06-83938

Libertad y Orden

REPÚBLICA DE COLOMBIA

DIVISIÓN DE PROPIEDAD INDUSTRIAL

Falta Tasa Art. 458 PCT Of

PATENTE DE INVENCIÓN

Industria y Comercio
SUPERINTENDENCIA

06-83938

TITULO: 2, 3, 4, 5-TETRAHIDRO-1H-BENZO(d) AZEPINAS 6