-il)etil]oxazol-4-ilmetil-amino}-propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

Polvo blanco

Punto de fusión 119 a 120°C

Ejemplo 608

Síntesis de diclorhidrato de 1-etil-7-(3-{(2-etilpiridin-3-ilmetil)-[2-(4-oxo-4H-furo[3,2-c]piridin-5-il)etil]amino}-propoxi)-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

595

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7 y del Ejemplo 6, se sintetizó el compuesto objetivo.

Amorfo blanco

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (3H, s), 1,01 (3H, t, J = 7,0 Hz), 1,15-1,31 (3H, m), 1,33 (3H, s), 1,75-2,41 (2H, m), 2,93-3,26 (3H, m), 3,31 (3H, s), 3,54-4,93 (11H, m), 6,58-7,03 (4H, m), 7,39 (1H, d, J = 8,9 Hz), 7,46-7,85 (2H, m), 7,90 (1H, s), 8,42-8,92 (2H, m).

Ejemplo 609

Síntesis de diclorhidrato de 1-etil-7-(3-{(2-etilpiridin-3-ilmetil)-[2-(2-metil-4-oxo-4H-furo[3,2-c]piridin-5-il)-etil]amino}-propoxi)-3,3,5-trimetil-1,5-dihidrobenzo[b]-[1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7 y del Ejemplo 6, se sintetizó el compuesto objetivo.

Amorfo blanco

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (3H, s), 1,01 (3H, t, J = 7,0 Hz), 1,15-1,31 (3H, m), 1,32 (3H, s), 1,82-2,00 (2H, m), 2,39 (3H, s), 2,63-2,92 (2H, m), 2,93-3,20 (2H, m), 3,31 (3H, s), 3,51-4,88 (10H, m), 6,38-6,53 (2H, m), 6,54-6,92 (2H, m), 7,39 (1H, d, J = 9,0 Hz), 7,40-7,77 (2H, m), 8,09-8,80 (2H, m).

Ejemplo 610

Síntesis de diclorhidrato de 1-etil-3,3,5-trimetil-7-{3-[[2-(4-oxo-4H-furo[3,2-c]piridin-5-il)etil]-(2-propil-piridin-3-ilmetil)-amino]propoxi}-1,5-dihidrobenzo[b][1,4]-diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7 y del Ejemplo 6, se sintetizó el compuesto objetivo.

Amorfo blanco

^{1}H-NMR (DMSO-d_6) δppm:

0,76 (3H, s), 0,90 (3H, t, J = 6,7 Hz), 1,02 (3H, t, J = 7,0 Hz), 1,33 (3H, s), 1,51-1,72 (2H, m), 1,73-2,00 (2H, m), 2,61-3,12 (4H, m), 3,31 (3H, s), 3,33-4,10 (10H, m), 6,55-7,03 (4H, m), 7,39 (1H, d, J = 9,0 Hz), 7,43-7,68 (2H, m), 7,85-7,95 (1H, m), 8,10-8,78 (2H, m).

Ejemplo 611

Síntesis de diclorhidrato 1-etil-3,3,5-trimetil-7-{3-[[2-(2-metil-4-oxo-4H-furo[3,2-c]piridin-5-il)etil]-(2-propil-piridin-3-ilmetil)amino]propoxi}-1,5-dihidrobenzo[b][1,4]-diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7 y del Ejemplo 6, se sintetizó el compuesto objetivo.

Amorfo blanco

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (3H, s), 0,91 (3H, t, J = 7,1 Hz), 1,02 (3H, t, J = 7,0 Hz), 1,33 (3H, s), 1,55-1,76 (2H, m), 2,39 (3H, s), 2,51-2,88 (2H, m), 2,90-3,19 (2H, m), 3,31 (3H, s), 3,55-4,81 (12H, m), 6,42-6,70 (2H, m), 6,78-6,92 (2H, m), 7,39 (1H, d, J = 8,9 Hz), 7,43-7,88 (2H, m), 7,92-8,89 (2H, m).

Ejemplo 612

Síntesis de diclorhidrato de 1-etil-3,3,5-trimetil-7-{3-[(2-piridin-3-il-etil)tiazol-5-ilmetilamino]propoxi}-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7 y del Ejemplo 6, se sintetizó el compuesto objetivo.

Polvo blanco

Punto de fusión 163 a 166°C

Ejemplo 613

Síntesis de diclorhidrato de 7-{3-[(2,5-dimetil-oxazol-4-ilmetil)-(2-piridin-3-il-etil)amino]propoxi}-1-etil-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7 y del Ejemplo 6, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,74 (3H, s), 0,99 (3H, t, J = 7,0 Hz), 1,31 (3H, s), 2,20-2,30(2H,m), 2,36 (3H, s), 2,38 (3H, s), 2,70-3,85 (6H, m), 3,31 (3H, s), 3,66 (1H, dq, J = 7,0, 7,0 Hz), 4,05 (1H, dq, J = 7,0, 7,0 Hz), 4,12 (2H, t, J = 6,0 Hz), 4,33 (2H, bs), 6,92 (1H, dd, J = 8,9 y 2,8 Hz), 6,94 (1H, d, J = 2,8 Hz), 7,42 (1H, d, J = 8,9 Hz), 7,71 (1H, bs), 8,13 (1H, bs), 8,61-8,70 (1H, m), 8,72 (1H, s), 10,60(1H, bs).

Ejemplo 614

Síntesis de diclorhidrato de N-(2-{[[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]-diazepin-7-iloxi)propil]-(2-piridin-3-il-etil)amino]metil}-fenil)metanosulfonamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7 y del Ejemplo 6, se sintetizó el compuesto objetivo.

Amorfo blanco

^{1}H-NMR (DMSO-d_6) δppm:

0,73 (3H, s), 0,99 (3H, t, J = 7,0 Hz), 1,30 (3H, s), 2,2-2,35 (2H,m), 3,04 (3H, s), 3,05-3,95 (6H, m), 3,30 (3H, s), 3,65 (1H, dq, J = 7,0, 7,0 Hz), 4,04 (1H, dq, J = 7,0, 7,0 Hz), 4,04-4,20 (2H, m), 4,59 (2H, bs), 6,82-6,95 (2H, m), 7,33-7,50 (3H, m), 7,50-7,60 (1H, m), 7,60-7,75 (1H, m), 7,84 (1H, d, J = 6,8 Hz), 7,96-8,16 (1H, m), 8,57-8,70 (1H, m), 8,68 (1H, bs)), 10,37 (1H, bs).

Ejemplo 615

Síntesis de diclorhidrato de 1-etil-3,3,5-trimetil-7-(4-{(2-metilpiridin-3-ilmetil)-[2-(4-oxo-4H-furo[3,2-c]-piridin-5-il)etil]-amino}butoxi)-1,5-dihidrobenzo[b][1,4]-diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7 y del Ejemplo 6, se sintetizó el compuesto objetivo.

Amorfo blanco

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (3H, s), 1,01 (3H, t, J = 7,1 Hz), 1,32 (3H, s), 1,62-2,14 (4H, m), 2,39 (3H, s), 2,50-2,53 (3H, m), 2,73-3,08 (4H, m), 3,14-4,85 (11H, m), 6,70-6,85 (1H, m), 6,86-7,02 (3H, m), 7,40 (1H, d, J = 8,9 Hz), 7,67-7,99 (3H, m), 8,51-9,03 (2H, m).

Ejemplo 616

Síntesis de diclorhidrato de 1-etil-3,3,5-trimetil-7-{4-[[2-(2-metil-4-oxo-4H-furo[3,2-c]piridin-5-il)etil]-(2-metilpiridin-3-ilmetil)amino]butoxi}-1,5-dihidrobenzo[b]-[1,4]-diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el

procedimiento del Ejemplo 7 y del Ejemplo 6, se sintetizó el compuesto objetivo.

Amorfo blanco

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (3H, s), 1,01 (3H, t, J = 7,0 Hz), 1,32 (3H, s), 1,53-2,15 (4H, m), 2,39 (3H, s), 2,42-2,96 (7H, m), 3,26-4,88 (11H, m), 6,41-6,63 (1H, m), 6,65-6,84 (1H, m), 6,87-6,95 (2H, m), 7,40 (1H, d, J = 8,8 Hz), 7,52-7,89 (2H, m), 8,46-8,88 (2H, m).

Ejemplo 617

Síntesis de diclorhidrato de 1-etil-3,3,5-trimetil-7-(4-{(2-metilpiridin-3-ilmetil)-[2-(1-oxo-1H-isoquinolin-2-il)-etil]amino}-butoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7 y del Ejemplo 6, se sintetizó el compuesto objetivo.

Amorfo blanco

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (3H, s), 1,01 (3H, t, J = 7,1 Hz), 1,32 (3H, s), 1,60-2,14 (4H, m), 2,47-3,08 (7H, m), 3,16-4,77 (11H, m), 6,58-6,80 (1H, m), 6,83-7,00 (2H, m), 7,39 (1H, d, J = 8,9 Hz), 7,43-7,62 (2H, m), 7,63-7,99 (3H, m), 8,12-8,30 (1H, m), 8,55-9,02 (2H, m).

Ejemplo 618

Síntesis de diclorhidrato de 1-etil-3,3,5-trimetil-7-(4-{[2-(4-oxo-4H-furo-[3,2-c]piridin-5-il)etil]piridin-4-il-metilamino}-butoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7 y del Ejemplo 6, se sintetizó el compuesto objetivo.

Amorfo blanco

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (3H, s), 1,01 (3H, t, J = 7,1 Hz), 1,32 (3H, s), 1,42-1,91 (4H, m), 3,31 (3H, s), 3,33-4,71 (12H, m), 6,63-6,98 (4H, m), 7,39 (1H, d, J = 8,7 Hz), 7,61-7,70 (1H, m), 7,77-7,94 (3H, m), 8,66-8,82 (2H, m).

Ejemplo 619

Síntesis de diclorhidrato de 1-etil-3,3,5-trimetil-7-(4-{[2-(2-metil-4-oxo-4H-furo[3,2-c]piridin-5-il)etil]piridin-4-ilmetilamino}-butoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7 y del Ejemplo 6, se sintetizó el compuesto objetivo.

Amorfo blanco

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (3H, s), 1,01 (3H, t, J = 7,1 Hz), 1,31 (3H, s), 1,57-1,99 (4H, m), 2,49 (3H, s), 3,08-4,62 (15H, s), 6,53-6,58 (1H, m), 6,69-6,76 (1H, m), 6,86-6,94 (2H, m), 7,39 (1H, d, J = 8,8 Hz), 7,58-7,65 (1H, m), 7,83-8,13 (2H, m), 8,72-8,89 (2H, m).

Ejemplo 620

Síntesis de diclorhidrato de 1-etil-3,3,5-trimetil-7-(4-{[2-(1-oxo-1H-isoquinolin-2-il)etil]piridin-4-ilmetil-amino}-butoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el

procedimiento del Ejemplo 7 y del Ejemplo 6, se sintetizó el compuesto objetivo.

Amorfo blanco

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (3H, s), 1,01 (3H, t, J = 7,1 Hz), 1,32 (3H, s), 1,60-1,99 (4H, m), 3,07-4,70 (15H, m), 6,69 (1H, d, J = 7,3 Hz), 6,83-6,98 (2H, m), 7,39 (1H, d, J = 8,8 Hz) 7,48-7,55 (2H, m), 7,65-7,76 (2H, m), 7,82-8,12 (2H, m), 8,20 (1H, d, J = 7,9 Hz), 8,70-8,93 (2H, m).

Ejemplo 621

Síntesis de diclorhidrato de 7-(3-{(2-chloro-piridin-3-ilmetil)-[2-(2-metil-4-oxo-4H-furo[3,2-c]piridin-5-il)-etil]amino}-propoxi)-1-etil-3,3,5-trimetil-1,5-dihidro-benzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7 y del Ejemplo 6, se sintetizó el compuesto objetivo.

Amorfo blanco

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (3H, s), 1,01 (3H, t, J = 7,0 Hz), 1,32 (3H, s), 2,08-2,33 (2H, m), 2,39 (3H, s), 3,17-4,85 (15H, m), 6,57 (1H, s), 6,70-6,94 (3H, m), 7,40 (1H, d, J = 9,0 Hz) 7,42-7,74 (2H, m), 8,21-8,57 (2H, m).

Ejemplo 622

Síntesis de 1-etil-3,3,5-trimetil-7-(3-{[2-(2-metil-4-oxo-4H-tieno[3,2-c]piridin-5-il)etil]piridin-4-ilmetil-amino}-propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

^{1}H-NMR ($CDCl_3$) δppm:

0,87 (s, 3H), 1,16 (t, J = 7,1 Hz, 3H), 1,53 (s, 3H), 1,81-

602

1,94 (m, 2H), 2,56 (s, 3H), 2,72 (t, J = 6,2 Hz, 2H), 2,83-2,90 (m, 2H), 3,38 (s, 3H), 3,67 (s, 2H), 3,66-3,78 (m, 1H), 3,88 (t, J = 6,1 Hz, 2H), 4,08-4,23 (m, 3H), 6,48 (d, J = 7,1 Hz, 1H), 6,53-6,62 (m, 3H), 6,96 (d, J = 7,1 Hz, 1H), 7,07-7,08 (m, 2H), 7,19 (d, J = 8,9 Hz, 1H), 8,28-8,32 (m, 2H).

Ejemplo 623

Síntesis de diclorhidrato de 1-etil-3,3,5-trimetil-7-(3-{[2-(3-metil-4-oxo-4H-furo[3,2-c]piridin-5-il)etil]piridin-4-ilmetil-amino}-propoxi)-1,5-dihidrobenzo[b][1,4]-diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (s, 3H), 1,01 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,08 (br, 2H), 2,22 (s, 3H), 3,20-3,40 (m, 2H), 3,30 (s, 3H), 3,53-3,70 (m, 3H), 3,89-4,13 (m, 5H), 4,24 (br, 2H), 6,67 (br, 1H), 6,70-6,83 (m, 2H), 7,38 (d, J = 9,0 Hz, 1H), 7,62 (br, 2H), 7,89 (br, 2H), 8,71 (br, 2H).

Ejemplo 624

Síntesis de diclorhidrato de 1-etil-3,3,5-trimetil-7-(3-{[2-(4-metil-7-oxo-7H-furo[2,3-c]piridin-6-il)etil]piridin-4-ilmetil-amino}propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (s, 3H), 1,01 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,10

(br, 2H), 2,17 (s, 3H), 3,20-3,39 (m, 2H), 3,30 (s, 3H), 3,61-3,72 (m, 3H), 3,83-4,11 (m, 5H), 4,16 (br, 2H), 6,77 (br, 1H), 6,85 (br, 1H), 6,96 (s, 1H), 7,31 (br, 1H), 7,38 (d, J = 9,0 Hz, 1H), 7,80 (br, 2H), 8,14 (s, 1H), 8,68 (br, 2H).

Ejemplo 625

Síntesis de diclorhidrato de 7-(3-{(2-butilpiridin-3-ilmetil)-[2-(2-metil-4-oxo-4H-furo[3,2-c]piridin-5-il)-etil]amino}propoxi)-1-etil-3,3,5-trimetil-1,5-dihidrobenzo-[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7 y del Ejemplo 6, se sintetizó el compuesto objetivo.

Amorfo blanco

^{1}H-NMR (DMSO-d_6) δppm:

0,76 (3H, s), 0,86 (3H, t, J = 7,3 Hz), 1,02 (3H, t, J = 7,0 Hz), 1,21-1,40 (5H, m), 1,47-1,67 (2H, m), 1,83-2,06 (2H, m), 2,39 (3H, s), 2,60-3,01 (6H, m), 3,17 (3H, s), 3,22-4,19 (8H, m) 6,35-6,67 (2H, m), 6,69-6,92 (2H, m), 7,39 (1H, d, J = 8,9 Hz) 7,42-7,71 (2H, m), 8,17-8,42 (1H, m), 8,53-8,65 (1H, m).

Ejemplo 626

Síntesis de diclorhidrato de 7-{3-[(2,4-dimetil-thiazol-5-ilmetil)-(2-piridin-3-il-etil)amino]propoxi}-1-etil-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7 y del Ejemplo 6, se sintetizó el compuesto objetivo.

Amorfo blanco

^{1}H-NMR (DMSO-d_6) δppm:

0,74 (3H, s), 0,99 (3H, t, J = 7,0 Hz), 1,31 (3H, s), 2,26 (2H,bs), 2,39 (3H, s), 2,59 (3H, s), 3,11-3,61 (6H, m), 3,31 (3H, s), 3,67 (1H, t, dq = 7,0, 7,0 Hz), 4,05 (1H, dq, J = 7,0, 7,0 Hz), 4,09-4,17 (2H, m), 4,62 (2H, bs), 6,84-6,95 (2H, m), 7,41 (1H, d, J = 8,9 Hz), 7,89 (1H, dd, J = 7,8 y 5,6 Hz), 8,35 (1H, d, J = 7,8 Hz), 8,76 (1H, d, J = 5,6 Hz), 8,84 (1H, s), 11,2 (1H, bs).

Ejemplo 627

Síntesis de 1-etil-3,3,5-trimetil-7-(3-{[2-(4-oxo-4H-furo-[3,2-c]piridin-5-il)etil]pyridazin-4-ilmetilamino}-propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

Polvo blanco

^{1}H-NMR ($CDCl_3$) δppm:

0,86 (3H, s), 1,16 (3H, t, J = 7,1 Hz), 1,53 (3H, s), 1,87-1,97 (2H, m), 2,73 (2H, t, J = 6,8 Hz), 2,87-2,95 (2H, m), 3,39 (3H, s), 3,66-3,77 (3H, m), 3,85 (2H, t, J = 5,9 Hz), 4,10-4,24 (3H, m), 6,48 (1H, d, J = 7,4 Hz), 6,59 (1H, d, J = 2,7 Hz), 6,65 (1H, dd, J = 2,7 y 9,0 Hz), 6,95 (1H, t, J = 0,8 Hz), 7,09 (1H, d, J = 7,4 Hz), 7,19 (1H, d, J = 9,0 Hz), 7,25-7,28 (1H, m), 7,51 (1H, d, J = 2,1 Hz), 8,89 (1H, dd, J = 1,2 y 5,2 Hz), 9,08 (1H, s).

Ejemplo 628

Síntesis de clorhidrato de N-[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)-propil]-N-(2-piridin-3-iletil)bencenosulfonamida

Usando un material de partida apropiado y siguiendo el

procedimiento del Ejemplo 4 y del Ejemplo 6, se sinstetizó el compuesto objetivo.

Amorfo blanco

^{1}H-NMR (DMSO-d_6) δppm:

0,74 (3H, s), 1,01 (3H, t, J = 7,0 Hz), 1,32 (3H, s), 1,85-1,97(2H, m), 3,03 (2H, t, J = 7,0 Hz), 3,03-3,62 (4H, m), 3,31 (3H, s), 3,67 (1H, dq, J = 7,0, 7,0 Hz), 3,98 (2H, t, t = 7,0 Hz), 4,06 (1H, dq, J = 7,0, 7,0 Hz), 6,84-6,95 (2H, m), 7,41 (1H, d, J = 8,9 Hz), 7,54-7,63(2H, m), 7,63-7,72 (1H, m), 7,75-7,84 (2H, m), 7,84-7,92 (1H, m), 8,34 (1H, d, J = 7,4 Hz), 8,74 (1H, d, J = 5,2 Hz), 8,78 (1H, bs).

Ejemplo 629

Síntesis de diclorhidrato de 7-(3-{(2,6-dimetilpiridin-3-ilmetil)-[2-(4-oxo-4H-furo[3,2-c]piridin-5-il)etil]amino}-propoxi)-1-etil-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]-diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7 y del Ejemplo 6, se sintetizó el compuesto objetivo.

Amorfo blanco

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (3H, s), 1,01 (3H, t, J = 7,0 Hz), 1,32 (3H, s), 1,99-3,04 (12H, m), 3,05-4,82 (11H, m), 6,55-7,04 (4H, m), 7,41 (1H, d, J = 8,9 Hz) 7,44-7,82 (2H, m), 7,91 (1H, s), 8,38-8,92 (1H, m).

Ejemplo 630

Síntesis de 7-(3-{(2,6-dimetilpiridin-3-ilmetil)-[2-(2-metil-4-oxo-4H-furo[3,2-c]piridin-5-il)etil]amino}-propoxi)-1-etil-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]-diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

Polvo blanco

Punto de fusión 114 a 116°C

Ejemplo 631

Síntesis de N-[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil]-N-[2-(2-metil-4-oxo-4H-furo[3,2-c]piridin-5-il)etil]benceno-sulfonamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 4, se sintetizó el compuesto objetivo.

Polvo blanco

Punto de fusión 179,6 a 182,5°C

Ejemplo 632

Síntesis de diclorhidrato de 1-etil-3,3,5-trimetil-7-(3-{[2-(7-metil-4-oxo-4H-furo[3,2-c]piridin-5-il)etil]piridin-4-ilmetil-amino}-propoxi)-1,5-dihidrobenzo[b][1,4]-diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (s, 3H), 1,01 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,00 (br, 2H), 2,16 (s, 3H), 3,21-3,35 (m, 2H), 3,30 (s, 3H), 3,53-3,70 (m, 3H), 3,93 (br, 4H), 4,00-4,19 (m, 3H), 6,70-6,81 (m, 2H), 6,95 (s, 1H), 7,37 (d, J = 9,0 Hz, 1H), 7,45 (br, 1H), 7,78 (br, 2H), 7,93 (br, 1H), 8,67 (br, 2H).

607

Ejemplo 633

Síntesis de clorhidrato de N-[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)-propil]-N-(2-piridin-3-iletil)benzamida

Se agregó cloruro de benzoilo (0,091 ml, 0,78 mmoles) a una solución de acetonitrilo (3 ml) de 1-etil-3,3,5-trimetil-7-[3-(2-piridin-3-iletilamino)propoxi]-1,5-dihidro-benzo[b][1,4]diazepina-2,4-diona (0,39 g, 0,71 mmoles) y trietilamina (0,12 ml, 0,86 mmoles) mientras se enfriaba en un baño de hielo, y la mezcla se agitó a temperatura ambiente durante la noche. Se agregó agua a la mezcla de reacción, y se realizó la extracción con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio anhidro y se concentró bajo presión reducida. El residuo así obtenido se purificó por cromatografía líquida de media presión (gel de sílice, acetato de etilo:alcohol isopropílico = 100:0→92:8). El producto purificado se concentró bajo presión reducida y el residuo resultante se disolvio en acetato de etilo (10 ml). Se agregó una solución 1N de HCl ethanol (0,65 ml) a la solución, y se concentró bajo presión reducida. El residuo se recristalizó a partir de acetato de etilo para obtener de este modo 0,28 g (rendimiento: 54%) de clorhidrato de N-[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]-diazepin-7-iloxi)-propil]-N-(2-piridin-3-iletil)benzamida como un polvo blanco.

Punto de fusión 179 a 191°C

Ejemplo 634

Síntesis de N-[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil]-N-[2-(1-

608

oxo-1H-isoquinolin-2-il)etil]bencenosulfonamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 4, se sintetizó el compuesto objetivo.

Polvo blanco

Punto de fusión 134 a 137°C

Ejemplo 635

Síntesis de la [3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil]-[2-(1-oxo-1H-isoquinolin-2-il)etil]amida del ácido piridina-3-sulfónico

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 4, se sintetizó el compuesto objetivo.

Polvo blanco

Punto de fusión 160 a 164°C

Ejemplo 636

Síntesis de diclorhidrato de 1-etil-3,3,5-trimetil-7-(3-{[2-(4-metil-7-oxo-7H-tieno[2,3-c]piridin-6-il)etil]-piridin-4-ilmetil-amino}propoxi)-1,5-dihidrobenzo[b][1,4]-diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (s, 3H), 1,01 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,05 (br, 2H), 2,24 (s, 3H), 3,30-3,40 (m, 2H), 3,30 (s, 3H), 3,63-3,70 (m, 3H), 3,82 (br, 4H), 3,95-4,10 (m, 1H), 4,25 (br, 2H), 6,72 (br, 1H), 6,80 (br 1H), 7,35-7,43 (m, 3H),

7,85 (br, 2H), 8,07-8,11 (m, 1H), 8,66 (br, 2H).

Ejemplo 637

Síntesis de la [3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil]-[2-(2-metil-4-oxo-4H-furo[3,2-c]piridin-5-il)etil]amida del ácido piridina-3-sulfónico

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 4, se sintetizó el compuesto objetivo.

Polvo blanco

Punto de fusión 163,3 a 166,3°C

Ejemplo 638

Síntesis de diclorhidrato de 1-etil-3,3,5-trimetil-7-(2-{(2-metilpiridin-3-ilmetil)-[2-(4-oxo-4H-furo[3,2-c]-piridin-5-il)etil]-amino}etoxi)-1,5-dihidrobenzo[b][1,4]-diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7 y del Ejemplo 6, se sintetizó el compuesto objetivo.

Amorfo blanco

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (3H, s), 1,02 (3H, t, J = 7,0 Hz), 1,33 (3H, s), 2,61 (3H, s), 2,77-3,05 (4H, m), 3,32 (3H, s), 3,48-3,71 (3H, m), 3,94-4,16 (5H, m), 6,63 (1H, d, J = 7,3 Hz), 6,83-6,91 (3H, m), 7,39 (1H, d, J = 8,8 Hz), 7,55 (1H, d, J = 7,6 Hz), 7,65 (1H, t, J = 6,2 Hz), 7,84 (1H, d, J = 2,1 Hz), 8,34-8,38 (1H, m), 8,51 (1H, d, J = 5,9 Hz).

Ejemplo 639

Síntesis de difosfato de la [3-(1-etil-3,3,5-trimetil-2,4-

dioxo-2,3,4,5-tetrahidro-1H-benzo-[b][1,4]diazepin-7-iloxi)propil]-(2-piridin-3-iletil)amida del ácido piridina-3-sulfónico

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 4 y del Ejemplo 458, se sintetizó el compuesto objetivo.

Amorfo blanco

^{1}H-NMR (DMSO-d_6) δppm:

0,74 (3H, s), 1,01 (3H, t, J = 7,0 Hz), 1,32 (3H, s), 1,89-2,08 (2H, m), 2,80-2,98 (2H, m), 3,31 (3H, s), 3,31-5,00 (8H, m), 6,84-6,96 (2H, m), 7,30 (1H, dd, J = 8,0 y 4,8 Hz), 7,40 (1H, d, J = 8,7 Hz), 7,54-7,74 (2H, m), 8,18-8,27 (1H, m), 8,42 (1H, dd, J = 4,8 y 1,5 Hz), 8,44 (1H, d, J = 1,8 Hz), 8,83 (1H, dd, J = 4,8 Hz, J = 1,5 Hz), 8,99 (1H, d, J = 1,8 Hz).

Ejemplo 640

Síntesis de clorhidrato de la [3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil]-(2-piridin-3-il-etil)amida del ácido 2,4-dimetil-tiazol-5-sulfónico

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 4 y del Ejemplo 6, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (3H, s), 1,01 (3H, t, J = 7,0 Hz), 1,32 (3H, s), 1,89-2,25 (2H, m), 2,49 (3H, s), 2,62 (3H, s), 3,08 (2H, t, J = 7,0 Hz), 3,32 (3H, s), 3,32-3,90 (3H, m), 3,54 (2H, t, J = 7,0 Hz), 4,01 (2H, t, J = 7,0 Hz), 4,01-4,20 (1H, m), 6,84-6,96 (2H, m), 7,41 (1H, d, J = 8,9 Hz), 7,90 (1H, dd, J = 8,0

y 5,4 Hz), 8,37 (1H, d, J = 8,0 Hz), 8,75 (1H, d, J = 5,4 Hz), 8,82 (1H, s).

Ejemplo 641

Síntesis de 1-etil-3,3,5-trimetil-7-(3-{[2-(7-oxo-7H-tieno[2,3-c]piridin-6-il)etil]piridin-3-ilmetilamino}-propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,85 (s, 3H), 1,14 (t, J = 7,1 Hz, 3H), 1,52 (s, 3H), 1,81-1,93 (m, 2H), 2,72 (t, J = 6,8 Hz, 2H), 2,89 (t, J = 6,1 Hz, 2H), 3,38 (s, 3H), 3,68 (s, 2H), 3,60-3,75 (m, 1H), 3,86 (t, J = 6,0 Hz, 2H), 4,05-4,21 (m, 3H), 6,55 (d, J = 7,1 Hz, 1H), 6,60-6,68 (m, 2H), 6,96-7,03 (m, 1H), 7,07 (d, J = 7,1 Hz, 1H), 7,12-7,18 (m, 2H), 7,42-7,50 (m, 1H), 7,66-7,70 (m, 1H), 8,35-8,37 (m, 1H), 8,47 (s, 1H).

Ejemplo 642

Síntesis de diclorhidrato de 1-etil-7-(3-{[2-(2-etil-4-oxo-4H-tieno[3,2-c]piridin-5-il)etil]piridin-3-ilmetilamino}-propoxi)3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (s, 3H), 1,01 (t, J = 7,0 Hz, 3H), 1,28 (t, J = 7,5 Hz, 3H), 1,32 (s, 3H), 2,25 (br, 2H), 2,87 (q, J = 7,5 Hz, 2H), 3,20-3,35 (m, 2H), 3,32 (s, 3H), 3,51-3,69 (m, 3H), 3,97-4,15

(m, 5H), 4,28 (br, 2H), 6,90 (br, 3H), 7,22 (s, 1H), 7,42 (d, J = 9,0 Hz, 1H), 7,50-7,68 (m, 2H), 8,18 (br, 1H), 8,73 (br, 1H), 8,80 (br, 1H).

Ejemplo 643

Síntesis de diclorhidrato de 1-etil-7-(3-{[2-(7-metoxi-2-oxo-3,4-dihidro-2H-quinolin-1-il)etil]piridin-3-ilmetil-amino}propoxi)-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]-diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (s, 3H), 1,02 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,31 (br, 2H), 2,51-2,60 (m, 2H), 2,77-2,82 (m, 2H), 3,28 (br, 2H), 3,32 (s, 3H), 3,50-3,70 (m, 3H), 3,77 (s, 3H), 4,01-4,14 (m, 3H), 4,43 (br, 2H), 4,68 (br, 2H), 6,60 (dd, J = 2,0, 8,2 Hz, 1H), 6,79 (br, 1H), 6,91 (dd, J = 2,8, 9,0 Hz, 1H), 6,94 (d, J = 2,8 Hz, 1H), 7,14 (d, J = 8,2 Hz, 1H), 7,41 (d, J = 9,0 Hz, 1H), 7,90 (br, 1H), 8,67 (br, 1H), 8,87 (br, 1H), 9,12 (br, 1H).

Ejemplo 644

Síntesis de la [3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil]-[2-(1-oxo-1H-isoquinolin-2-il)etil]amida del ácido 2,4-dimetil-tiazol-5-sulfónico

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 4, se sintetizó el compuesto objetivo.

Polvo blanco

Punto de fusión 76 a 84°C

Ejemplo 645

Síntesis de diclorhidrato de 1-etil-3,3,5-trimetil-7-(3-{[2-(4-oxo-2-trifluorometil-4H-furo[3,2-c]piridin-5-il)-etil]piridin-4-ilmetilamino}propoxi)-1,5-dihidrobenzo[b]-[1,4]-diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (s, 3H), 1,02 (t, J = 7,0 Hz, 3H), 1,32 (t, J = 7,5 Hz, 3H), 2,45-2,60 (m, 2H), 3,20-3,35 (m, 2H), 3,30 (s, 3H), 3,59-3,70 (m, 3H), 3,81 (br, 4H), 3,98-4,06 (m, 1H), 4,13 (br, 2H), 6,63-6,80 (m, 3H), 7,36 (d, J = 9,0 Hz, 1H), 7,61-7,87 (m, 4H), 8,65 (br, 2H).

Ejemplo 646

Síntesis de diclorhidrato de 1-etil-3,3,5-trimetil-7-(3-{(2-metilpiridin-3-ilmetil)-[2-(4-oxo-2-trifluorometil-4H-furo[3,2-c]piridin-5-il)etil]amino}propoxi)-1,5-dihidro-benzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (s, 3H), 1,02 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 1,98 (br, 2H), 2,74 (br, 5H), 3,20-3,35 (m, 2H), 3,31 (s, 3H), 3,55-3,69 (m, 3H), 3,99-4,10 (m, 5H), 6,70-6,90 (m, 3H), 7,39 (d, J = 9,0 Hz, 1H), 7,76 (br, 3H), 8,26 (br, 1H), 8,59 (br, 1H).

Ejemplo 647

Síntesis de diclorhidrato de 7-(3-{(2,4-dimetilpiridin-3-ilmetil)-[2-(4-oxo-4H-furo[3,2-c]piridin-5-il)etil]amino}-propoxi)-1-etil-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]-diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,76 (s, 3H), 1,02 (t, J = 7,0 Hz, 3H), 1,33 (s, 3H), 1,99 (br, 2H), 2,43 (br, 3H), 2,62 (br, 3H), 2,73 (br, 4H), 3,33 (s, 3H), 3,61-3,70 (m, 3H), 3,90-4,10 (m, 5H), 6,59 (br, 1H), 6,82-6,92 (m, 3H), 7,40 (d, J = 9,0 Hz, 1H), 7,49 (br, 2H), 7,87 (br, 1H), 8,40 (br, 1H).

Ejemplo 648

Síntesis de 1-etil-3,3,5-trimetil-7-{3-[[2-(4-oxo-4H-furo-[3,2-c]piridin-5-il)etil]-(2-trifluorometilpiridin-3-il-metil)amino]propoxi}-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,86 (s, 3H), 1,15 (t, J = 7,1 Hz, 3H), 1,53 (s, 3H), 1,85-1,94 (m, 2H), 2,78 (t, J = 7,2 Hz, 2H), 2,89 (t, J = 6,2 Hz, 2H), 3,38 (s, 3H), 3,63-3,76 (m, 1H), 3,87-3,93 (m, 4H), 4,03-4,22 (m, 3H), 6,41-6,44 (m, 1H), 6,61 (d, J = 2,7 Hz, 1H), 6,67 (dd, J = 9,0 y 2,7 Hz, 1H), 6,94-6,95 (m, 1H), 7,01-7,08 (m, 2H), 7,19 (d, J = 9,0 Hz, 1H), 7,50-7,51 (m,

1H), 7,79-7,81 (m, 1H), 8,46 (d, J = 3,6 Hz, 1H).

Ejemplo 649

Síntesis de 1-etil-3,3,5-trimetil-7-{3-[[2-(2-metil-4-oxo-4H-furo[3,2-c]piridin-5-il)etil]-(2-trifluorometilpiridin-3-ilmetil)amino]propoxi}-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,86 (s, 3H), 1,15 (t, J = 7,1 Hz, 3H), 1,53 (s, 3H), 1,87-1,95 (m, 2H), 2,43 (s, 3H), 2,78 (t, J = 7,2 Hz, 2H), 2,88 (t, J = 6,2 Hz, 2H), 3,38 (s, 3H), 3,63-3,76 (m, 1H), 3,86 (s, 2H), 3,92 (t, J = 6,0 Hz, 2H), 4,05-4,22 (m, 3H), 6,34-6,37 (m, 1H), 6,53 (s, 1H), 6,63 (d, J = 2,7 Hz, 1H), 6,68 (dd, J = 9,0 y 2,7 Hz, 1H), 6,99 (d, J = 7,4 Hz, 1H), 7,01-7,09 (m, 1H), 7,19 (d, J = 9,0 Hz, 1H), 7,80-7,84 (m, 1H), 8,45 (d, J = 3,6 Hz, 1H).

Ejemplo 650

Síntesis de diclorhidrato de 1-etil-3,3,5-trimetil-7-(3-{[3-(2-metil-4-oxo-4H-furo[3,2-c]piridin-5-il)propil]-piridin-4-ilmetilamino}propoxi)-1,5-dihidrobenzo[b][1,4]-diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,76 (s, 3H), 1,02 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,22 (br, 4H), 2,39 (s, 3H), 3,10 (br, 2H), 3,21 (br, 2H), 3,31

(s, 3H), 3,45-3,70 (m, 1H), 4,01-4,10 (m, 5H), 4,58 (br, 2H), 6,56 (s, 1H), 6,79 (d, J = 7,4 Hz, 1H), 6,87-6,92 (m, 2H), 7,40 (d, J = 9,0 Hz, 1H), 7,57 (d, J = 7,4 Hz, 1H), 8,08 (br, 2H), 8,82 (br, 2H).

Ejemplo 651

Síntesis de clorhidrato de la [3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-il-oxi)propil]-(2-piridin-3-iletil)amida del ácido pirazin-2-carboxílico

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 45, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (3H, s), 1,01 (3H, t, J = 7,0 Hz), 1,32 (3H, s), 1,89-2,25 (2H, m), 3,00-3,23 (2H, m), 3,29 y 3,32 (3H, s), 3,32-3,78 (4H, m), 3,78-3,95(2H, m), 3,95-4,29 (2H, m), 6,67-6,80 (1H, m), 6,92-7,07 (1H, m), 7,36 y 7,42 (1H, d, J = 9,5 Hz), 7,80 y 7,95 (1H, dd, J = 7,7 y 5,6 Hz), 8,14 y 8,48(1H, d, J = 8,0 Hz), 8,52-9,02 (5H, m).

Ejemplo 652

Síntesis de diclorhidrato de 1-etil-3,3,5-trimetil-7-{3-[[2-(4-oxo-4H-furo[3,2-c]piridin-5-il)etil]-(2,4,6-trimetilpiridin-3-ilmetil)amino]propoxi}-1,5-dihidro-benzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,76 (s, 3H), 1,02 (t, J = 7,0 Hz, 3H), 1,33 (s, 3H), 2,00

(br, 2H), 2,36 (br, 3H), 2,43-2,62 (m, 6H), 2,76 (br, 4H), 3,33 (s, 3H), 3,55-3,68 (m, 3H), 3,95 (br, 2H), 4,03-4,11 (m, 3H), 6,59 (br, 1H), 6,80-6,94 (m, 3H), 7,27 (br, 1H), 7,39-7,47 (m, 2H), 7,89 (s, 1H).

Ejemplo 653

Síntesis de N-[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil]-N-(2-piridin-3-iletil)nicotinamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 459, se sintetizó el compuesto objetivo.

Polvo blanco. Punto de fusión 135,5 a 138,1°C

Ejemplo 654

Síntesis de 2,5-fosfato de N-[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)-propil]-N-piridin-4-ilmetilnicotinamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 633 y del Ejemplo 458, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (3H, s), 1,00 (3H, t, J = 7,0 Hz), 1,32 (3H, s), 1,82-2,27(2H, m), 3,29 (3H, s), 3,36-3,52 (2H, m), 3,52-4,25 (4H, m), 4,57 y 4,78 (2H, s), 6,53-7,09 (2H, m), 7,09-7,56 (4H, m), 7,69-8,05 (1H, m), 8,37-8,88 (4H, m).

Ejemplo 655

Síntesis de clorhidrato de la [3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil]-(2-piridin-3-iletil)amida del ácido tiazol-4-carboxílico

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 45, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,74 (3H, s), 1,00 (3H, t, J = 7,0 Hz), 1,32 (3H, s), 1,89-2,25 (2H, m), 2,87-3,21 (2H, m), 3,31 (3H, s), 3,31-4,27 (8H, m), 6,74-6,94 (1H, m), 6,95-7,05 (1H, m), 7,28-7,47 (1H, m), 7,65-7,94 (1H, m), 8,01 (1H, bs), 8,06-8,50 (1H, m), 8,50-8,94 (2H, m), 9,05-9,22 (1H, m).

Ejemplo 656

Síntesis de 1,5-metanosulfonato de N-[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]-diazepin-7-iloxi)propil]-2-piridin-3-il-N-piridin-4-il-metilacetamida

Se agregó hexafluorofosfato de benzotriazol-1-iloxitris(dimetilamino)fosfonio (BOP) (0,3 g, 0,68 mmoles) a una solución de diclorometano (6 ml) de 1-etil-3,3,5-trimetil-7-{3-[(piridin-4-ilmetil)amino]propoxi}-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona (0,39 g, 0,73 mmoles), clorhidrato del ácido 3-piridilacético (0,14 g, 0,8 mmoles) y trietilamina (0,31 ml, 2,2 mmoles) mientras se enfriaba en un baño de hielo y la mezcla se agitó a temperatura ambiente durante la noche. Se agregó agua a la mezcla de reacción, y se realizó la extracción con diclorometano. La capa orgánica se secó sobre sulfato de sodio anhidro y se concentró bajo presión reducida. El residuo así obtenido se purificó por cromatografía líquida de media presión (NH-gel de sílice, acetato de etilo:alcohol isopropílico = 100:0→91:9). El producto purificado se

concentró bajo presión reducida y el residuo resultante se disolvió en etanol (10 ml). Se agregó ácido metanosulfónico (0,047 ml, 0,72 mmoles) a la solución y se concentró bajo presión reducida. El residuo resultante se lavó con dietil éter por decantación para obtener de este modo 0,17 g (rendimiento: 35%) de 1,5-metanosulfonato de N-[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil]-2-piridin-3-il-N-piridin-4-ilmetilacetamida como un sólido amorfo blanco amarillo pálido.

^{1}H-NMR (DMSO-d_6) δppm:

0,73 (3H, s), 1,00 (3H, t, J = 7,3 Hz), 1,32 (3H, s), 1,85-2,25 (2H, m), 2,35 (4,5H, s), 3,29 y 3,30 (3H, s), 3,30-3,97 (2H, m), 3,97-4,27 (6H, m), 4,79 y 4,99 (2H, s), 6,82-7,04 (2H, m), 7,33-7,48 (1H, m), 7,54-7,95 (3H, m), 8,10-8,23 (1H, m), 8,57-8,90 (4H, m).

Ejemplo 657

Síntesis de clorhidrato de la [3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil]-(2-piridin-3-iletil)amida del ácido oxazol-4-carboxílico

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 45, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,74 (3H, s), 1,00 (3H, t, J=7,3 Hz), 1,32 (3H, s), 1,98-2,25 (2H, m), 3,03-3,21 (2H, m), 3,31 (3H, s), 3,40-4,22 (8H, m), 6,74-7,05 (2H, m), 7,31-7,47 (1H, m), 7,75-8,03 (1H, m), 8,32 (1H, d, J=7,3 Hz), 8,37-8,60 (2H, m), 8,60-8,97 (2H, m).

Ejemplo 658

Síntesis de clorhidrato de la [3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil]-(2-piridin-3-iletil)amida del ácido tiofen-3-carboxílico

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 633, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,74 (3H, s), 1,00 (3H, t, J = 7,2 Hz), 1,32 (3H, s), 1,88-2,25 (2H, m), 3,09 (2H, bs), 3,31 (3H, s), 3,32-4,30 (8H, m), 6,64-7,18 (3H, m), 7,39 (1H, d, J = 9,3 Hz), 7,55 (1H, dd, J = 4,9 y 2,9 Hz), 7,62 (1H, bs), 7,67-8,22 (1H, m), 8,22-0,18 (3H, m).

Ejemplo 659

Síntesis de clorhidrato de la [3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil]-(2-piridin-3-iletil)amida del ácido furan-2-carboxílico

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 633, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,74 (3H, s), 1,01 (3H, t, J = 7,0 Hz), 1,32 (3H, s), 1,92-2,12 (2H, m), 3,01-3,21 (2H, m), 3,31 (3H, s), 3,30-3,90 (5H, m), 4,00-4,15 (3H, m), 6,56-6,62 (1H, m), 6,85-7,00 (3H, m), 7,36-7,45 (1H, m), 7,78 (1H, s), 7,85-8,00 (1H, m), 8,38 (1H, bs), 8,74 (1H, d, J = 5,3 Hz), 8,82 (1H, bs).

Ejemplo 660

Síntesis de 1,3,3,5-tetrametil-7-{3-[(piridin-4-ilmetil)-amino]propoxi}-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 77, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,87 (3H, s), 1,53 (3H, s), 1,92-2,10 (2H, m), 2,84 (2H, t, J = 6,8 Hz), 3,39 (3H, s), 3,41 (3H, s), 3,85 (2H, s), 4,08 (2H, t, J = 6,2), 6,71 (1H, d, J = 2,7 Hz), 6,80 (1H, dd, J = 2,7 y 9,0 Hz), 7,14 (1H, d, J = 9,0), 7,20-7,34 (2H, m), 8,45-8,65 (2H, m).

Ejemplo 661

Síntesis de 1-etil-7-{2-hidroxi-3-[2-(1-oxo-1H-isoquinolin-2-il)etilamino]propoxi}-3,3,5-trimetil-1,5-dihidrobenzo[b]-[1,4]-diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,84 (3H, s), 1,14 (3H, t, J = 7,0 Hz), 1,52 (3H, s), 2,75-3,04 (2H, m), 3,11 (2H, t, J = 6,1 Hz), 3,78 (3H, s), 3,59-3,79 (1H, m), 3,89-4,29 (6H, m), 6,52 (1H, d, J = 7,3 Hz), 6,68-6,86 (2H, m), 7,11 (1H, d, J = 7,3 Hz), 7,18 (1H, d, J = 8,7 Hz), 7,43-7,57 (2H, m), 7,57-7,74 (1H, m), 8,42 (1H, d, J = 8,2 Hz).

Ejemplo 662

Síntesis de 1-etil-3,3,5-trimetil-7-{3-[(piridin-3-il-metil)amino]propoxi}-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 77, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,86 (3H, s), 1,14 (3H, t, J = 7,1 Hz), 1,52 (3H, s), 1,96-2,06 (2H, m), 2,85 (2H, t, J = 6,8 Hz), 3,39 (3H, s), 3,65-3,74 (1H, m), 3,85 (2H, s), 4,07 (2H, t, J = 6,1 Hz), 4,10-4,21 (1H, m), 6,71 (1H, d, J=2,8 Hz), 6,80 (1H, dd, J = 9,0 y 2,8 Hz), 7,19 (1H, d, J=9,0 Hz), 7,22-7,29 (1H, m), 7,65-7,68 (1H, m), 8,50 (1H, d, J = 1,6 Hz), 8,58-8,61 (1H, m).

Ejemplo 663

Síntesis de 1-etil-3,3,5-trimetil-7-{3-[2-(2-metil-4-oxo-4H-furo[3,2-c]piridin-5-il)etilamino]propoxi}-1,5-dihidro-benzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 18, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,85 (3H, s), 1,14 (3H, t, J = 7,1 Hz), 1,52 (3H, s), 1,92-2,00 (2H, m), 2,41 (3H, s), 2,88 (2H, t, J = 6,8 Hz), 3,03 (2H, t, J = 6,2 Hz) 3,39 (3H, s), 3,62-3,74 (1H, m), 4,02 (2H, t, J = 6,1 Hz), 4,14 (2H, t, J = 6,2 Hz), 4,16-4,22 (1H, m), 6,42 (1H, d, J = 9,0 Hz), 6,54 (1H, s), 6,70 (1H, d, J = 2,7 Hz), 6,72-6,82 (1H, m), 7,13-7,20 (2H, m).

Ejemplo 664

Síntesis de 1-etil-3,3,5-trimetil-7-{3-[(piridin-2-il-metil)amino]propoxi}-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el

procedimiento del Ejemplo 77, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,86 (3H, s), 1,14 (3H, t, J = 7,1 Hz), 1,52 (3H, s), 2,03-2,09 (2H, m), 2,91 (2H, t, J = 6,7 Hz), 3,48 (3H, s), 3,64-3,76 (1H, m), 3,97 (2H, s), 4,10 (2H, t, J = 6,2 Hz), 4,14-4,23 (1H, m), 6,73 (1H, d, J = 2,7 Hz), 6,82 (1H, dd, J = 9,0 y 2,7 Hz), 7,16-7,21 (2H, m), 7,27-7,32 (1H, m), 7,85 (1H, td, J = 7,7, 1,8 Hz), 8,58-8,56 (1H, m).

Ejemplo 665

Síntesis de 1-etil-3,3,5-trimetil-7-{3-[2-(4-oxo-4H-furo-[3,2-c]piridin-5-il)etilamino]propoxi}-1,5-dihidro-benzo-[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 18, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,86 (3H, s), 1,14 (3H, t, J=7,1 Hz), 1,52 (3H, s), 1,91-2,00 (2H, m), 2,85 (2H, t, J=6,7 Hz), 3,03 (2H, t, J = 6,2 Hz), 3,39 (3H, s), 3,66-3,76 (1H, m), 4,02 (2H, t, J = 6,1 Hz), 4,09-4,24 (3H, m), 6,48 (1H, d, J = 7,4 Hz), 6,69 (1H, d, J=2,8 Hz), 6,76 (1H, dd, J = 9,0, 2,8 Hz), 6,97 (1H, d, J=2,0 Hz), 7,16-7,24 (2H, m), 7,48 (1H, d, J = 2,1 Hz).

Ejemplo 666

Síntesis de 1-etil-3,3,5-trimetil-7-{3-[(2-metilpiridin-3-ilmetil)amino]propoxi}-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 77, se sintetizó el compuesto

objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,86 (3H, s), 1,14 (3H, t, J = 7,0 Hz), 1,53 (3H, s), 1,98-2,07 (2H, m), 2,57 (3H, s), 2,89 (2H, t, J = 6,8 Hz), 3,39 (3H, s), 3,62-3,73 (1H, m), 3,82 (2H,s), 4,07-4,21 (3H, m), 6,71 (1H, d, J = 2,8 Hz), 6,80 (1H, dd, J = 9,0 y 2,8 Hz), 7,10 (1H, dd, J = 7,7 y 4,9 Hz), 7,20 (1H, d, J = 9,0 Hz), 7,59-7,62 (1H, m), 8,38-8,41 (1H, m).

Ejemplo 667

Síntesis de 1-etil-3,3,5-trimetil-7-{3-[(6-metilpiridin-3-ilmetil)amino]propoxi}-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 77, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,86 (3H, s), 1,14 (3H, t, J = 7,1 Hz), 1,52 (3H, s), 1,95-2,07 (2H, m), 2,54 (3H, s), 2,84 (2H, t, J = 6,8 Hz), 3,39 (3H, s), 3,64-3,76 (1H, m), 3,80 (2H,s), 4,04-4,20 (3H, m), 6,71 (1H, d, J = 2,8 Hz), 6,79 (1H, dd, J = 9,0 y 2,8 Hz), 7,11 (1H, d, J = 7,9 Hz), 7,19 (1H, d, J = 9,0 Hz), 7,56 (1H, dd, J = 7,9 y 2,3 Hz), 8,44-8,45 (1H, m).

Ejemplo 668

Síntesis de 1-etil-7-[3-(4-methoxibenzilamino)propoxi]-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 77, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,86 (3H, s), 1,14 (3H, t, J = 7,0 Hz), 1,52 (3H, s), 2,00 (2H, quin, J = 6,5 Hz), 2,83 (2H, t, J = 6,5 H), 3,39 (3H, s), 3,70 (1H, dq, J = 7,0, 7,0 Hz), 3,76 (2H, s), 3,80 (3H, s), 4,07 (2H, t, J = 6,5 Hz), 4,18 (1H, dq, J = 7,0, 7,0 Hz), 6,71 (1H, d, J = 2,7 Hz), 6,80 (1H, dd, J = 2,7 y 9,0 Hz), 6,86 (2H, d, J = 8,5 Hz), 7,19 (1H, d, J = 9,0 Hz), 7,24 (2H, d, J = 8,5 Hz).

Ejemplo 669

Síntesis de 1-etil-3,3,5-trimetil-7-{3-[(5-metilpiridin-3-ilmetil)amino]propoxi}-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 77, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,86 (3H, s), 1,14 (3H, t, J = 7,1 Hz), 1,50 (3H, s), 1,98-2,05 (2H, m), 2,32 (3H, s), 2,85 (2H, t, J = 6,8 Hz), 3,39 (3H, s), 3,62-3,72 (1H, m), 3,81 (2H,s), 4,05-4,17 (3H, m), 6,71 (1H, s), 6,80 (1H, dd, J = 9,0 y 2,8 Hz), 7,19 (1H, d, J = 9,0 Hz), 7,48 (1H, s), 8,34-8,38 (2H, m).

Ejemplo 670

Síntesis de 1-etil-7-{3-[(2-etilpiridin-3-ilmetil)amino]-propoxi}-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 77, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,86 (3H, s), 1,14 (3H, t, J = 7,1 Hz), 1,29 (3H, t, J = 7,5

Hz), 1,52 (3H, s), 1,99-2,05 (2H, m), 2,82-2,91 (4H, m), 3,39 (3H, s), 3,62-3,75 (1H, m), 3,84 (2H,s), 4,09 (2H, t, J = 6,2 Hz) 4,10-4,23 (1H, m), 6,71 (1H, d, J = 2,8 Hz), 6,80 (1H, dd, J = 9,0 y 2,8 Hz), 7,09 (1H, dd, J = 7,6 y 4,9 Hz), 7,20 (1H, d, J = 9,0 Hz), 7,63 (1H, d, J = 7,7 Hz), 8,43-8,46 (1H, m).

Ejemplo 671

Síntesis de 1-etil-3,3,5-trimetil-7-{3-[(2-propilpiridin-3-ilmetil)amino]propoxi}-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 77, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,86 (3H, s), 0,99 (3H, t, J = 7,4 Hz), 1,14 (3H, t, J = 7,1 Hz), 1,52 (3H, s), 1,69-1,81 (2H, m), 1,99-2,07 (2H, m), 2,77-2,90 (4H, m), 3,39 (3H, s), 3,60-3,73 (1H, m), 3,84 (2H, s), 4,06-4,23 (3H, m), 6,72 (1H, s), 6,79 (1H, dd, J = 9,0 y 2,8 Hz), 7,06-7,09 (1H, m), 7,20 (1H, d, J = 8,0 Hz), 7,63 (1H, d, J = 7,7 Hz), 8,42-8,45 (1H, m).

Ejemplo 672

Síntesis de 1-etil-3,3,5-trimetil-7-{4-[(2-metilpiridin-3-ilmetil)amino]butoxi}-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 77, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,86 (3H, s), 1,14 (3H, t, J = 7,1 Hz), 1,54 (3H, s), 1,67-

1,75 (2H, m), 1,85-1,92 (2H, m), 2,58 (3H, s), 2,76 (2H, t, J = 7,0 Hz), 3,39 (3H, s), 3,60-3,77 (1H, m), 3,80 (2H,s), 3,99 (2H, t, J = 6,3 Hz), 4,11-4,22 (1H, m), 6,74 (1H, s), 6,79 (1H, dd, J = 8,9 y 2,8 Hz), 7,10 (1H, dd, J = 7,6 y 4,9 Hz), 7,19 (1H, d, J = 9,0 Hz), 7,61 (1H, d, J = 6,1 Hz), 8,38-8,41 (1H, m).

Ejemplo 673

Síntesis de 1-etil-3,3,5-trimetil-7-{4-[(piridin-4-il-metil)amino]butoxi}-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 77, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,86 (3H, s), 1,14 (3H, t, J = 7,1 Hz), 1,52 (3H, s), 1,64-1,78 (2H, m), 1,83-1,95 (2H, m), 2,72 (2H, t, J = 7,1 Hz), 3,39 (3H, s), 3,63-3,73 (1H, m), 3,84 (2H,s), 3,99 (2H, t, J = 6,3 Hz), 4,09-4,21 (1H, m), 6,71 (1H, s), 6,79 (1H, dd, J = 9,0 y 2,8 Hz), 7,19 (1H, d, J = 9,0 Hz), 7,26-7,29 (2H, m), 8,55 (2H, dd, J = 4,4 y 1,6 Hz).

Ejemplo 674

Síntesis de 1-etil-3,3,5-trimetil-7-{3-[(pyridazin-4-il-metil)amino]propoxi}-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 77, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,86 (3H, s), 1,15 (3H, t, J = 7,1 Hz), 1,52 (3H, s), 1,97-

628

2,06 (2H, m), 2,85 (2H, t, J = 6,7 Hz), 3,40 (3H, s), 3,65-3,75 (1H, m), 3,90 (2H,s), 4,09 (2H, t, J = 6,0 Hz), 4,10-4,22 (1H, m), 6,71 (1H, d, J = 2,8 Hz), 6,80 (1H, dd, J = 9,0 y 2,8 Hz), 7,21 (1H, d, J = 9,0 Hz), 7,46-7,49 (1H, m), 9,11 (1H, dd, J = 5,2 y 1,2 Hz), 9,21 (1H, s).

Ejemplo 675

Síntesis de 7-{3-[(2,6-dimetilpiridin-3-ilmetil)amino]-propoxi}-1-etil-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]-diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 77, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,86 (3H, s), 1,14 (3H, t, J = 7,1 Hz), 1,52 (3H, s), 1,97-2,05 (2H, m), 2,50 (3H, s), 2,54 (3H, s), 2,87 (2H, t, J = 6,7 Hz), 3,39 (3H, s), 3,60-3,77 (1H, m), 3,78 (2H, s), 4,06-4,24 (3H, m), 6,71 (1H, s), 6,80 (1H, dd, J = 9,0 y 2,8 Hz), 6,95 (1H, d, J = 7,3 Hz), 7,20 (1H, d, J = 9,0 Hz), 7,48 (1H, d, J = 7,7 Hz).

Ejemplo 676

Síntesis de 1-etil-3,3,5-trimetil-7-{2-[(2-metilpiridin-3-ilmetil)amino]etoxi}-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 77, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,85 (3H, s), 1,14 (3H, t, J = 7,1 Hz), 1,52 (3H, s), 2,59 (3H, s), 3,02-3,10 (2H, m), 3,39 (3H, s), 3,65-3,76 (1H, m),

3,89 (2H,s), 4,09-4,21 (3H, m), 6,73-6,75 (1H, m), 6,80-6,85 (1H, m), 7,10-7,14 (1H, m), 7,19-7,23 (1H, m), 7,65 (1H, dd, J = 7,7 y 1,5 Hz), 8,40-8,42 (1H, m).

Ejemplo 677

Síntesis de N-[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil]-N-[2-(1-oxo-1H-isoquinolin-2-il)etil]nicotinamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 459, se sintetizó el compuesto objetivo.

Amorfo blanco

^{1}H-NMR ($CDCl_3$) δppm:

0,82 (3H, s), 1,13 (3H, t, J = 7,0 Hz), 1,51 (3H, s), 1,88-2,45 (2H, m), 3,37 (3H, s), 3,42-3,60 (2H, m), 3,60-3,90 (3H, m), 3,95 (2H, t, J = 6,2 Hz), 4,01-4,27 (1H, m), 4,40 (2H, t, J = 6,2 Hz), 6,40-6,67 (2H, m), 7,43(4H, m), 7,43-7,61 (2H, m), 7,61-7,76 (2H, m), 8,13-8,78 (3H, m).

Ejemplo 678

Síntesis de clorhidrato de N-[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)-propil]-2-metil-N-(2-piridin-3-iletil)benzamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 633, se sintetizó el compuesto objetivo.

Polvo blanco

Punto de fusión 155,3 a 159,3°C (desc.)

Ejemplo 679

Síntesis de N-[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil]-2-metoxi-

N-(2-piridin-3-iletil)isonicotinamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 459, se sintetizó el compuesto objetivo.

Polvo blanco

Punto de fusión 112,8 a 113,9°C

Ejemplo 680

Síntesis de clorhidrato de la [3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil]-(2-piridin-3-iletil)amida del ácido ciclohexanocarboxílico

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 633, se sintetizó el compuesto objetivo.

Polvo blanco

Punto de fusión 153,4 a 157,5°C (desc.)

Ejemplo 681

Síntesis de clorhidrato de la N-[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)-propil]-N-(2-piridin-3-il-etil)-acetamida

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 633, se sintetizó el compuesto objetivo.

Amorfo blanco

^{1}H-NMR (DMSO-d_6) δppm:

0,73 y 0,74(3H, s), 1,01 (3H, t, J = 7,0 Hz), 1,32 (3H, s), 1,85-2,12 (2H, m), 1,93 y 1,95 (3H, s), 2,92-3,11 (2H, m), 3,12-3,95 (5H, m), 3,32 (3H, s), 3,95-4,16 (3H, m), 6,88-7,00 (2H, m), 7,40 (1H, dd, J = 8,8 y 2,7 Hz), 7,89 (1H, dt, J =

8,1 y 5,5 Hz), 8,36 (1H, d, J = 8,1Hz,), 8,74 (1H, d, J = 5,5 Hz), 8,77-8,86 (1H, m).

Ejemplo 682

Síntesis de 7-(4-amino-butoxi)-1-etil-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 2, se sintetizóel compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,86 (3H, s), 1,14 (3H, t, J = 7,1 Hz), 1,52 (3H, s), 1,60-1,70 (2H, m), 1,82-1,90 (2H, m), 2,80 (2H, t, J = 7,0 Hz), 3,40 (3H, s), 3,64-3,76 (1H, m), 4,00 (2H, t, J = 6,3 Hz), 4,12-4,24 (1H, m), 6,72 (1H, d, J = 2,7 Hz), 6,81 (1H, dd, J = 9,0 y 2,7 Hz), 7,20 (1H, d, J = 9,0 Hz).

Ejemplo 683

Síntesis de 7-(2-amino-etoxi)-1-etil-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 2, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

0,86 (3H, s), 1,15 (3H, t, J = 7,1 Hz), 1,53 (3H, s), 3,13 (2H, t, J = 5,1 Hz), 3,40 (3H, s), 3,47-3,76 (1H, m), 4,01 (2H, t, J = 5,1 Hz), 4,11-4,24 (1H, m), 6,75 (1H, d, J = 2,8 Hz), 6,83 (1H, dd, J = 9,0 y 2,8 Hz), 7,21 (1H, d, J = 9,0 Hz).

Ejemplo 684

Síntesis de diclorhidrato de 1,5-dimetil-7-{3-[[2-(2-metil-4-oxo-4H-furo-[3,2-c]piridin-5-il)etil]-(2-metilpiridin-3-

ilmetil)amino]-propoxi}espiro[benzo[b][1,4]diazepina-3,1'-ciclobutano]-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 7, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

1,64 (br, 4H), 2,28 (br, 2H), 2,42 (s, 3H), 2,49 (s, 3H), 2,75 (br, 2H), 2,84-2,88 (m, 4H), 3,39 (s, 3H), 3,40 (s, 3H), 3,64 (br, 2H), 3,89 (br, 2H), 4,00 (br, 2H), 6,33-6,35 (m, 1H), 6,51 (br, 1H), 6,56-6,69 (m, 2H), 6,89-6,92 (m, 2H), 7,47 (br, 1H), 8,32 (br, 2H).

Ejemplo 685

Síntesis de 7-[3-(1,3-Dioxo-1,3-dihidroisoindol-2-il)-propoxi]-1,5-dimetilespiro[benzo[b][1,4]diazepina-3,1'-ciclobutano]-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 1, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

1,57-1,67 (m, 4H), 2,11-2,23 (m, 2H), 2,78-2,90 (m, 2H), 3,35 (s, 3H), 3,37 (s, 3H), 3,93 (t, J = 6,7 Hz, 2H), 4,05 (t, J = 5,9 Hz, 2H), 6,61 (d, J = 2,8 Hz, 1H), 6,71 (dd, J = 9,0 y 2,8 Hz, 1H), 7,12 (d, J = 9,0 Hz, 1H), 7,71-7,75 (m, 2H), 7,83-7,86 (m, 2H).

Ejemplo 686

Síntesis de 7-(3-Aminopropoxi)-1,5-dimetilespiro-[benzo[b]-[1,4]diazepina-3,1'-ciclobutano]-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 2, se sintetizó el compuesto

objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

1,63-1,68 (m, 4H), 1,96-2,01 (m, 2H), 2,78-2,83 (m, 2H), 2,93 (t, J = 6,7 Hz, 2H), 3,38 (s, 3H), 3,42 (s, 3H), 4,07 (t, J = 6,2 Hz, 2H), 6,74 (d, J = 2,7 Hz, 1H), 6,80 (dd, J = 8,9 y 2,7 Hz, 1H), 7,16 (d, J = 8,9 Hz, 1H).

Ejemplo 687

Síntesis de 1,5-Dimetil-7-{3-[(2-metilpiridin-3-ilmetil)-amino]propoxi}espiro[benzo[b][1,4]diazepina-3,1'-ciclo-butano]-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 77, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

1,62-1,68 (m, 4H), 2,00-2,05 (m, 2H), 2,57 (s, 3H), 2,82-2,91 (m, 4H), 3,39 (s, 3H), 3,41 (s, 3H), 3,82 (s, 2H), 4,08 (t, J = 6,1 Hz, 2H), 6,73 (d, J = 2,7 Hz, 1H), 6,79 (dd, J = 8,9 y 2,7 Hz, 1H), 7,10 (dd, J = 7,6 y 4,9 Hz, 1H), 7,16 (d, J = 8,9 Hz, 1H), 7,62 (dd, J = 7,6 y 1,4 Hz, 1H), 8,40 (dd, J = 4,9 y 1,4 Hz, 1H).

Ejemplo 688

Síntesis de diclorhidrato de 1-etil-3,3,5-trimetil-7-(3-{[2-(1-oxo-1H-isoquinolin-2-il)etil]tiazol-2-ilmetilamino}-propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 6, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (s, 3H), 1,01 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,20

(br, 2H), 3,30 (s, 3H), 3,21-3,58 (m, 4H), 3,61-3,71 (m, 1H), 4,00-4,11 (m, 3H), 4,42 (br, 2H), 4,81 (br, 2H), 6,69 (d, J = 7,0 Hz, 1H), 6,82-6,89 (m, 2H), 7,38 (d, J = 9,0 Hz, 1H), 7,50-7,54 (m, 2H), 7,66-7,75 (m, 2H), 7,89 (br, 2H), 8,21 (d, J = 8,0 Hz, 1H).

Ejemplo 689

Síntesis de clorhidrato de 1-etil-7-(3-{(3-fluorobenzil)-[2-(1-oxo-1H-isoquinolin-2-il)etil]amino}propoxi)-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 6, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (s, 3H), 1,01 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,29 (br, 2H), 3,31 (s, 3H), 3,50 (br, 4H), 3,61-3,68 (m, 1H), 4,02-4,18 (m, 3H), 4,48-4,60 (m, 4H), 6,72 (d, J = 7,2 Hz, 1H), 6,85-6,90 (m, 2H), 7,30-7,42 (m, 2H), 7,46-7,81 (m, 7H), 8,23 (d, J = 8,0 Hz, 1H).

Ejemplo 690

Síntesis de clorhidrato de 1-etil-7-(3-{(3-methoxibenzil)-[2-(1-oxo-1H-isoquinolin-2-il)etil]amino}propoxi)-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 6, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (s, 3H), 1,01 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,27 (br, 2H), 3,21-3,30 (m, 5H), 3,42 (s, 3H), 3,51 (br, 2H), 3,61-3,72 (m, 1H), 4,02-4,18 (m, 3H), 4,38-4,61 (m, 4H), 6,73

(d, J = 7,2 Hz, 1H), 6,86-6,90 (m, 2H), 7,01 (d, J = 8,8 Hz, 1H), 7,18 (d, J = 7,6 Hz, 1H), 7,31-7,42 (m, 3H), 7,51-7,56 (m, 2H), 7,68-7,77 (m, 2H), 8,21 (d, J = 8,0 Hz, 1H).

Ejemplo 691

Síntesis de clorhidrato de 1-etil-3,3,5-trimetil-7-(3-{[2-(1-oxo-1H-isoquinolin-2-il)etil]tiofen-2-ilmetilamino}-propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 6, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,75 (s, 3H), 1,01 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,29 (br, 2H), 3,21-3,29 (m, 5H), 3,49 (br, 4H), 3,62-3,70 (m, 1H), 4,01-4,29 (m, 3H), 4,48 (br, 2H), 6,72 (d, J = 7,1 Hz, 1H), 6,86-6,93 (m, 2H), 7,15 (br, 1H), 7,40 (d, J = 8,9 Hz, 1H), 7,50-7,55 (m, 3H), 7,67-7,74 (m, 3H), 8,21 (d, J = 8,0 Hz, 1H).

Ejemplo 692

Síntesis de clorhidrato de 7-(3-{bis-[2-(1-oxo-1H-isoquinolin-2-il)etil]amino}propoxi)-1-etil-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 6, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,74 (s, 3H), 1,00 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,28 (br, 2H), 3,29 (s, 3H), 3,61 (br, 2H), 3,61-3,71(m, 5H), 3,95-4,09 (m, 1H), 4,17 (br, 2H), 4,45 (br, 4H), 6,71-6,74 (m, 2H), 6,91-6,97 (m, 2H), 7,40 (d, J = 9,0 Hz, 1H), 7,49-

7,57 (m, 4H), 7,67-7,74 (m, 4H), 8,15 (d, J = 8,2 Hz, 2H).

Ejemplo 693

Síntesis de diclorhidrato de 1-etil-7-(3-{[2-(7-methoxi-2-oxo-3,4-dihidro-2H-quinolin-1-il)etil]piridin-4-ilmetil-amino}propoxi)-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]-diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 6, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,74 (s, 3H), 1,00 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,25 (br, 4H), 3,01-3,31 (m, 4H), 3,31 (s, 3H), 3,61-3,70 (m, 1H), 4,00-4,12 (m, 5H), 4,61 (br, 2H), 6,65 (d, J = 7,4 Hz, 1H), 6,86-6,91 (m, 2H), 7,39 (d, J = 8,9 Hz, 1H), 7,47-7,53 (m, 2H), 7,65-7,74 (m, 2H), 8,08 (br, 2H), 8,21 (d, J = 8,0 Hz, 1H), 8,80 (br, 2H).

Ejemplo 694

Síntesis de diclorhidrato de 1-etil-3,3,5-trimetil-7-(3-{[2-(2-oxo-2H-quinolin-1-il)etil]piridin-4-ilmetilamino}-propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 6, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,74 (s, 3H), 1,00 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,28 (br, 2H), 3,21-3,49 (m, 5H), 3,60-3,70 (m, 3H), 4,01-4,19 (m, 3H), 4,78 (br, 4H), 6,64 (d, J = 7,4 Hz, 1H), 6,88 (br, 2H), 7,30 (br, 1H), 7,39 (d, J = 8,9 Hz, 1H), 7,55-8,20 (m, 6H), 8,82 (br, 2H).

Ejemplo 695

Síntesis de diclorhidrato de 1-etil-7-{3-[(2-(6-methoxi-2-oxo-2H-quinolin-1-il)etil)piridin-4-ilmetilamino]propoxi}-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 6, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,74 (s, 3H), 1,00 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,17 (br, 2H), 3,01-3,35 (m, 5H), 3,53-3,70 (m, 3H), 3,82 (s, 3H), 4,01-4,12 (m, 3H), 4,67 (br, 4H), 6,63 (d, J = 7,4 Hz, 1H), 6,83-6,89 (m, 2H), 7,21 (d, J = 9,2 Hz, 1H), 7,32 (s, 1H), 7,39 (d, J = 9,0 Hz, 1H), 7,70 (br, 1H), 7,91 (d, J = 9,5 Hz, 1H), 8,00 (br, 2H), 8,82 (br, 2H).

Ejemplo 696

Síntesis de triclorhidrato de 1-etil-7-(3-{[2-(6-methoxiquinolin-2-iloxi)etil]piridin-4-ilmetilamino}-propoxi)-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 6, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,74 (s, 3H), 1,00 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,09 (br, 2H), 3,01 (br, 2H), 3,31 (s, 3H), 3,70-3,90 (m, 4H), 3,98-4,18 (m, 5H), 4,33 (br, 2H), 4,80 (br, 2H), 6,50 (d, J= 9,6 Hz, 1H), 6,79-6,90 (m, 2H), 7,21-7,25 (m, 1H), 7,30-7,39 (m, 2H), 7,85 (d, J = 9,6 Hz, 1H), 8,20 (d, J = 8,9 Hz, 1H), 8,21 (br, 2H), 8,88 (br, 2H).

Ejemplo 697

Síntesis de diclorhidrato de 1-etil-3,3,5-trimetil-7-(3-{[2-(2-oxo-3,4-dihidro-2H-quinolin-1-il)etil]piridin-4-ilmetilamino}propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 6, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,74 (s, 3H), 1,00 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,10 (br, 2H), 2,51-2,60 (m, 2H), 2,85 (br, 4H), 3,31 (s, 3H), 3,10-3,35 (m, 2H), 3,52-3,70 (m, 3H), 4,01-4,11 (m, 3H), 4,22 (br, 2H), 6,85-6,89 (m, 2H), 7,00-7,02 (m, 1H), 7,13 (br, 1H), 7,19-7,24 (m, 2H), 7,40 (d, J = 8,8 Hz, 1H), 7,82 (br, 2H), 8,73 (br, 2H).

Ejemplo 698

Síntesis de diclorhidrato de 1-etil-3,3,5-trimetil-7-{3-[(2-(4-oxo-4H-tieno[3,2-c]piridin-5-il)etil)piridin-4-ilmetilamino]propoxi}-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 6, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,74 (s, 3H), 1,00 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,08 (br, 2H), 3,05 (br, 2H), 3,31 (s, 3H), 3,53-3,70 (m, 1H), 3,95-4,09 (m, 5H), 4,31 (br, 4H), 6,71-6,83 (m, 2H), 6,95 (br, 1H), 7,39 (d, J = 8,9 Hz, 1H), 7,45-7,47 (m, 1H), 7,57-7,64 (m, 2H), 7,88 (br, 2H), 8,72 (br, 2H).

Ejemplo 699

Síntesis de diclorhidrato de 1-etil-3,3,5-trimetil-7-(3-{[2-(7-oxo-7H-tieno[2,3-c]piridin-6-il)etil]piridin-4-il-metilamino}propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 6, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,74 (s, 3H), 1,00 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,32 (br, 2H), 3,33 (s, 3H), 3,26-3,37 (m, 2H), 3,43 (br, 2H), 3,62-3,70 (m, 1H), 4,00-4,13 (m, 3H), 4,53 (br, 2H), 4,82 (br, 2H), 6,82-6,89 (m, 2H), 6,92-6,93 (m, 1H), 7,38-7,42 (m, 2H), 7,69 (d, J = 7,2 Hz, 1H), 8,09 (d, J = 5,2 Hz, 1H), 8,44 (br, 2H), 9,00 (br, 2H).

Ejemplo 700

Síntesis de diclorhidrato de 1-etil-7-(3-{[2-(8-metoxi-2-oxo-2H-quinolin-1-il)etil]piridin-4-ilmetilamino}propoxi)-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 6, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,74 (s, 3H), 1,01 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,33 (br, 2H), 3,32 (s, 3H), 3,25-3,38 (m, 2H), 3,53-3,69 (m, 3H), 3,86 (s, 3H), 4,03-4,10 (m, 1H), 4,14 (br, 2H), 4,65 (br, 2H), 4,81 (br, 2H), 6,64 (d, J = 9,4 Hz, 1H), 6,89-6,95 (m, 2H), 7,21-7,33 (m, 3H), 7,41 (d, J = 8,9 Hz, 1H), 7,92 (d, J = 9,4 Hz, 1H), 8,14 (br, 2H), 8,68 (br, 2H).

640

Ejemplo 701

Síntesis de triclorhidrato de 1-etil-7-(3-{[2-(8-metoxi-quinolin-2-iloxi)etil]piridin-4-ilmetilamino}propoxi)-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 6, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,74 (s, 3H), 1,00 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,26 (br, 2H), 3,15-3,21 (m, 2H), 3,31 (s, 3H), 3,58-3,65 (m, 1H), 3,90 (s, 3H), 3,98-4,12 (m, 5H), 4,51-4,80 (m, 4H), 6,52 (d, J = 9,6 Hz, 1H), 6,83-6,89 (m, 2H), 7,08-7,11 (m, 1H), 7,19-7,21 (m, 1H), 7,32-7,48 (m, 2H), 7,89 (d, J = 9,6 Hz, 1H), 8,00 (br, 2H), 8,80 (br, 2H).

Ejemplo 702

Síntesis de diclorhidrato de 1-etil-3,3,5-trimetil-7-(3-{[2-(4-oxo-4H-furo[3,2-c]piridin-5-il)etil]piridin-4-il-metilamino}propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 6, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,74 (s, 3H), 1,01 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,16 (br, 2H), 3,09 (br, 2H), 3,31 (s, 3H), 3,60-3,75 (m, 3H), 3,91-4,08 (m, 3H), 4,38 (br, 4H), 6,77-6,87 (m, 3H), 6,94 (br, 1H), 7,39 (d, J = 9,0 Hz, 1H), 7,70 (br, 1H), 7,90 (br, 1H), 8,11 (br, 2H), 8,84 (br, 2H).

Ejemplo 703

Síntesis de diclorhidrato de 1-etil-7-(3-{[2-(6-methoxi-2-oxo-3,4-dihidro-2H-quinolin-1-il)etil]piridin-4-ilmetil-amino}propoxi)-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]-diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 6, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,74 (s, 3H), 1,01 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,16 (br, 2H), 2,48-2,54 (m, 2H), 2,77 (br, 2H), 3,31 (s, 3H), 3,25-3,34 (m, 2H), 3,53-3,69 (m, 3H), 3,76 (s, 3H), 3,98-4,10 (m, 3H), 4,33 (br, 2H), 4,74 (br, 2H), 6,60 (d, J = 8,3 Hz, 1H), 6,74 (br, 1H), 6,82-6,91 (m, 2H), 7,13 (d, J = 8,3 Hz, 1H), 7,40 (d, J = 9,0 Hz, 1H), 7,98 (br, 2H), 8,80 (br, 2H).

Ejemplo 704

Síntesis de diclorhidrato de 1-etil-7-(3-{[2-(7-methoxi-2-oxo-3,4-dihidro-2H-quinolin-1-il)etil]piridin-4-ilmetil-amino}propoxi)-3,3,5-tri-metil-1,5-dihidrobenzo[b][1,4]-diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 6, se sintetizó el compuesto objetivo.

^{1}H-NMR (DMSO-d_6) δppm:

0,74 (s, 3H), 1,01 (t, J = 7,0 Hz, 3H), 1,32 (s, 3H), 2,22 (br, 2H), 2,48-2,53 (m, 2H), 2,83 (br, 2H), 3,10-3,25 (m, 2H), 3,31 (s, 3H), 3,53-3,63 (m, 3H), 3,73 (s, 3H), 4,00-4,10 (m, 3H), 4,32 (br, 2H), 4,61 (br, 2H), 6,74-6,77 (m, 1H), 6,84-6,91 (m, 3H), 7,16 (br, 1H), 7,40 (d, J = 8,9 Hz, 1H), 8,00 (br, 2H), 8,83 (br, 2H).

642

Ejemplo 704A

Síntesis de 1,3,3-trimetil-8-(3-{[2-(1-oxo-1H-isoquinolin-2-il)etil]piridin-4-ilmetilamino}propoxi)-1,5-dihidrobenzo-[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 8, se sintetizó el compuesto objetivo.

^{1}H-NMR ($CDCl_3$) δppm:

1,05 (3H, br), 1,52 (3H, br), 1,88 - 1,93 (2H, m), 2,71 (2H, t, J = 6,7 Hz), 2,88 (2H, t, J = 6,0 Hz), 3,41 (3H, s), 3,67 (2H, s), 3,84 (2H, t, J = 5,9 Hz), 4,10 (2H, t, J= 6,0 Hz), 6,41 (1H, d, J = 7,3 Hz), 6,52 (1H, dd, J = 8,8 y 2,6 Hz), 6,61 (1H, d, J = 2,6 Hz), 6,87 (1H, d, J = 8,8 Hz), 6,97 (1H, d, J = 7,3 Hz), 7,08 (2H, d, J = 5,7 Hz), 7,49-7,53 (2H, m), 7,64 - 7,69 (1H, m), 7,78 (1H, br), 8,26 (2H, d, J = 5,7 Hz), 8,38 (1H, d, J = 7,3 Hz).

Ejemplo 704B

Síntesis de 1,3,3-trimetil-8-{3-[2-(1-oxo-1H-isoquinolin-2-il)etilamino]propoxi}-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

Usando un material de partida apropiado y siguiendo el procedimiento del Ejemplo 18, se sintetizó el compuesto objetivo.

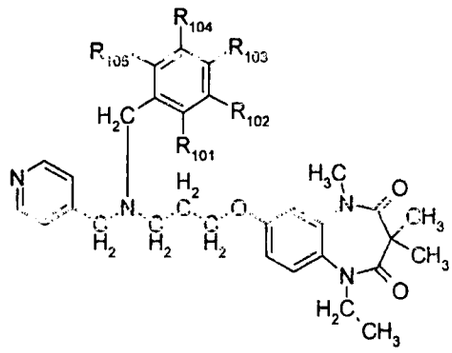
^{1}H-NMR ($CDCl_3$) δppm:

1,05 (3H, br), 1,55 (3H, br), 1,93-1,99 (2H, m), 2,86 (2H, t, J = 6,7 Hz), 3,06 (2H, t, J = 6,2 Hz), 3,43 (3H, s), 4,01 (2H, t, J = 6,2 Hz), 4,09-4,15 (3H, m), 6,46 (1H, d, J= 7,4 Hz), 6,66-6,72 (2H, m), 6,87 (1H, d, J = 8,6 Hz), 7,11 (1H,

d, J = 7,3 Hz), 7,46-7,51 (2H, m), 7,61-7,67 (1H, m), 7,87 (1H, br), 8,41 (1H, d, J = 8,0 Hz).

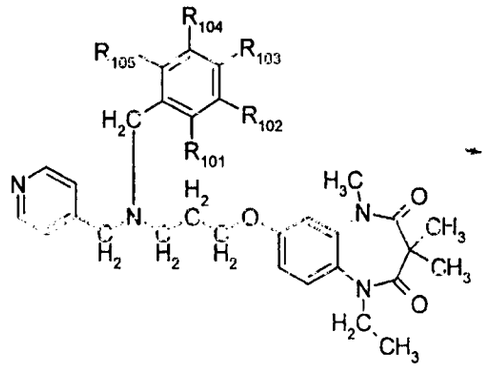
Usando materiales de partida apropiados y siguiendo los procedimientos de los Ejemplos arriba mencionados, se prepararon los compuestos mostrados en las Tablas 34 a 76.

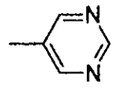
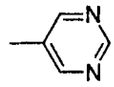
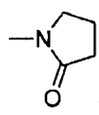
Tabla 34



Ejemplo	No.	R101	R102	R103	R104	R105	MS (M+1)
Ejemplo	705	-H	-H	-H	-H	-H	501
Ejemplo	706	-H	-H	$-C_6H_5$	-H	-H	577
Ejemplo	707	-H	-H	$-OCH_3$	-H	-H	531
Ejemplo	708	-H	$-OCH_3$	-H	-H	-H	531
Ejemplo	709	-H	-H	$-NHCOCH_3$	-H	-H	558
Ejemplo	710	-Cl	-H	-H	-H	-H	535
Ejemplo	711	-H	-Cl	-H	-H	-H	535
Ejemplo	712	-H	-H	-Cl	-H	-H	535
Ejemplo	713	$-OCH_3$	-H	-H	-H	-H	531
Ejemplo	714	-H	$-C_6H_5$	-H	-H	-H	577
Ejemplo	715	-H	-H	-2-TIENILO	-H	-H	583
Ejemplo	716	-H	-H	-3-PIRIDILO	-H	-H	578
Ejemplo	717	-H	-3-PIRIDILO	-H	-H	-H	578
Ejemplo	718	-3-PIRIDILO	-H	-H	-H	-H	578

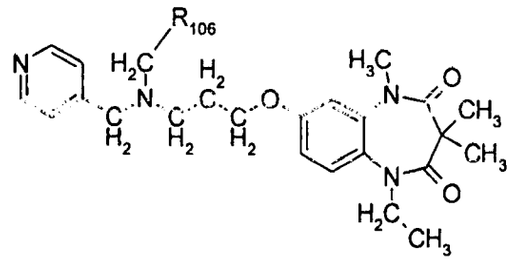
Tabla 35



Ejemplo No.		R101	R102	R103	R104	R105	MS (M+1)
Ejemplo	719	-H	-H		-H	-H	568
Ejemplo	720	-H	-H		-H	-H	567
Ejemplo	712	-H		-H	-H	-H	567
Ejemplo	722	-H	-H		-H	-H	579
Ejemplo	723	-H		-H	-H	-H	579
Ejemplo	724	-H	-H		-H	-H	584

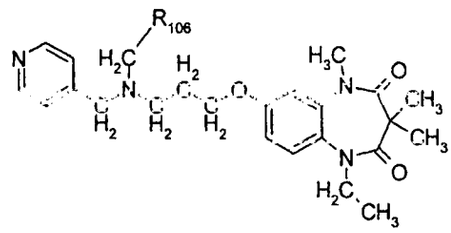
646

Tabla 36



Ejemplo No.		R106	MS(M+1)
Ejemplo	725	-3-FURILO	491
Ejemplo	726	-2-PIRIDILO	502
Ejemplo	727	-3-PIRIDILO	502
Ejemplo	728	-4-PIRIDILO	502
Ejemplo	729	-2-TIENILO	507
Ejemplo	730	-3-TIENILO	507
Ejemplo	731	$-CH=CHC_6H_5$(trans)	527
Ejemplo	732	-2-FURILO	491
Ejemplo	733	$-CH_2C_6H_5$	515
Ejemplo	734	$-CH(CH_3)C_6H_5$	529
Ejemplo	735	$-(CH_2)_2C_6H_5$	529
Ejemplo	736	-2-BENZTIAZOLILO	558

Tabla 37



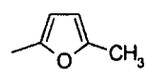
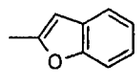
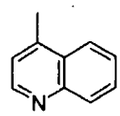
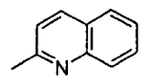
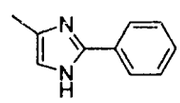
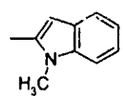
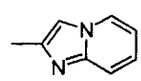
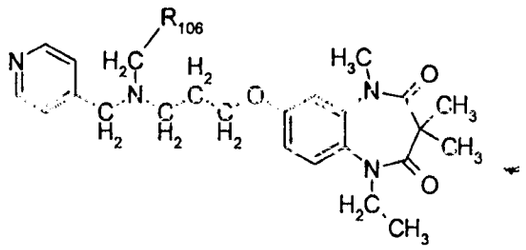
Ejemplo No.	R106	MS (M+1)
Ejemplo 737		491
Ejemplo 738		505
Ejemplo 739		521
Ejemplo 740		541
Ejemplo 741		552
Ejemplo 742		552
Ejemplo 743		567
Ejemplo 744		554
Ejemplo 745		541

Tabla 38



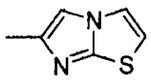
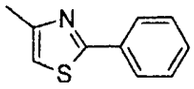
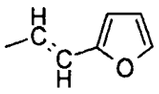
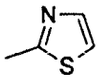
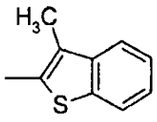
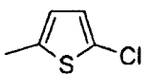
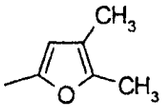
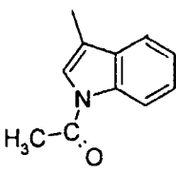
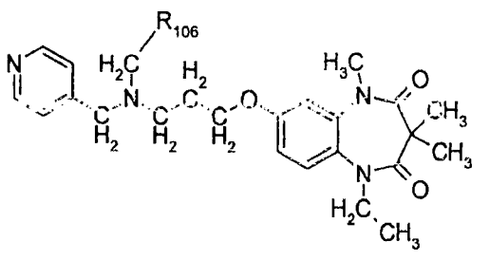
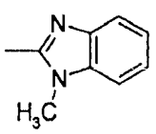
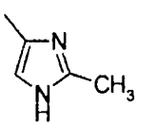
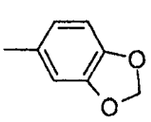
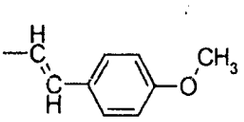
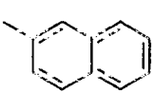
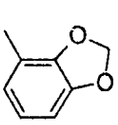
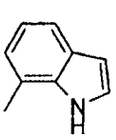
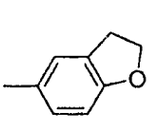
Ejemplo No.	R106	MS(M+1)
Ejemplo 746		547
Ejemplo 747		584
Ejemplo 748		517
Ejemplo 749		508
Ejemplo 750		571
Ejemplo 751		541
Ejemplo 753		519
Ejemplo 753		582

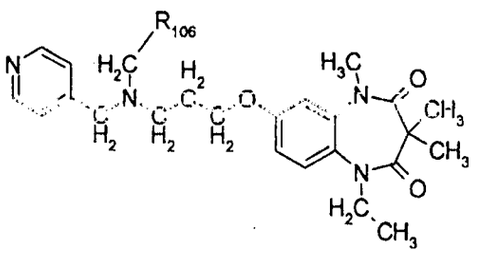
Tabla 39

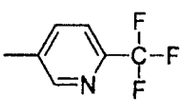
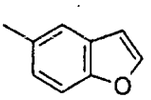
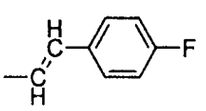
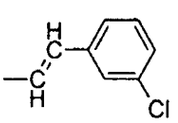
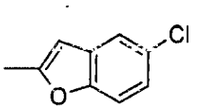
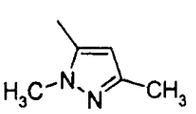
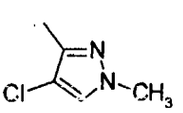
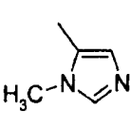
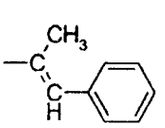


Ejemplo No.	R106	MS(M+1)
Ejemplo 754		555
Ejemplo 755		505
Ejemplo 756		545
Ejemplo 757		557
Ejemplo 758		551
Ejemplo 759		545
Ejemplo 760		540
Ejemplo 761		543

650

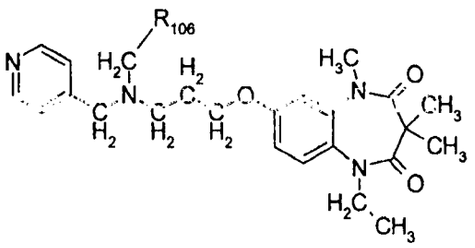
Tabla 40

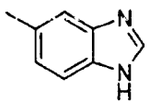
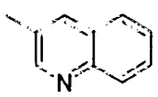
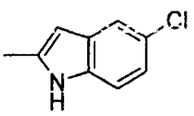
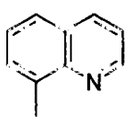
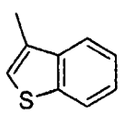
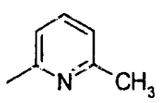
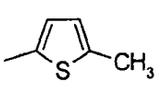
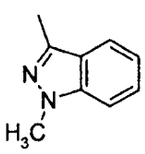


Ejemplo No.	R106	MS(M+1)
Ejemplo 762		570
Ejemplo 763		541
Ejemplo 764		545
Ejemplo 765		561
Ejemplo 766		575
Ejemplo 767		519
Ejemplo 768		539
Ejemplo 769		505
Ejemplo 770		541

651

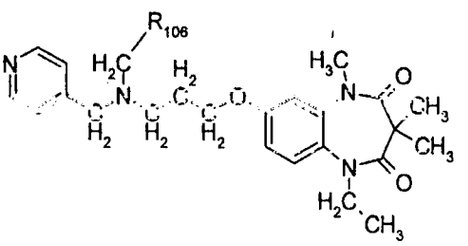
Tabla 41



Ejemplo No.	R106	MS(M+1)
Ejemplo 771		541
Ejemplo 772		552
Ejemplo 773		574
Ejemplo 774		552
Ejemplo 775		557
Ejemplo 776		516
Ejemplo 777		521
Ejemplo 778		555

652

Tabla 42



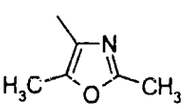
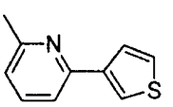
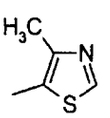
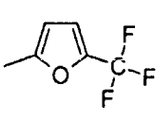
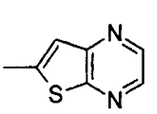
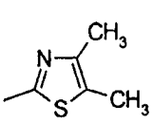
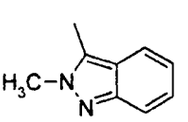
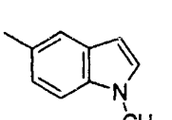
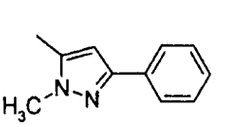
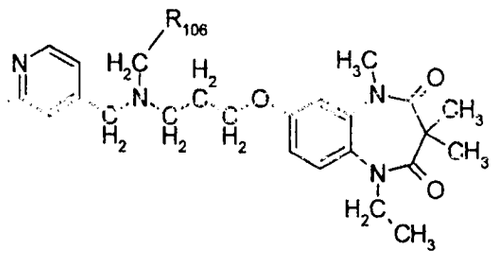
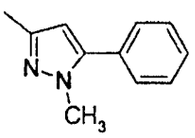
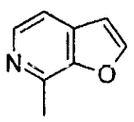
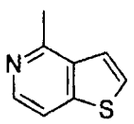
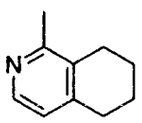
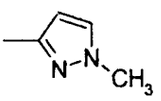
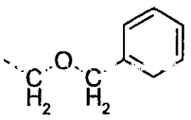
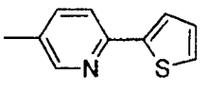
Ejemplo No.	R106	MS(M+1)
Ejemplo 779		520
Ejemplo 780		584
Ejemplo 781		522
Ejemplo 782		559
Ejemplo 783		559
Ejemplo 784		536
Ejemplo 785		555
Ejemplo 786		554
Ejemplo 787		581

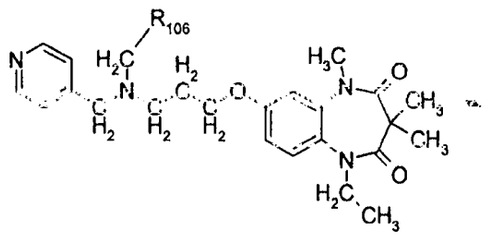
Tabla 43



Ejemplo No.	R106	MS(M+1)
Ejemplo 788		581
Ejemplo 789		542
Ejemplo 790		558
Ejemplo 791		556
Ejemplo 792		505
Ejemplo 793		545
Ejemplo 794		584

655

Tabla 44



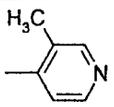
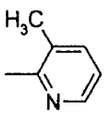
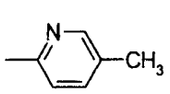
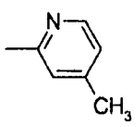
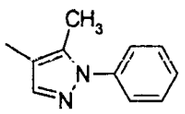
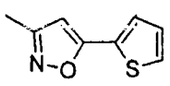
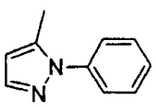
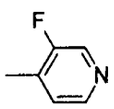
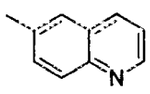
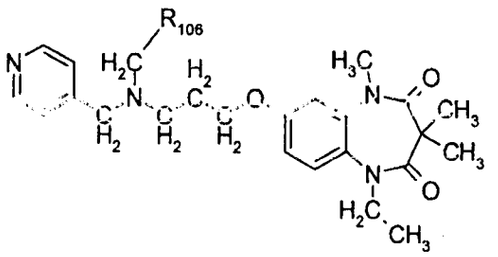
Ejemplo No.	R106	MS(M+1)
Ejemplo 795		516
Ejemplo 796		516
Ejemplo 797		516
Ejemplo 798		516
Ejemplo 799		581
Ejemplo 800		574
Ejemplo 801		567
Ejemplo 802		520
Ejemplo 803		552

Tabla 45



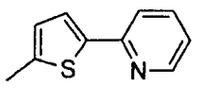
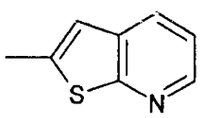
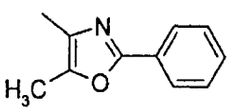
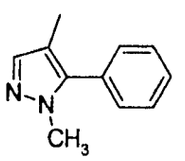
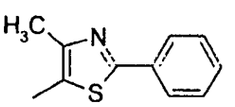
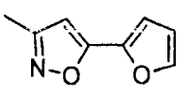
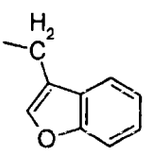
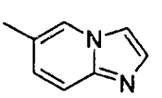
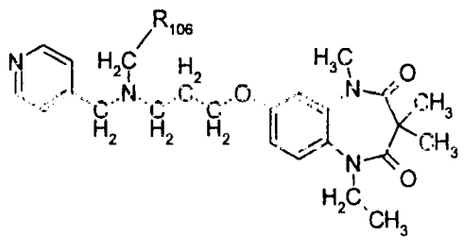
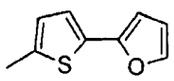
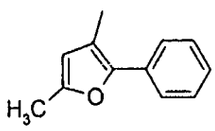
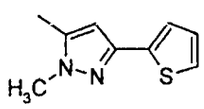
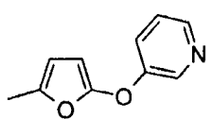
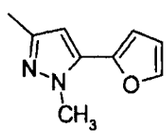
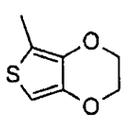
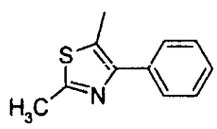
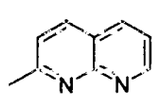
Ejemplo No.	R106	MS(M+1)
Ejemplo 804		584
Ejemplo 805		558
Ejemplo 806		582
Ejemplo 807		581
Ejemplo 808		598
Ejemplo 809		558
Ejemplo 810		555
Ejemplo 811		541

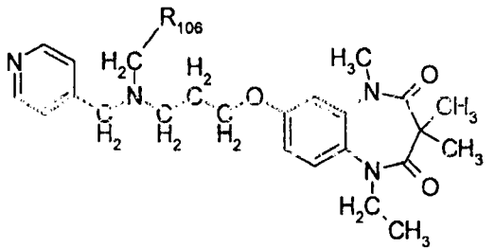
Tabla 46

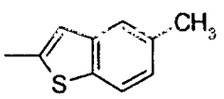
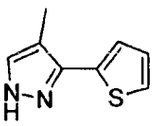
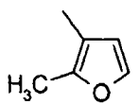
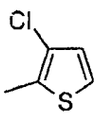
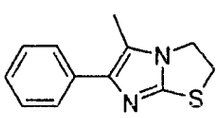
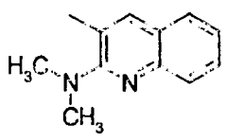
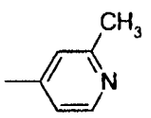
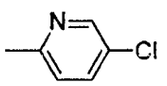


Ejemplo No.	R106	MS(M+1)
Ejemplo 812		573
Ejemplo 813		581
Ejemplo 814		587
Ejemplo 815		584
Ejemplo 816		571
Ejemplo 817		565
Ejemplo 818		598
Ejemplo 819		553

658

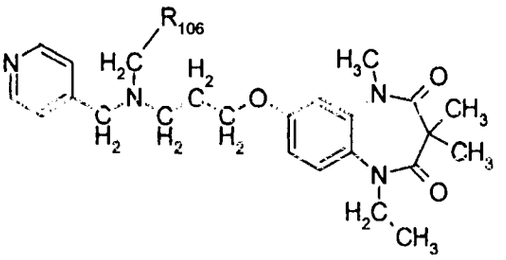
Tabla 47



Ejemplo No.	R106	MS(M+1)
Ejemplo 820		571
Ejemplo 821		573
Ejemplo 822		505
Ejemplo 823		541
Ejemplo 824		625
Ejemplo 825		595
Ejemplo 826		516
Ejemplo 827		536

659

Tabla 48



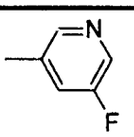
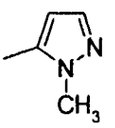
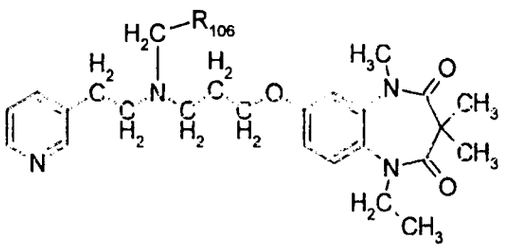
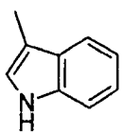
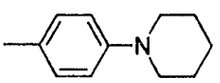
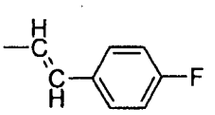
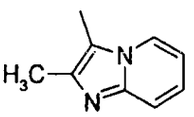
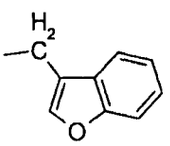
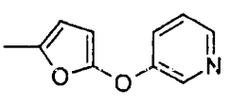
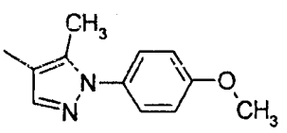
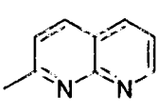
Ejemplo No.	R106	MS(M+1)
Ejemplo 828		520
Ejemplo 829		505

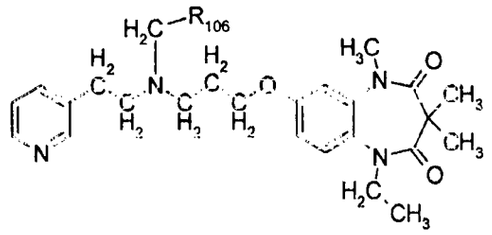
Tabla 49

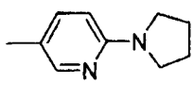
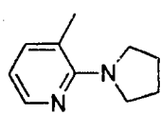
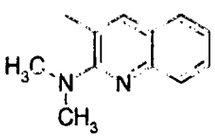
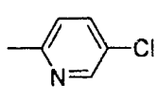
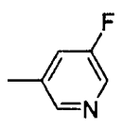
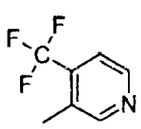
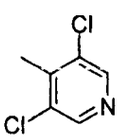
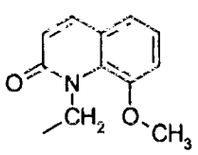


Ejemplo No.	R106	MS(M+1)
Ejemplo 830		554
Ejemplo 831		598
Ejemplo 832		559
Ejemplo 833		569
Ejemplo 834		569
Ejemplo 835		598
Ejemplo 836		625
Ejemplo 837		567

661

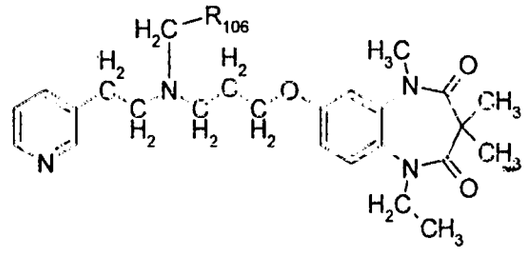
Tabla 50

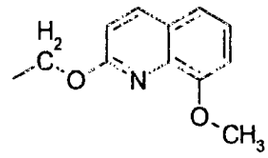
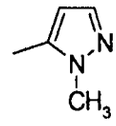
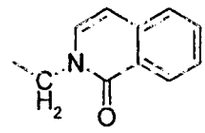


Ejemplo No.	R106	MS(M+1)
Ejemplo 838		585
Ejemplo 839		585
Ejemplo 840		609
Ejemplo 841		550
Ejemplo 842		534
Ejemplo 843		584
Ejemplo 844		584
Ejemplo 845		626

662

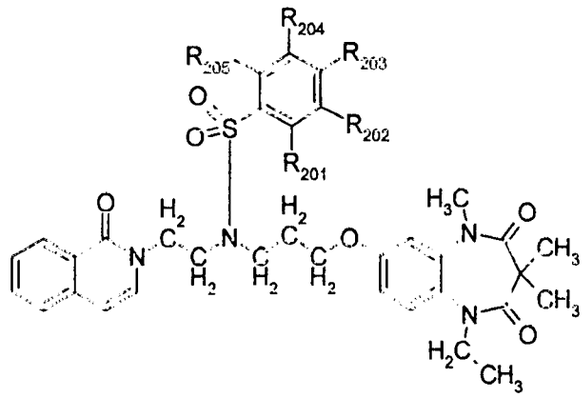
Tabla 51



Ejemplo No.	R106	MS(M+1)
Ejemplo 846		626
Ejemplo 847		519
Ejemplo 848		596

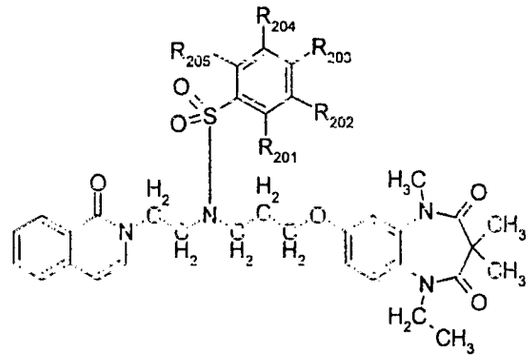
663

Tabla 52



Ejemplo No.	R201	R202	R203	R204	R205	MS(M+1)
Ejemplo 849	-H	-H	$-OCH_3$	-H	-H	661
Ejemplo 850	-H	-H	-Cl	-H	-H	665
Ejemplo 851	-H	-H	-H	-H	$-CH_3$	645
Ejemplo 852	-H	-H	-F	-H	-H	649
Ejemplo 853	-H	-H	-H	-H	-Cl	665
Ejemplo 854	-H	-H	-H	-H	$-CO_2CH_3$	689
Ejemplo 855	-CN	-H	-H	-H	-H	656
Ejemplo 856	-H	$-OCH_3$	-H	-H	-H	661
Ejemplo 857	-H	-F	-H	-H	-H	649
Ejemplo 858	-H	-H	-H	-H	-F	649
Ejemplo 859	-H	$-CH_3$	-H	-H	-H	645
Ejemplo 860	-H	-Cl	-H	-H	-H	665
Ejemplo 861	-H	-H	-H	-H	-H	631
Ejemplo 862	-H	-H	$-NHCOCH_3$	-H	-H	688
Ejemplo 863	-H	-H	$-CH_3$	-H	-H	645
Ejemplo 864	-H	$-CO_2H$	-H	-H	-H	675
Ejemplo 865	-H	-CN	-H	-H	-H	656
Ejemplo 866	-H	-H	-CN	-H	-H	656

Tabla 53



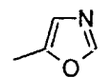
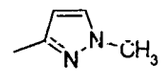
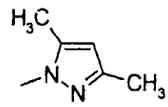
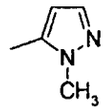
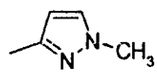
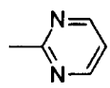
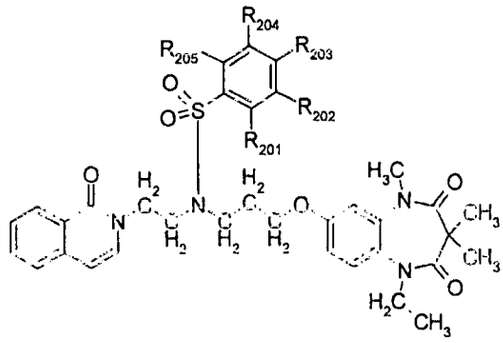
Ejemplo No.	R201	R202	R203	R204	R205	MS(M+1)
Ejemplo 867	-H	-H		-H	-H	698
Ejemplo 868	-H	-H		-H	-H	711
Ejemplo 869	-H	-H		-H	-H	725
Ejemplo 870	-H		-H	-H	-H	711
Ejemplo 871	-H	-H		-H	-H	714
Ejemplo 872	-H		-H	-H	-H	711
Ejemplo 873	-H		-H	-H	-H	709

Tabla 54



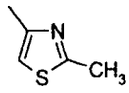
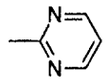
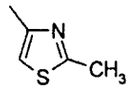
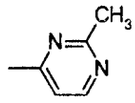
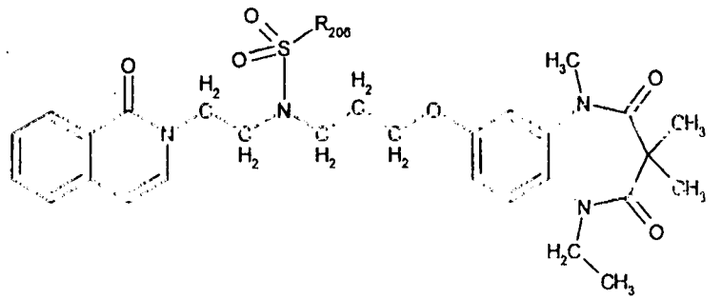
Ejemplo No.	R201	R202	R203	R204	R205	MS(M+1)
Ejemplo 874	-H		-H	-H	-H	728
Ejemplo 875	-H	-H		-H	-H	709
Ejemplo 876	-H	-H		-H	-H	728
Ejemplo 877	-H		-H	-H	-H	723

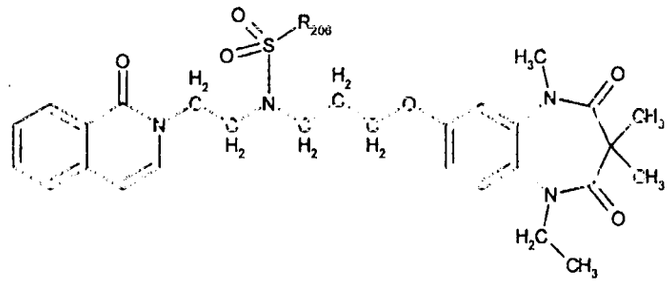
Tabla 55



Ejemplo No.		R206	MS(M+1)
Ejemplo	878	-2-TIENILO	637
Ejemplo	879	$-CH_2C_6H_5$	645
Ejemplo	880	-3-TIENILO	637
Ejemplo	881	-2-FURILO	621

667

Tabla 56



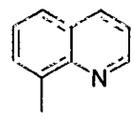
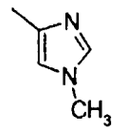
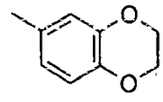
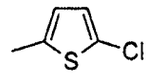
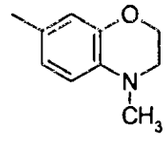
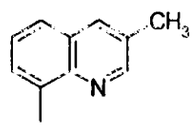
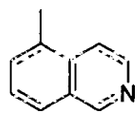
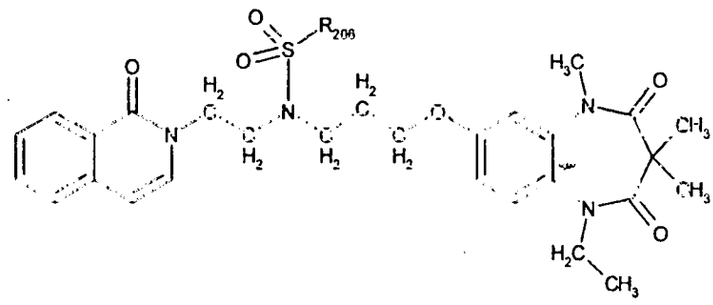
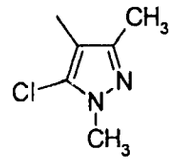
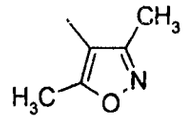
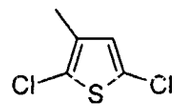
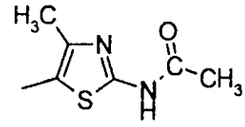
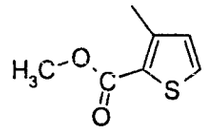
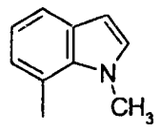
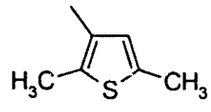
Ejemplo No.	R206	MS(M+1)
Ejemplo 882		682
Ejemplo 883		635
Ejemplo 884		689
Ejemplo 885		671
Ejemplo 886		702
Ejemplo 887		696
Ejemplo 888		682

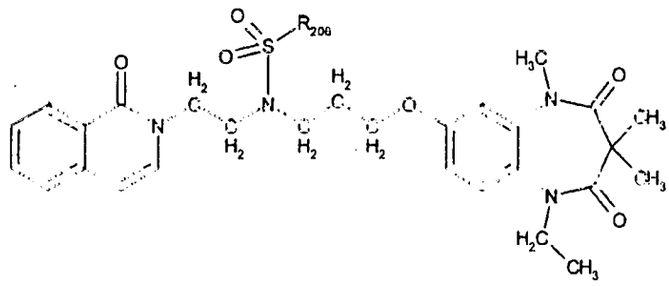
Tabla 57



Ejemplo No.	R206	MS(M+1)
Ejemplo 889		683
Ejemplo 890		650
Ejemplo 891		705
Ejemplo 892		709
Ejemplo 893		695
Ejemplo 894		684
Ejemplo 895		665

669

Tabla 58



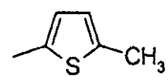
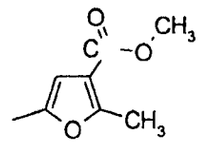
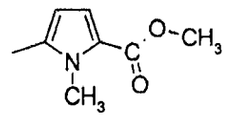
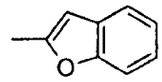
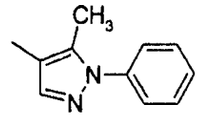
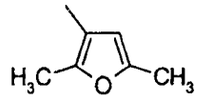
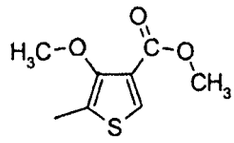
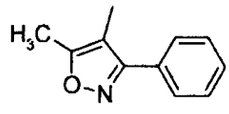
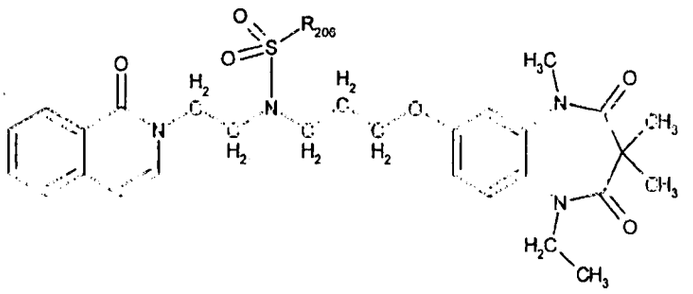
Ejemplo No.	R206	MS(M+1)
Ejemplo 896		651
Ejemplo 897		693
Ejemplo 898		692
Ejemplo 899		671
Ejemplo 900		711
Ejemplo 901		649
Ejemplo 902		725
Ejemplo 903		712

Tabla 59



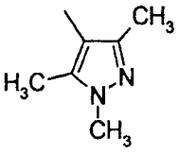
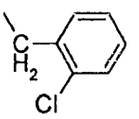
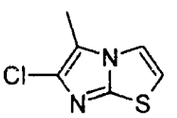
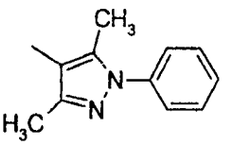
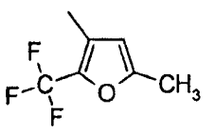
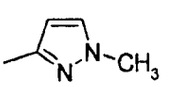
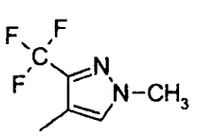
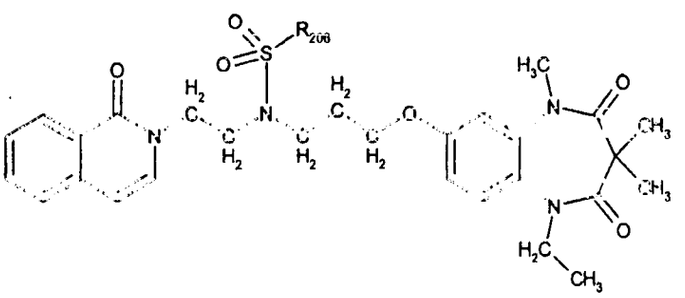
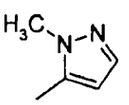
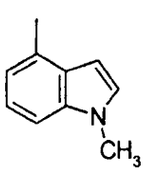
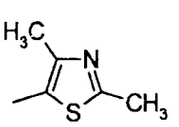
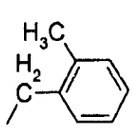
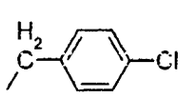
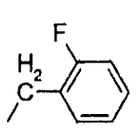
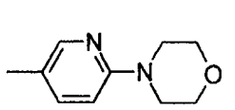
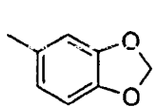
Ejemplo	No.	R206	MS(M+1)
Ejemplo	904		663
Ejemplo	905		679
Ejemplo	906		711
Ejemplo	907		725
Ejemplo	908		703
Ejemplo	909		635
Ejemplo	910		703

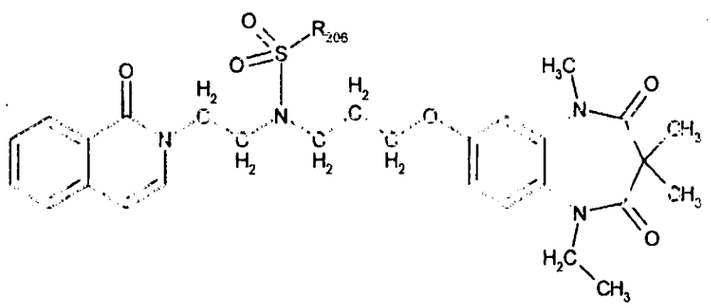
Tabla 60

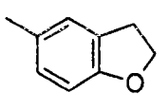
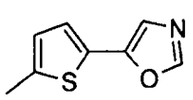
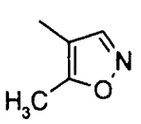
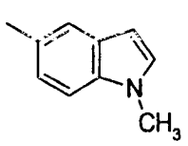
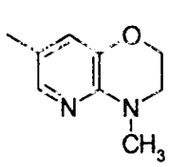
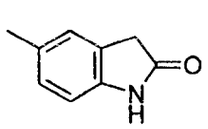
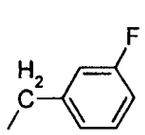


Ejemplo No.	R206	MS(M+1)
Ejemplo 911		635
Ejemplo 912		684
Ejemplo 913		666
Ejemplo 914		659
Ejemplo 915		679
Ejemplo 916		663
Ejemplo 917		717
Ejemplo 918		675

672

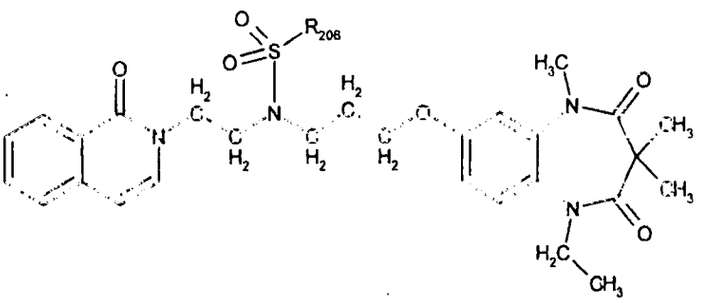
Tabla 61

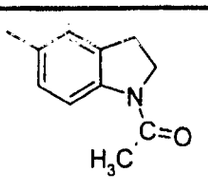
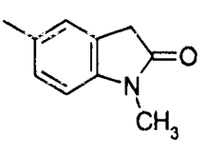
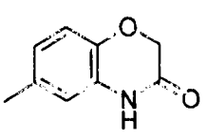
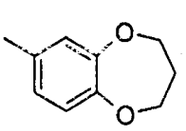
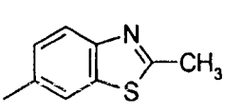
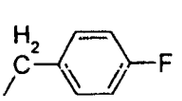
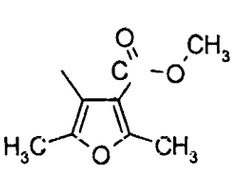


Ejemplo No.	R206	MS(M+1)
Ejemplo 919		673
Ejemplo 920		704
Ejemplo 921		636
Ejemplo 922		684
Ejemplo 923		703
Ejemplo 924		686
Ejemplo 925		663

623

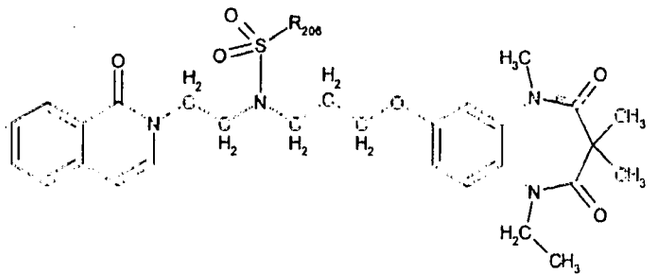
Tabla 62

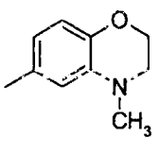
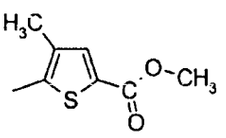
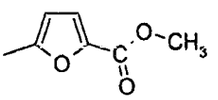
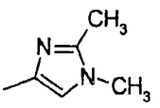
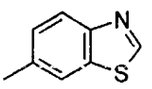
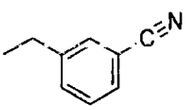
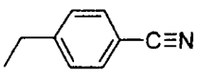
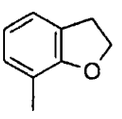


Ejemplo No.	R206	MS(M+1)
Ejemplo 926		714
Ejemplo 927		700
Ejemplo 928		702
Ejemplo 929		703
Ejemplo 930		702
Ejemplo 931		663
Ejemplo 932		707

624

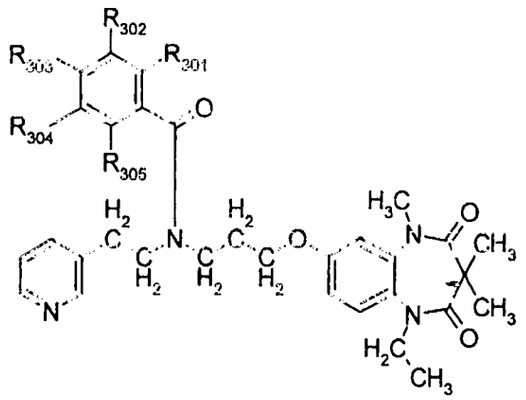
Tabla 63



Ejemplo No.	R206	MS(M+1)
Ejemplo 933		702
Ejemplo 934		709
Ejemplo 935		679
Ejemplo 936		649
Ejemplo 937		688
Ejemplo 938		670
Ejemplo 939		670
Ejemplo 940		673

675

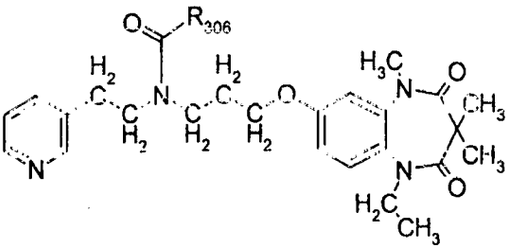
Tabla 64



Ejemplo	No.	R301	R302	R303	R304	R305	MS(M+1)
Ejemplo	941	-H	-H	-H	-H	-H	529
Ejemplo	942	-H	-H	$-CH_3$	-H	-H	543
Ejemplo	943	-H	-H	-Cl	-H	-H	563
Ejemplo	944	-H	-H	-F	-H	-H	547
Ejemplo	945	-H	-H	$-OCH_3$	-H	-H	559
Ejemplo	946	$-OCH_3$	-H	-H	-H	-H	559
Ejemplo	947	-Cl	-H	-H	-H	-H	563
Ejemplo	948	$-CH_3$	-H	-H	-H	-H	543
Ejemplo	949	-F	-H	-H	-H	-H	547
Ejemplo	950	-H	$-OCH_3$	-H	-H	-H	559
Ejemplo	951	-H	-Cl	-H	-H	-H	563
Ejemplo	952	-H	$-CH_3$	-H	-H	-H	543
Ejemplo	953	-H	-F	-H	-H	-H	547

676

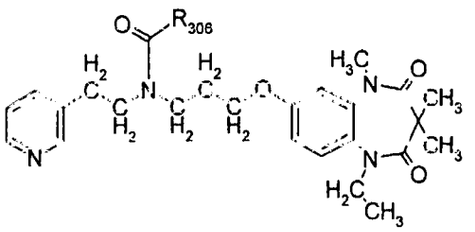
Tabla 65

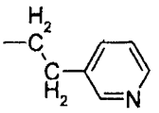
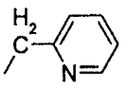
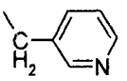
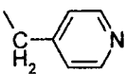
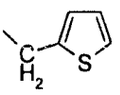
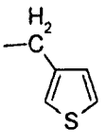
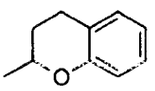
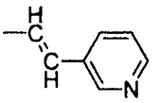
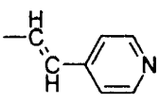


Ejemplo	No.	R306	MS(M+1)
Ejemplo	954	$-CH_2OC_6H_5$	559
Ejemplo	955	$-(CH_2)_2C_6H_5$	557
Ejemplo	956	$-CH=CHC_6H_5$(trans)	555
Ejemplo	957	-2-PIRIDILO	530
Ejemplo	958	-3-PIRIDILO	530
Ejemplo	959	-4-PIRIDILO	530
Ejemplo	960	-2-FURILO	519
Ejemplo	961	-2-TIENILO	535
Ejemplo	962	-3-FURILO	519
Ejemplo	963	-3-TIENILO	535
Ejemplo	964	2-BENZTIAZOLILO	586

677

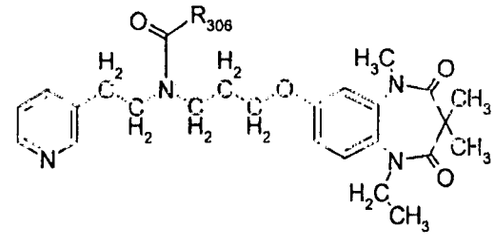
Tabla 66



Ejemplo No.	R306	MS(M+1)
Ejemplo 965		558
Ejemplo 966		544
Ejemplo 967		544
Ejemplo 968		544
Ejemplo 969		549
Ejemplo 970		549
Ejemplo 971		585
Ejemplo 972		556
Ejemplo 973		556

678

Tabla 67



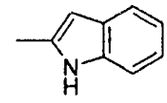
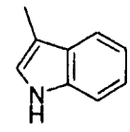
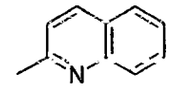
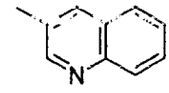
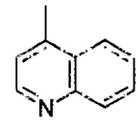
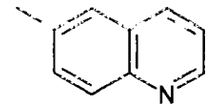
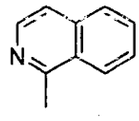
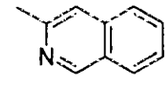
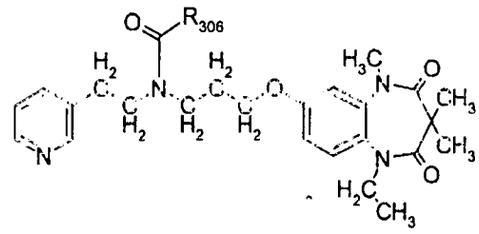
Ejemplo No.	R306	MS(M+1)
Ejemplo 974		568
Ejemplo 975		568
Ejemplo 976		580
Ejemplo 977		580
Ejemplo 978		580
Ejemplo 979		580
Ejemplo 980		580
Ejemplo 981		580

Tabla 68



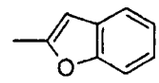
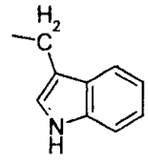
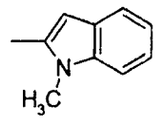
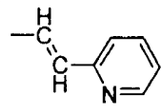
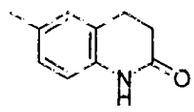
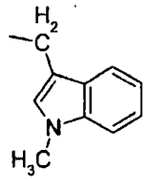
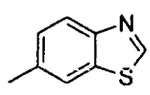
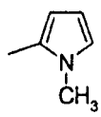
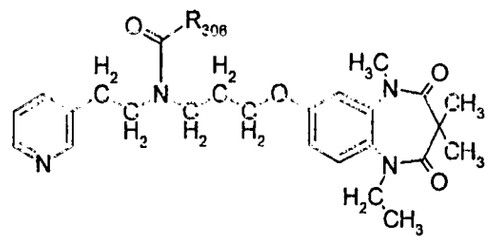
Ejemplo No.	R306	MS(M+1)
Ejemplo 982		569
Ejemplo 983		582
Ejemplo 984		582
Ejemplo 985		556
Ejemplo 986		598
Ejemplo 987		596
Ejemplo 988		586
Ejemplo 989		532

Tabla 69



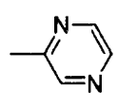
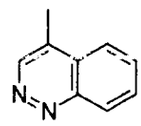
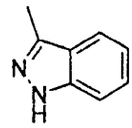
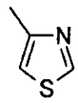
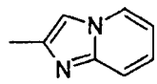
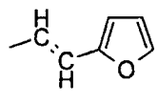
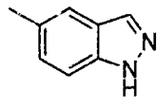
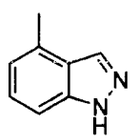
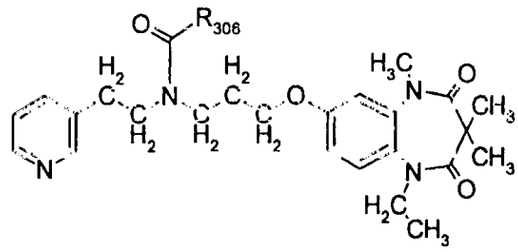
Ejemplo No.	R306	MS(M+1)
Ejemplo 990		531
Ejemplo 991		581
Ejemplo 992		569
Ejemplo 993		536
Ejemplo 994		569
Ejemplo 995		545
Ejemplo 996		569
Ejemplo 997		569

Tabla 70



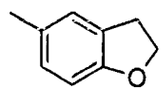
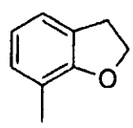
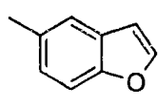
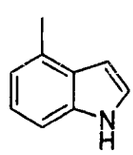
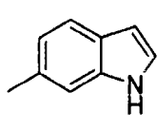
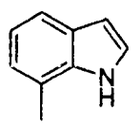
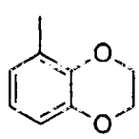
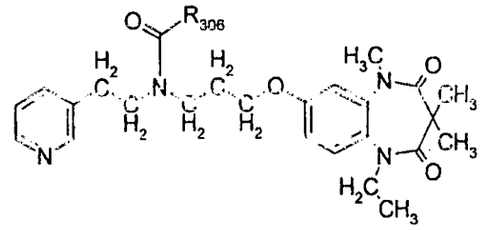
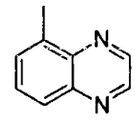
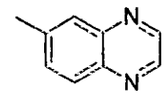
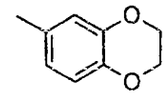
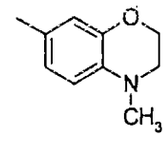
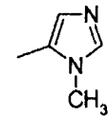
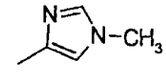
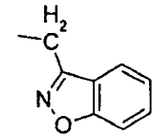
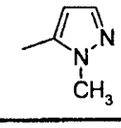
Ejemplo No.	R306	MS(M+1)
Ejemplo 998		571
Ejemplo 999		571
Ejemplo 1000		569
Ejemplo 1001		568
Ejemplo 1002		568
Ejemplo 1003		568
Ejemplo 1004		587

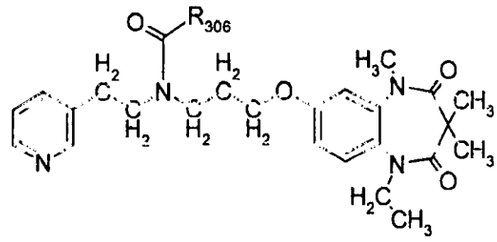
Tabla 71



Ejemplo No.	R306	MS(M+1)
Ejemplo 1005		581
Ejemplo 1006		581
Ejemplo 1007		587
Ejemplo 1008		600
Ejemplo 1009		533
Ejemplo 1010		533
Ejemplo 1011		584
Ejemplo 1012		533

683

Tabla 72



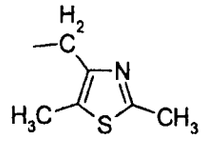
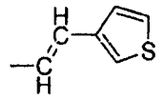
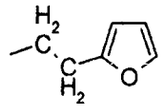
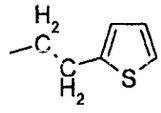
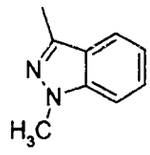
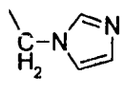
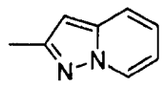
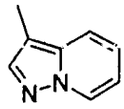
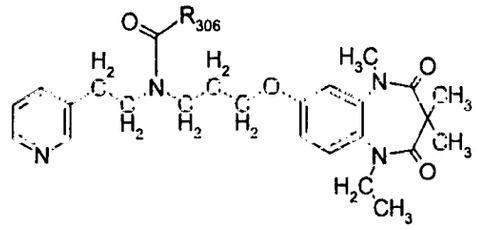
Ejemplo No.	R306	MS(M+1)
Ejemplo 1013		578
Ejemplo 1014		561
Ejemplo 1015		547
Ejemplo 1016		563
Ejemplo 1017		583
Ejemplo 1018		533
Ejemplo 1019		569
Ejemplo 1020		569

Tabla 73



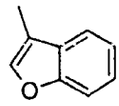
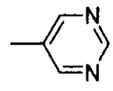
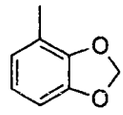
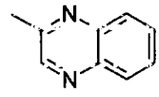
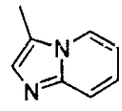
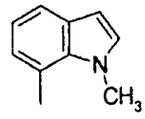
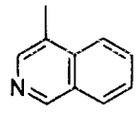
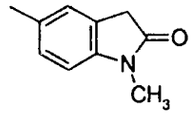
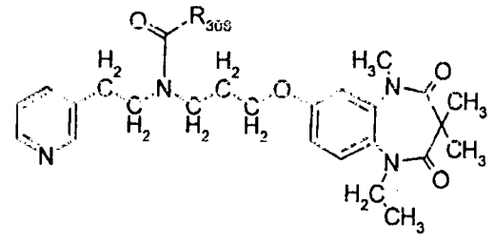
Ejemplo No.	R306	MS(M+1)
Ejemplo 1021		569
Ejemplo 1022		531
Ejemplo 1023		573
Ejemplo 1024		581
Ejemplo 1025		569
Ejemplo 1026		582
Ejemplo 1027		580
Ejemplo 1028		598

Tabla 74



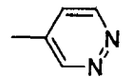
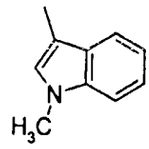
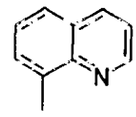
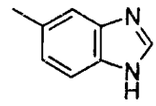
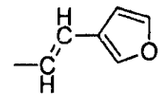
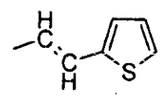
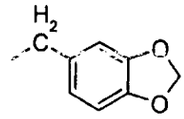
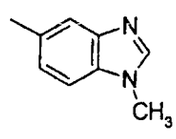
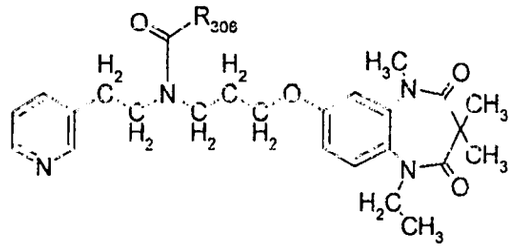
Ejemplo No.	R306	MS (M+1)
Ejemplo 1029		531
Ejemplo 1030		582
Ejemplo 1031		580
Ejemplo 1032		569
Ejemplo 1033		545
Ejemplo 1034		561
Ejemplo 1035		587
Ejemplo 1036		583

Tabla 75



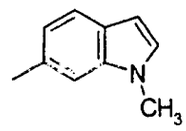
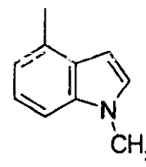
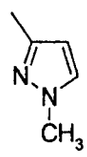
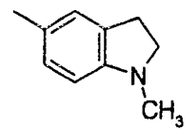
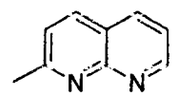
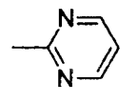
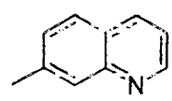
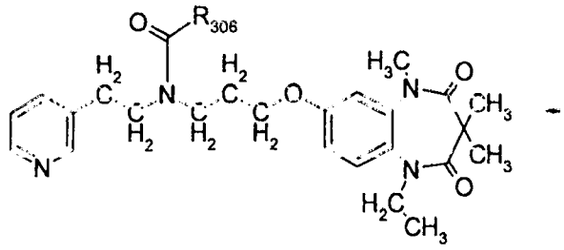
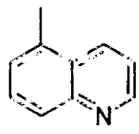
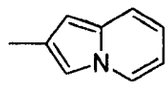
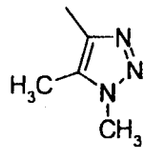
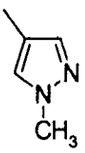
Ejemplo No.	R306	MS(M+1)
Ejemplo 1037		582
Ejemplo 1038		582
Ejemplo 1039		533
Ejemplo 1040		584
Ejemplo 1041		581
Ejemplo 1042		531
Ejemplo 1043		580

Tabla 76



Ejemplo No.	R306	MS(M+1)
Ejemplo 1044		580
Ejemplo 1045		568
Ejemplo 1046		548
Ejemplo 1047		533

Prueba farmacológica 1

(1) Producción de líneas celulares CHO-K1 que expresan Kv1.5 humanos

Las líneas celulares CHO-K1 que expresan en forma estable los canales Kv1.5 humanos fueron preparadas de la siguiente manera.

Se clonó cADN de Kv1.5 humano de longitud completa de una biblioteca de cADN de corazón humano (producido por Stratagene). La secuencia de Kv1.5 humano obtenida corresponde a la secuencia descripta en FASEB J. 5, 331-337 (1991).

El cADN de Kv1.5 humano obtenido se insertó en un plásmido que codifica un promotor de CMV y un marcador de resistencia G418 para producir un vector de expresión de Kv1.5. El vector de expresión de Kv1.5 humano fue transfectado en células CHO-K1 por el método de la lipofectamina. Después de cultivar las células en un medio F-12 (producido por Invitrogen Corp.) que contenía 10% de FBS (producido por Invitrogen Corp.) durante 3 o 4 días, se reemplazó el medio con un medio F-12 que contenía FBS que incluía 1.000 µg/ml de G418 (producido por Invitrogen Corp.), y se aislaron colonias individuales. La cantidad de expresión del canal Kv1.5 en las colonias individuales se cuantificó al nivel mRNA por RT-PCR y luego se cuantificó al nivel de proteína por transferencia western. Finalmente, la corriente expresada se analizó por el método de clampeo de membrana ("patch clamp"). Las líneas celulares que expresan una corriente de 200 pA o más por célula fueron seleccionadas como líneas celulares que expresan canales para la medición

de la actividad por el método de campleo de membrana..

(2) Producción de la línea celular CHO que expresa GIRK1/4 humano

Las líneas celulares CHO que expresan en forma estable los canales GIRK1/4 humanos fueron preparadas de la siguiente manera.

Se clonó cADN de GIRK1 humano de longitud completa a partir de bibliotecas de cADN derivado de células HuH y células HeLa. El cADN de GIRK4 de longitud completa se amplificó de una biblioteca de cADN de corazón humano (producido por Clontech Laboratories, Inc.) por PCR usando cebadores sintéticos mostrados en la Tabla 1, y clonados en el sitio de enzimas de restricción Eco-RI de pCR-Blunt (producido por Invitrogen Corporation) o en el sitio HincII de pUC118 (producido por Takara Bio, Inc.).

Tabla 77

Cebador	Secuencia

690

hGIRK1-S	5'-ATGTCTGCACTCCGAAGGAAATTTG-3'	SEQ ID No.1
hGIRK1-A	5'-TTATGTGAAGCGATCAGAGTTC-3'	SEQ ID No.2
hGIRK1-S2	5'-GCAGGGTACCCCTTCGTATTATGTCTGCACTCC-3'	SEQ ID No.3
hGIRK1-A3	5'-GGTGTCTGCCGAGATTTGA-3'	SEQ ID No.4
hGIRK1-A4	5'-CCGAGTGTAGGCGATCACCC-3'	SEQ ID No.5
hGIRK4-S	5'-ATGGCTGGCGATTCTAGGAATGCC-3'	SEQ ID No.6
hGIRK4-A	5'-TCTCACCGAGCCCCTGGCCTCCC-3'	SEQ ID No.7
hGIRK4-S2	5'-AACCAGGACATGGAGATTGG-3'	SEQ ID No.8
hGIRK4-A2	5'-GAGAACAGGAAAGCGGACAC-3'	SEQ ID No.9

Las secuencias de cADN de GIRK1 y GIRK4 humanos obtenidas corresponden a secuencias conocidas (base de datos NCBI: GIRK1 (NM_002239) y GIRK4 (NM_000890) respectivamente). Las secuencias de cADN de GIRK1 y GIRK4 obtenidas fueron clonadas en el sitio de la enzima de restricción Eco-RI de pCR-Blunt (que se puede obtener de Invitrogen Corporation) o en el sitio HincII de pUC118 (que se puede obtener de Takara Bio, Inc.). Se construyó un vector de expresión de GIRK4 por inserción en el sitio BamHI-XhoI de pcDNA5/FRT. Se construyó un vector de expresión GIRK1 por inserción en el sitio KpnI-XhoI de pcDNA3.1(+) o pCAG_neo. Las células FLP-IN-CHO (producido por Invitrogen Corporation) fueron transfectadas con vectores de expresión GIRK1 y GIRK4 humanos usando Lipofectamine 2000 (producido por Invitrogen Corporation) de acuerdo con el protocolo adjuntado con el reactivo o usando un método de inducción electrónico ("Nucleofector Kit-T", producido por Amaxa). Primero, las células transfectadas con el vector de expresión GIRK4 fueron cultivadas en un medio F12 que contenía 10% de suero (producido por Sigma) suplementado con 600 µg/ml de higromicina en una incubadora con 5% de dióxido de carbono a 37°C. Luego las células que

expresan GIRK4 fueron transfectadas con el vector de expresión GIRK1 y fueron cultivadas en medio F12 que contenía 10% de suero suplementado con 350 µg/ml de G418 y 600 µg/ml de higromicina en una incubadora con 5% de dióxido de carbono a 37°C para seleccionar líneas celulares que expresan GIRK1/4. Las poblaciones celulares cuyo crecimiento se observó después de aproximadamente 2 semanas fueron aisladas usando anillos de clonación, y se proliferaron las colonias individuales obtenidas. Se extrajo ARN de colonias individuales, y se sintetizó cADN de hebra simple por un kit de síntesis de cADN (producido por Invitrogen Corporation), y la cantidad de expresión se cuantificó al nivel de mARN por PCR en tiempo real (Applied Biosystems, Ltd.). Finalmente, se analizó la corriente expresada por el método de clampeo de membrana descripto más abajo. Las líneas celulares que expresan una corriente de 500 pA o más por célula fueron seleccionadas como líneas celulares que expresan canales para la medición de la actividad por el método de clampeo de membrana.

(3) Medición de la corriente del canal de iones por el método de clampeo de membrana (línea celular CHO-K1 que expresa Kv1.5 humano).

Se llevó a cabo un experimento usando una configuración de clampeo de membrana a temperatura ambiente (20 a 26°C). Se montó una cámara de perfusión que tenía un diámetro de 20 mm (caudal: aprox. 5 ml/min) en la platina de un microscopio invertido con contraste de fases (producido por Nikon Corporation) colocado en una mesa aislada de vibraciones. Un portaobjetos recubierto con poli-L-lisina (producida por

Sigma) (diámetro: 15 mm, producido por Matsunami Glass Ind., Ltd.) en el cual se cultivaron células que expresan Kv1.5 humano fue colocado en la cámara de perfusión.

Se aplicaron pulsos de estimulación despolarizantes y se registró la corriente iónica usando un amplificador de clampeo de membrana (EPC-7 o EPC-7 PLUS, producido por HEKA) y una computadora personal (fabricada por IBM Corp.) en la cual se instaló software para adquisición de datos y análisis de la corriente del canal de iones (PULSE 8.77, producido por HEKA). La corriente se midió en la configuración de células enteras de la técnica de clampeo de membrana. La punta (resistencia: 2 a 4 MΩ) de una pipeta de vidrio de borosilicato (producido por Sutter Instrument Co.) se colocó suavemente sobre la membrana celular usando un micromanipulador mecánico tridimensional (producido por Shoshin EM Corporation). La débil succión dio por resultado una formación de sello giga (la resistencia de la pipeta aumentó a más de 1 GΩ). Subsiguientemente, se aplicó una succión más fuerte para romper la membrana celular. La corriente capacitativa derivada de la membrana celular fue corregida usando un amplificador de clampeo de membrana. Subsiguientemente, se midió la resistencia en serie (Rs) entre la pipeta y el interior de la célula y se corrigió.

La composición de la solución extracelular usada se muestra más abajo. A menos que se especifique de otra manera, estos componentes se obtuvieron de Wako Pure Chemical Industries, Ltd.

NaCl 140 mM,

KCl 40 mM,

$CaCl_2$ 1,8 mM,

$MgCl_2$ 1 mM,

NaH_2PO_4 0,33 mM,

HEPES 5 mM

Glucosa 5,5 mM (pH = 7.4)

Cada compuesto de prueba se preparó como una solución stock concentrada 1000 veces que se disolvió en DMSO y luego se diluyó en la solución extracelular.

La composición de la solución interna de electrodos usada se muestra más abajo. A menos que se especifique de otra manera, estos componentes se obtuvieron de Wako Pure Chemical Industries, Ltd.

KOH 100 mM,

KCl 40 mM,

Ácido aspártico 70 mM,

$MgCl_2$ 1 mM,

MgATP 5 mM,

K_2 fosfato de creatina 5 mM,

HEPES 5 mM

EGTA 5 mM (pH = 7,2)

(4) Medición de la corriente del canal de iones por el método de clampeo de membrana (línea celular CHO-K1 que expresa GIRK1/4 humano)

Se llevó a cabo un experimento usando una configuración de clampeo de membrana a temperatura ambiente (20 a 26°C). Se montó una cámara de perfusión que tenía un diámetro de 20 mm (caudal: aprox. 5 ml/min) en la platina de un microscopio invertido con contraste de fases (producido por Nikon Corporation) colocado en una mesa con aislamiento de

vibraciones. Un portaobjetos recubierto con poli-L-lisina (producido por Sigma) (diámetro: 15 mm, producido por Matsunami Glass Ind., Ltd.) en el cual se cultivaron células que expresaban GIRK1/4 humano fue colocado en la cámara de perfusión.

Se aplicaron pulsos de estimulación hiperpolarizantes y se registró la corriente iónica usando un amplificador de clampeo de membrana (EPC-7 o EPC-7 PLUS, fabricado por HEKA) y una computadora personal (fabricada por IBM Corp.) en donde se instaló un software para adquisición de datos y análisis de la corriente del canal de iones (PULSE 8.77, fabricado por HEKA). La corriente se midió en la configuración de célula entera de la técnica de clampeo de membrana. La punta (resistencia: 2 a 4 MΩ) de una pipeta de vidrio de borosilicato (producida por Sutter Instrument Co.) se colocó suavemente sobre la membrana celular usando un micromanipulador mecánico tridimensional (producido por Shoshin EM Corporation). La débil succión dio por resultado una formación de sello giga (La resistencia de la pipeta aumentó a más de 1 GΩ). Subsiguientemente, se aplicó succión más fuerte para romper la membrana celular. La corriente capacitativa derivada de la membrana celular fue corregida usando un amplificador de clampeo de membrana. Subsiguientemente, la resistencia en serie (Rs) entre la pipeta y el interior de la célula se midió y se corrigió.

La composición de la solución extracelular usada se muestra más abajo. A menos que se especifique de otra manera, estos componentes fueron obtenidos de Wako Pure Chemical Industries, Ltd.

NaCl	140 mM,
KCl	4 mM,
$CaCl_2$	1,8 mM,
$MgCl_2$	1 mM,
NaH_2PO_4	0,33 mM,
HEPES	5 mM
Glucosa	5,5 mM (pH = 7.4)

Cada compuesto de prueba se preparó como una solución stock concentrada 1000 veces que se disolvió en DMSO y luego se diluyó en la solución extracelular.

La composición de la solución interna de electrodos usada se muestra más abajo. A menos que se especifique de otra manera, estos componentes fueron obtenidos de Wako Pure Chemical Industries, Ltd.

KOH	100 mM,
KCl	40 mM,
Ácido aspártico	70 mM,
$MgCl_2$	1 mM,
MgATP	5 mM,
K_2 fosfato de creatina	5 mM,
HEPES	5 mM
EGTA	5 mM (pH = 7,2)

(5) Medición de la corriente Kv1.5 humana

Mientras se mantenía el potencial de membrana a -80 mV, se aplicaron pulsos despolarizantes (-80 mV durante 0,05 segundos → +40 mV durante 0,2 segundos → -40 mV durante 0,2 segundos → -80 mV durante 0,05 segundos) una frecuencia de estimulación de 1 Hz para medir la corriente del canal Kv1.5. Más específicamente, primero, mientras se perfundía una

solución extracelular que contenía 0,1% de DMSO y se mantenía el potencial de membrana a -80 mV, se aplicaron pulsos despolarizantes. La corriente obtenida durante la aplicación de pulsos se registró como una corriente en ausencia de los compuestos de prueba. Subsiguientemente, mientras se perfundía una solución extracelular que contenía 0,1 µM de un compuesto de prueba y se mantenía el potencial de membrana a -80 mV, se aplicaron pulsos despolarizantes. Después que se estabilizó el efecto inhibidor del compuesto de prueba, se registró la corriente. Se repitió el mismo procedimiento usando una solución extracelular que contenía 1 µM del compuesto de prueba y luego usando una solución extracelular que contenía 10 µM del compuesto de prueba. Se registró la corriente obtenida usando la solución que contenía el compuesto de prueba a cada concentración.

Los datos se analizaron usando la corriente de meseta registrada durante la estimulación despolarizante a +40 mV. La corriente de meseta se refiere a la corriente promedio que fluye durante un período de 195 a 199 milisegundos desde el comienzo de la estimulación con pulsos despolarizantes a +40 mV.

Usando la corriente de meseta en presencia del compuesto de prueba y la corriente de meseta" en ausencia del compuesto de prueba, se calculó la corriente relativa en la solución que contenía el compuesto de prueba a cada concentración de acuerdo con la siguiente fórmula:

Corriente relativa =

(Corriente de meseta en presencia del compuesto de prueba)/

(Corriente de meseta en ausencia del compuesto de prueba)

(6) Medición de la corriente de GIRK1/4 humano

Mientras se mantuvo el potencial de membrana a -80 mV, se aplicaron pulsos hiperpolarizantes (-80 mV durante 0,05 segundos → -120 mV durante 0,2 segundos → -80 mV durante 0,05 segundos) a una frecuencia de estimulación de 1 Hz para medir la corriente del canal GIRK1/4. Más específicamente, primero, mientras se perfundía una solución extracelular que contenía 0,1% de DMSO y se mantenía el potencial de membrana a -80 mV, se aplicaron pulsos hiperpolarizantes. La corriente obtenida durante la aplicación de los pulsos se registró como la corriente en ausencia de los compuestos de prueba. Subsiguientemente, mientras se perfundía una solución extracelular que contenía 0,1 μM de un compuesto de prueba y se mantenía el potencial de membrana a -80 mV, se aplicaron pulsos hiperpolarizantes. Después que se estabilizó el efecto inhibidor del compuesto de prueba, se registró la corriente. Se repitió el mismo procedimiento usando una solución extracelular que contenía 1 μM del compuesto de prueba y luego usando una solución extracelular que contenía 10 μM del compuesto de prueba. Se registró la corriente obtenida usando la solución que contenía el compuesto de prueba a cada concentración.

Los datos fueron analizados usando la corriente de meseta registrada durante la estimulación despolarizante a -120 mV. La corriente de meseta se refiere a la corriente promedio que fluye durante un período de 195 a 199 milisegundos desde el comienzo de la estimulación con pulsos despolarizantes a -120 mV.

Usando la corriente de meseta en presencia del compuesto

de prueba y la corriente de meseta en ausencia del compuesto de prueba, se calculó la corriente relativa en la solución que contenía el compuesto de prueba a cada concentración de acuerdo con la siguiente fórmula:

Corriente relativa =

(Corriente de meseta en presencia del compuesto de prueba)/ (Corriente de meseta en ausencia del compuesto de prueba)

(7) Cálculo de la actividad inhibidora sobre la corriente iónica del canal Kv1.5 y la corriente del canal GIRK1/4

La concentración para una inhibición del 50% de la corriente del canal Kv1.5 o la corriente del canal GIRK1/4 (valor IC50) se calculó de acuerdo con la siguiente ecuación de regresión no lineal:

Corriente relativa = 1/(1+ [Concentración del compuesto]/ $IC_{50})^{nH}$, en donde nH es el coeficiente de Hill.

La Tabla 78 muestra los resultados de prueba.

Tabla 78

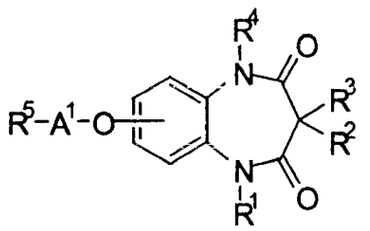
Compuesto de prueba	KV1.5 IC_{50} (μM)	GIRK1/4 IC_{50} (μM)
Compuesto del ejemplo 8	0,40	0,93
Compuesto del ejemplo 10	0,58	3,6
Compuesto del ejemplo 14	0,58	0,72
Compuesto del ejemplo 19	0,54	1,4
Compuesto del ejemplo 23	0,18	0,25
Compuesto del ejemplo 31	1,30	2,90
Compuesto del ejemplo 45	0,69	2,15
Compuesto del ejemplo 50	0,25	0,46

699

Compuesto del ejemplo 51	0,21	1,5
Compuesto del ejemplo 54	0,28	0,97
Compuesto del ejemplo 63	0,24	0,92
Compuesto del ejemplo 68	0,38	5,1
Compuesto del ejemplo 85	0,15	0,15
Compuesto del ejemplo 125	0,19	0,091
Compuesto del ejemplo 132	0,27	0,27
Compuesto del ejemplo 200	0,29	0,59
Compuesto del ejemplo 229	0,16	0,69
Compuesto del ejemplo 242	0,18	0,22
Compuesto del ejemplo 380	0,16	0,49
Compuesto del ejemplo 395	0,19	0,33
Compuesto del ejemplo 398	0,22	0,49
Compuesto del ejemplo 417	0,18	0,98
Compuesto del ejemplo 464	0,44	3,20
Compuesto del ejemplo 551	0,39	5,20
Compuesto del ejemplo 568	0,42	0,05
Compuesto del ejemplo 573	0,33	1,50
Compuesto del ejemplo 575	0,44	0,50
Compuesto del ejemplo 590	0,46	2,40
Compuesto del ejemplo 595	0,50	0,79
Compuesto del ejemplo 611	0,31	0,37
Compuesto del ejemplo 628	0,98	2,50
Compuesto del ejemplo 629	0,76	0,17
Compuesto del ejemplo 633	1,10	8,40
Compuesto del ejemplo 634	0,36	0,49

REIVINDICACIONES

1. Un compuesto de benzodiazepina representado por la Fórmula general (1):



(1)

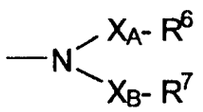
o una sal del mismo,

caracterizado porque R^1, R^2, R^3 y R^4 son cada uno independientemente hidrógeno o alquilo inferior;

R^2 y R^3 pueden estar unidos para formar alquileno inferior;

A^1 es alquileno inferior opcionalmente substituido con uno o más hidroxi; y

R^5 es un grupo representado por:



en donde R^6 y R^7 son cada uno independientemente hidrógeno o un grupo orgánico;

X_A y X_B son cada uno independientemente un enlace, alquileno inferior, alquenileno inferior, -CO-, $-SO_2-$, $-SO_2-$alquileno inferior, -CO-alquileno inferior, -CO-alquenileno inferior, alquileno inferior-N(alquilo inferior)-CO-alquileno inferior, alquileno inferior- N(alquilo inferior)-, alquileno inferior-N(alquilo inferior)-CO- o alquileno inferior-O-.

2. Un compuesto de benzodiazepina representado por la

Fórmula general (1) o una sal del mismo de acuerdo con la reivindicación 1, caracterizado porque R^6 y R^7 son cada uno independientemente hidrógeno, alquilo inferior, ciclo alquilo inferior, arilo o un grupo heterocíclico.

3. Un compuesto de benzodiazepina representado por la Fórmula general (1) o una sal del mismo de acuerdo con la reivindicación 2, caracterizado porque R^6 y R^7 son cada uno independientemente hidrógeno, alquilo inferior, ciclo alquilo inferior, arilo o un grupo heterocíclico monocíclico o policíclico saturado o insaturado que contiene por lo menos un heteroátomo seleccionado entre oxígeno, azufre y nitrógeno.

4. Un compuesto de benzodiazepina representado por la Fórmula general (1) o una sal del mismo de acuerdo con la reivindicación 3, caracterizado porque R^6 y R^7 son cada uno independientemente hidrógeno, alquilo inferior, ciclo alquilo inferior, fenilo, naftilo, furilo, tienilo, pirazolilo, oxazolilo, isoxazolilo, tiazolilo, pirrolilo, triazolilo, piridilo, pirimidinilo, piridazinilo, pirazinilo, imidazo[2,1-b]-tiazolilo, tieno[2,3-b]pirazinilo, 2,3-dihidroimidazo[2,1-b]tiazolilo, benzotiazolilo, indolilo, imidazo[1,2-a]-piridilo, benzotienilo, benzimidazolilo, 2,3-dihidrobenzo[b]furilo, benzofurilo, indazolilo, furo[2,3-c]piridilo, furo[3,2-c]piridilo, tieno[2,3-c]piridilo, tieno[3,2-c]piridilo, tieno[2,3-b]piridilo, benzo[1,3]-dioxolilo, benzisoxazolilo, pirazolo[2,3-a]piridilo, indolizinilo, 2,3-dihidroindolilo, isoquinolilo, 1,2,3,4-tetrahidro-1H-isoquinolilo, carboestirilo, 3,4-dihidrocarboestirilo, quinolilo, cromanilo, 5,6,7,8-

tetrahidroisoquinolilo, 3,4-dihidro-1H-isoquinolilo, naftiridinilo, 1,4-benzodioxanilo, cinolinilo, quinoxalinilo o 2,3-dihidrobenz-1,4-oxazinilo, cada uno de los cuales está opcionalmente substituido.

5. Un compuesto de benzodiazepina representado por la Fórmula general (1) o una sal del mismo de acuerdo con la reivindicación 4, caracterizado porque R^6 y R^7 son cada uno, uno de los siguientes (1) a (52):

(1) hidrógeno,

(2) alquilo inferior,

(3) ciclo alquilo inferior,

(4) fenilo opcionalmente substituido con uno o más substituyentes seleccionados entre el grupo que consiste en los siguientes (4-1) a (4-25):

(4-1) ciano,

(4-2) hidroxi,

(4-3) halógeno,

(4-4) alquilo inferior opcionalmente substituido con uno o más substituyentes seleccionados entre el grupo que consiste en halógeno, imidazolilo y morfolinilo,

(4-5) alcoxi inferior opcionalmente substituido con uno o más substituyentes seleccionados entre el grupo que consiste en amino y alquilo inferior amino,

(4-6) piridilo,

(4-7) tienilo,

(4-8) piperazinilo opcionalmente substituido con uno o más alquilo inferior,

(4-9) fenilo,

(4-10) pirazolilo opcionalmente substituido con uno o más

alquilo inferior,

(4-11) pirimidinilo opcionalmente substituido con uno o más alquilo inferior,

(4-12) piperidilo opcionalmente substituido con uno o más alquilo inferior,

(4-13) furilo,

(4-14) carboxi,

(4-15) alcoxicarbonilo inferior,

(4-16) amino opcionalmente substituido con uno o más substituyentes seleccionados entre el grupo que consiste en alcanoilo inferior y alquilsulfonilo inferior,

(4-17) alquiltio inferior,

(4-18) triazolilo,

(4-19) imidazolilo,

(4-20) pirrolidinilo opcionalmente substituido con uno o más oxo,

(4-21) alquilsulfonilo inferior,

(4-22) alquilenodioxi inferior opcionalmente substituido con uno o más halógeno,

(4-23) nitro,

(4-24) oxazolilo, y

(4-25) tiazolilo opcionalmente substituido con uno o más alquilo inferior,

(5) naftilo,

(6) furilo opcionalmente substituido con uno o más substituyentes seleccionados entre el grupo que consiste en alquilo inferior opcionalmente substituido con halógeno, carboxi, sulfo, piridiloxi, alcoxicarbonilo inferior y fenilo,

(7) tienilo opcionalmente substituido con uno o más substituyentes seleccionados entre el grupo que consiste en alquilo inferior, alquilenodioxi inferior, carboxi, halógeno, piridilo, alcoxi inferior, alcoxicarbonilo inferior, oxazolilo y furilo,

(8) imidazolilo opcionalmente substituido con uno o más substituyentes seleccionados entre el grupo que consiste en fenilo, alquilo inferior y halógeno,

(9) pirazolilo opcionalmente substituido con uno o más substituyentes seleccionados entre el grupo que consiste en alquilo inferior opcionalmente substituido con halógeno, halógeno, fenilo opcionalmente substituido con alcoxi inferior, furilo y tienilo,

(10) oxazolilo opcionalmente substituido con uno o más substituyentes seleccionados entre el grupo que consiste en alquilo inferior y fenilo,

(11) isoxazolilo opcionalmente substituido con uno o más substituyentes seleccionados entre el grupo que consiste en fenilo, alquilo inferior, tienilo y furilo,

(12) tiazolilo opcionalmente substituido con uno o más substituyentes seleccionados entre el grupo que consiste en alquilo inferior opcionalmente substituido con alcoxi inferior, fenilo y alcanoilamino inferior,

(13) pirrolilo opcionalmente substituido con uno o más substituyentes seleccionados entre el grupo que consiste en alquilo inferior y alcoxicarbonilo inferior,

(14) triazolilo opcionalmente substituido con uno o más alquilo inferior,

(15) piridilo opcionalmente substituido con uno o más

705

substituyentes seleccionados entre el grupo que consiste en alquilo inferior opcionalmente substituido con halógeno, oxo, hidroxi, alcoxi inferior, halógeno, pirrolidinilo, morfolinilo y tienilo,

(16) pirimidinilo opcionalmente substituido con uno o más substituyentes seleccionados entre el grupo que consiste en alquilo inferior y fenilo,

(17) piridazinilo,

(18) pirazinilo,

(19) imidazo[2,1-b]tiazolilo opcionalmente substituido con uno o más halógeno,

(20) tieno[2,3-b]pirazinilo,

(21) 2,3-dihidroimidazo[2,1-b]tiazolilo opcionalmente substituido con uno o más fenilo,

(22) benzotiazolilo opcionalmente substituido con uno o más alquilo inferior,

(23) indolilo opcionalmente substituido con uno o más substituyentes seleccionados entre el grupo que consiste en alquilo inferior, alcanoilo inferior y halógeno,

(24) imidazo[1,2-a]piridilo opcionalmente substituido con uno o más alquilo inferior,

(25) benzotienilo opcionalmente substituido con uno o más alquilo inferior,

(26) benzimidazolilo opcionalmente substituido con uno o más alquilo inferior,

(27) 2,3-dihidrobenzo[b]furilo,

(28) benzofurilo opcionalmente substituido con uno o más halógeno,

(29) indazolilo opcionalmente substituido con uno o más

alquilo inferior,

(30) furo[2,3-c]piridilo opcionalmente substituido con uno o más substituyentes seleccionados entre el grupo que consiste en oxo y alquilo inferior,

(31) furo[3,2-c]piridilo opcionalmente substituido con uno o más substituyentes seleccionados entre el grupo que consiste en oxo, alquilo inferior opcionalmente substituido con halógeno, halógeno, furilo, piridilo y fenilo opcionalmente substituido con uno o más substituyentes seleccionados entre el grupo que consiste en amino y alcoxi inferior,

(32) tieno[2,3-c]piridilo opcionalmente substituido con uno o más substituyentes seleccionados entre el grupo que consiste en oxo grupo y alquilo inferior,

(33) tieno[3,2-c]piridilo opcionalmente substituido con uno o más substituyentes seleccionados entre el grupo que consiste en oxo y alquilo inferior,

(34) tieno[2,3-b]piridilo,

(35) benzo[1,3]dioxolilo opcionalmente substituido con uno o más halógeno,

(36) benzisoxazolilo,

(37) pirazolo[2,3-a]piridilo,

(38) indolizinilo,

(39) 2,3-dihidroindolilo opcionalmente substituido con uno o más substituyentes seleccionados entre el grupo que consiste en oxo, alquilo inferior y alcanoilo inferior,

(40) isoquinolilo opcionalmente substituido con uno o más substituyentes seleccionados entre el grupo que consiste en alquilo inferior, halógeno y oxo,

(41) 1,2,3,4-tetrahidro-1H-isoquinolilo opcionalmente

substituido con uno o más oxo,

(42) carboestirilo opcionalmente substituido con uno o más alcoxi inferior,

(43) 3,4-dihidrocarboestirilo opcionalmente substituido con uno o más alcoxi inferior,

(44) quinolilo opcionalmente substituido con uno o más substituyentes seleccionados entre el grupo que consiste en amino opcionalmente substituido con uno o dos alquilo inferior, alcoxi inferior, alquilo inferior y oxo,

(45) cromanilo opcionalmente substituido con uno o más alquilo inferior,

(46) 5,6,7,8-tetrahidroisoquinolilo opcionalmente substituido con uno o más oxo,

(47) 3,4-dihidro-1H-isoquinolilo opcionalmente substituido con uno o más oxo,

(48) naftiridinilo,

(49) 1,4-benzodioxanilo,

(50) cinolinilo,

(51) quinoxalinilo, o

(52) 2,3-dihidrobenz-1,4-oxazinilo opcionalmente substituido con uno o más substituyentes seleccionados entre el grupo que consiste en alquilo inferior y oxo.

6. Un compuesto de benzodiazepina representado por la Fórmula general (1) o una sal del mismo de acuerdo con la reivindicación 5, caracterizado porque R^6 y R^7 son cada uno, uno de los siguientes (4a), (6a), (7a), (15a), (30a), (31a), (32a), (33a), (40a) y (44a):

(4a) fenilo opcionalmente substituido con uno o más substituyentes seleccionados entre el grupo que consiste en

los siguientes (4a-1), (4a-4) y (4a-6):

(4a-1) ciano,

(4a-4) alquilo inferior opcionalmente substituido con uno o más halógeno, y

(4a-6) piridilo,

(6a) furilo,

(7a) tienilo,

(15a) piridilo opcionalmente substituido con uno o más alquilo inferior,

(30a) furo[2,3-c]piridilo opcionalmente substituido con uno o más oxo,

(31a) furo[3,2-c]piridilo opcionalmente substituido con uno o más substituyentes seleccionados entre el grupo que consiste en oxo y alquilo inferior,

(32a) tieno[2,3-c]piridilo opcionalmente substituido con uno o más oxo,

(33a) tieno[3,2-c]piridilo opcionalmente substituido con uno o más oxo,

(40a) isoquinolilo opcionalmente substituido con uno o más oxo, y

(44a) quinolilo opcionalmente substituido con uno o más oxo.

7. Un compuesto de benzodiazepina representado por la Fórmula general (1) o una sal del mismo de acuerdo con la reivindicación 5, que es seleccionado entre el grupo que consiste en los siguientes compuestos:

- triclorhidrato de 1-etil-3,3,5-trimetil-7-{3-[(2-piridin-3-iletil)piridin-4-ilmetilamino]propoxi}-1,5-dihidrobenzo[b]-[1,4]diazepina-2,4-diona,
- triclorhidrato de 3,3,5-trimetil-1-propil-7-{3-[(2-

piridin-3-iletil)piridin-4-ilmetilamino]propoxi}-1,5-dihidrobenzo-[b][1,4]diazepina-2,4-diona,

- triclorhidrato de 1,5-dietil-3,3-dimetil-7-{3-[(2-piridin-3-iletil)piridin-4-ilmetilamino]propoxi}-1,5-dihidrobenzo-[b][1,4]diazepina-2,4-diona,

- triclorhidrato de 1,3,3,5-tetrametil-7-{3-[(2-piridin-3-iletil)piridin-4-ilmetilamino]propoxi}-1,5-dihidrobenzo[b]-[1,4]diazepina-2,4-diona,

- diclorhidrato de 1-etil-3,3,5-trimetil-7-(3-{[2-(1-oxo-1H-isoquinolin-2-il)etil]piridin-4-ilmetilamino}propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona,

- diclorhidrato de 1-etil-3,3,5-trimetil-7-(3-{[2-(7-oxo-7H-furo[2,3-c]piridin-6-il)etil]piridin-4-ilmetilamino}-propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona

- diclorhidrato de N-metil-N-(2-{piridin-4-ilmetil-[3-(1,3,3,5-tetrametil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo-[b][1,4]diazepin-7-iloxi)propil]amino}etil)benzamida,

- diclorhidrato de 1,3,3,5-tetrametil-7-{3-[(2-metilbencil)-(2-piridin-3-iletil)amino]propoxi}-1,5-dihidrobenzo[b]-[1,4]diazepina-2,4-diona,

- triclorhidrato de 1,3,3,5-tetrametil-7-{3-[(2-piridin-3-iletil)-(quinolin-4-ilmetil)amino]propoxi}-1,5-dihidro-benzo[b][1,4]diazepina-2,4-diona,

- triclorhidrato de 1-etil-3,3,5-trimetil-7-{3-[(3-metilpiridin-4-ilmetil)-(2-piridin-3-iletil)amino]propoxi}-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona,

- diclorhidrato de 1-etil-3,3,5-trimetil-7-(3-{[2-(2-oxo-2H-quinolin-1-il)etil]piridin-4-ilmetilamino}propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona,

- diclorhidrato de 1-etil-3,3,5-trimetil-7-(3-{[2-(7-oxo-7H-tieno[2,3-c]piridin-6-il)etil]piridin-4-ilmetilamino}-propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona,
- 4-({[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil]-[2-(1-oxo-1H-isoquinolin-2-il)etil]amino}metil)benzonitrilo,
- 1-etil-3,3,5-trimetil-7-(3-{[2-(1-oxo-1H-isoquinolin-2-il)etil]tiofen-3-ilmetilamino}propoxi)-1,5-dihidrobenzo-[b][1,4]diazepina-2,4-diona,
- 1-etil-7-(3-{furan-2-ilmetil-[2-(1-oxo-1H-isoquinolin-2-il)etil]amino}propoxi)-3,3,5-trimetil-1,5-dihidrobenzo-[b][1,4]diazepina-2,4-diona,
- 7-{3-[bencil-(2-piridin-3-iletil)amino]propoxi}-1-etil-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona,
- 3-{[[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetra-hidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil]-(2-piridin-3-iletil)amino]metil}benzonitrilo,
- 1-etil-3,3,5-trimetil-7-{3-[(2-piridin-3-ilbencil)-(2-piridin-3-iletil)amino]propoxi}-1,5-dihidrobenzo[b][1,4]-diazepina-2,4-diona,
- 4-({[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetra-hidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil]-[2-(7-oxo-7H-furo[2,3-c]piridin-6-il)etil]amino}metil)benzonitrilo,
- 1-etil-3,3,5-trimetil-7-{3-[[2-(7-oxo-7H-furo[2,3-c]-piridin-6-il)etil]-(4-trifluorometilbencil)amino]-propoxi}-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona,
- 1-etil-3,3,5-trimetil-7-(3-{(2-metilbencil)-[2-(7-oxo-7H-furo[2,3-c]piridin-6-il)etil]amino}propoxi)-1,5-dihidro-benzo[b][1,4]diazepina-2,4-diona,

- 1-etil-3,3,5-trimetil-7-(3-{[2-(7-oxo-7H-furo[2,3-c]-piridin-6-il)etil]tiofen-2-ilmetilamino}propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona,
- diclorhidrato de 1-etil-3,3,5-trimetil-7-(3-{[2-(2-metil-4-oxo-4H-furo[3,2-c]piridin-5-il)etil]piridin-4-ilmetil-amino}propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona,
- 1-etil-3,3,5-trimetil-7-(3-{[2-(4-oxo-4H-furo[3,2-c]-piridin-5-il)etil]piridin-3-ilmetilamino}propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona,
- 1-etil-3,3,5-trimetil-7-(3-{[2-(4-oxo-4H-tieno[3,2-c]piridin-5-il)etil]piridin-3-ilmetilamino}propoxi)-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona,
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- diclorhidrato de 1-etil-3,3,5-trimetil-7-{3-[[2-(2-metil-4-oxo-4H-furo[3,2-c]piridin-5-il)etil]-(2-propil-piridin-3-ilmetil)amino]-propoxi}-1,5-dihidrobenzo[b][1,4]-diazepina-2,4-diona,

- clorhidrato de N-[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)-propil]-N-(2-piridin-3-iletil)bencenosulfonamida,
- diclorhidrato de 7-(3-{(2,6-dimetilpiridin-3-ilmetil)-[2-(4-oxo-4H-furo[3,2-c]piridin-5-il)etil]amino}propoxi)-1-etil-3,3,5-trimetil-1,5-dihidrobenzo[b][1,4]diazepina-2,4-diona,
- clorhidrato de N-[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)-propil]-N-(2-piridin-3-iletil)benzamida, y
- N-[3-(1-etil-3,3,5-trimetil-2,4-dioxo-2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepin-7-iloxi)propil]-N-[2-(1-oxo-1H-isoquinolin-2-il)etil]bencenosulfonamida.

8. Una composición farmacéutica que comprende un compuesto de benzodiazepina representado por la Fórmula (1) o una sal del mismo de acuerdo con la reivindicación 1, y un vehículo farmacológicamente aceptable.

9. Una composición farmacéutica de acuerdo con la reivindicación 8, para prevenir y/o tratar la arritmia.

10. Un compuesto de benzodiazepina representado por la Fórmula (1) o una sal del mismo de acuerdo con la reivindicación 1 para usar en la composición farmacéutica.

11. Uso de un compuesto de benzodiazepina representado por la Fórmula (1) o una sal del mismo de acuerdo con la reivindicación 1 como una composición farmacéutica.

12. Uso de un compuesto de benzodiazepina representado por Formula (1) o una sal del mismo de acuerdo con la reivindicación 1 para la producción de una composición farmacéutica.

7 B

13. Un método para prevenir y/o tratar la arritmia, que comprende administrar a un paciente un compuesto de benzodiazepina representado por la Fórmula (1) o una sal del mismo de acuerdo con la reivindicación 1.

COLO 14055-841-007-6LISTADO

LISTA DE SECUENCIAS
<110> OTSUKA PHARMACEUTICAL CO., LTD.
<120> COMPUESTO DE BENZODIAZEPINA Y COMPOSITION FARMACEUTICA
<130> P09-01

<150> JP 2008-041296
<151> 2008-2-22

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716

INTERNATIONAL SEARCH REPORT

International application No
PCT/JP2009/053623

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D243/12 C07D401/12 C07D401/14 C07D491/04 C07D405/14
C07D417/14 C07D409/14 C07D495/04 C07D471/04 C07D513/04
C07D413/14 A61K31/551 A61P9/06

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)
C07D

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96/40655 A (MERCK & CO INC [US]; CLAREMON DAVID A [US]; FREIDINGER ROGER M [US]; L) 19 December 1996 (1996-12-19) the whole document	1-13
A	STANLEY NATTEL AND LEIF CARLSSON: "Innovative approaches to anti-arrhythmic drug therapy" NATURE REVIEWS DRUG DISCOVERY, vol. 5, 2006, pages 1034-1049, XP002527589 cited in the application the whole document	1-13
A	JP 02 096133 A (FUJI PHOTO FILM CO LTD) 6 April 1990 (1990-04-06) page 334, compound C-12	1

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

☒ See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 May 2009	15/06/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Ladenburger, Claude

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/JP2009/053623

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9640655 A	19-12-1996	AT 196899 T	15-10-2000
		AU 704015 B2	01-04-1999
		AU 5968896 A	30-12-1996
		CA 2222492 A1	19-12-1996
		DE 69610628 D1	16-11-2000
		DE 69610628 T2	23-05-2001
		DK 832075 T3	20-11-2000
		EP 0832075 A1	01-04-1998
		ES 2151168 T3	16-12-2000
		GR 3034602 T3	31-01-2001
		JP 11506758 T	15-06-1999
		PT 832075 E	30-03-2001
		US 5691331 A	25-11-1997
JP 2096133 A	06-04-1990	NONE	

718

Industria y Comercio
SUPERINTENDENCIA

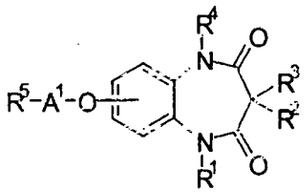
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
EXTRACTO PARA PUBLICACIÓN
SOLICITUD DE PATENTE DE INVENCIÓN PCT

(21) N° de solicitud:	(51) Int Cl: **C07D 243/012**
22) Fecha de solicitud:	(71)Solicitante(s) **OTSUKA PHARMACEUTICAL CO., LTD.**
(30) Prioridad (31) ***Prioridad*** (32) ***Fecha*** (33) ***País*** **2008-041296** **22/02/2008** **JP** **2008-227368** **04/09/2008** **JP**	(72) Inventor(es) **KUNIO OSHIMA Y OTROS**
	(74) Apoderado: **LUZ CLEMENCIA DE PAEZ**
(85) Fecha límite inicio fase nacional: 22/09/2010 (86) Datos relativos a la presentación de la solicitud PCT Fecha de presentación de la solicitud: 20/02/2009 No. de solicitud PCT/JP2009/053623	(87) Publicación internacional Fecha: 27/08/2009 N° publicación: ***WO 2009/104319 A1***

(54) Título: **COMPUESTO DE BENZODIAZEPINA Y COMPOSICIÓN FARMACÉUTICA**

Reivindicación(es):

1. Un compuesto de benzodiazepina representado por la Fórmula general (1):



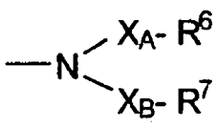
(1)

o una sal del mismo,
caracterizado porque R1, R2, R3 y R4 son cada uno independientemente hidrógeno o alquilo inferior;

R2 y R3 pueden estar unidos para formar alquileno inferior;

A1 es alquileno inferior opcionalmente substituido con uno o más hidroxi; y

R5 es un grupo representado por:



en donde R6 y R7 son cada uno independientemente hidrógeno o un grupo orgánico;

XA y XB son cada uno independientemente un enlace, alquileno inferior, alquenileno inferior, -CO-, -SO2-,-SO2- alquileno inferior, -CO-alquileno inferior, -CO-alquenileno inferior, alquileno inferior-N(alquilo inferior)-CO-alquileno inferior, alquileno inferior- N(alquilo inferior)-, alquileno inferior-N(alquilo inferior)-CO- o alquileno inferior-O-.

2. Un compuesto de benzodiazepina representado por la Fórmula general (1) o una sal del mismo de acuerdo con la reivindicación 1, caracterizado porque R6 y R7 son cada uno independientemente hidrógeno, alquilo inferior, ciclo alquilo inferior, arilo o un grupo heterocíclico.

3. Un compuesto de benzodiazepina representado por la Fórmula general (1) o una sal del mismo de acuerdo con la reivindicación 2, caracterizado porque R6 y R7 son cada uno independientemente hidrógeno, alquilo inferior, ciclo alquilo inferior, arilo o un grupo heterocíclico monocíclico o policíclico saturado o insaturado que contiene por lo menos un heteroátomo seleccionado entre oxígeno, azufre y nitrógeno.

4. Un compuesto de benzodiazepina representado por la Fórmula general (1) o una sal del mismo de acuerdo con la reivindicación 3, caracterizado porque R6 y R7 son cada uno independientemente hidrógeno, alquilo inferior, ciclo alquilo inferior, fenilo, naftilo, furilo, tienilo, pirazolilo, oxazolilo, isoxazolilo, tiazolilo, pirrolilo, triazolilo, piridilo, pirimidinilo, piridazinilo, pirazinilo, imidazo[2,1-b]-tiazolilo, tieno[2,3-b]pirazinilo, 2,3-dihidroimidazo[2,1-b]tiazolilo, benzotiazolilo, indolilo, imidazo[1,2-a]-piridilo, benzotienilo, benzimidazolilo, 2,3-dihidrobenzo[b]furilo, benzofurilo, indazolilo, furo[2,3-c]piridilo, furo[3,2-c]piridilo, tieno[2,3-c]piridilo, tieno[3,2-c]piridilo, tieno[2,3-b]piridilo, benzo[1,3]-dioxolilo, benzisoxazolilo, pirazolo[2,3-a]piridilo, indolizinilo, 2,3-dihidroindolilo, isoquinolilo, 1,2,3,4-tetrahidro-1H-isoquinolilo, carboestirilo, 3,4-dihidrocarboestirilo, quinolilo, cromanilo, 5,6,7,8-tetrahidroisoquinolilo, 3,4-dihidro-1H-isoquinolilo, naftiridinilo, 1,4-benzodioxanilo, cinolinilo, quinoxalinilo o 2,3-dihidrobenz-1,4-oxazinilo, cada uno de los cuales está opcionalmente substituido.

719

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 74,150
FECHA : SEPTIEMBRE 6 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-117060- -00000-0000
Fecha: 2010-09-22 11:31:40 Dep: 2020 DIR.NUEVASCR
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 722

***** 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 DE BOGOTA	062754387	156798806	06/09/2010	26,469,000.00

***** 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	554,000.00
		TOTAL : $	554,000.00

SON: QUINIENTOS CINCUENTA Y CUATRO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

OCHO: 14055 - 841 - 007 - 6

720

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-117060- -00000-0000
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Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 722

RECIBO OFICIAL DE CAJA : 10 - 75,695
FECHA : SEPTIEMBRE 13 DE 2010

***** 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 DE BOGOTA	062754387	156794820	13/09/2010	45,370,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
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		TOTAL : $	26,000.00

SON: VEINTISEIS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Clo: 14055-841-007-6

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT :

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-117060- -00000-0000
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Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 722

RECIBO OFICIAL DE CAJA : 10 - 75,696
FECHA : SEPTIEMBRE 13 DE 2010

***** 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 DE BOGOTA	062754397	156794820	13/09/2010	45,370,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
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SON: VEINTISEIS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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RECIBO OFICIAL DE CAJA : 10 - 75,697
FECHA : SEPTIEMBRE 13 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
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Act. 411 PRESENTACION Folios: 722

***** 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 DE BOGOTA	062754307	154794820	13/09/2010	45,370,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
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		TOTAL : $	26,000.00

SON: VEINTISEIS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

CCO: 14055-841-0076

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 10-117060- -00000-0000

Fecha: 2010-09-22 11:31:40 Dep: 2020 DIR NUEVASCR
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 722

PATENTE DE INVENCIÓN ☐ **MODELO DE UTILIDAD** ☐ **Art 33 Decisión 486/00**

- ☐ Indicación que se solicita 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 (De ser el caso formato de descuento)

Completa ☐ Incompleta ☐

PATENTE DE INVENCIÓN PCT ☐ **MODELO DE UTILIDAD PCT** ☐ **Art.33 Decisión 486/00, Circular Única**

- ☐ Indicación que se solicita una PCT
- ☐ Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
- ☐ Dibujos de ser estos pertinentes
- ☐ Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa ☐ Incompleta ☐

DISEÑO INDUSTRIAL ☐ **(Art. 119 Decisión 486/00)**

- ☐ Indicación que se solicita 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 ☐ **(Art. 92 Decisión 486/00)**

- ☐ Indicación que se solicita un esquema de trazado
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica de un esquema de trazado
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

Industria y Comercio
SUPERINTENDENCIA

Bogotá D.C.,
2020

Doctor(a)
SUAREZ DE PAEZ LUZ CLEMENCIA
Apoderado(a) y/o Representante de
OTSUKA PHARMACEUTICAL CO. , LTD.

REFERENCIA	Radicación No.	10 117060
	Solicitud internacional	PCT/JP2009/053623
	Fecha inicio fase nacional	22/09/2010
	Trámite	11
	Evento	378
	Actuación	430 . 13144
	Oficio No.	

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

1. El solicitante debe presentar un nuevo titulo que permita identificar la materia de la cual trata la solicitud, ya que el titulo relacionado no se encuentra con la precisión necesaria para identificar claramente el objeto de la solicitud de patente. (Regla 4.3 PCT, Art 26-27 D-486, Circular única 5.2.9)

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

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

ALBA CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista de fecha 08 OCT. 2010.
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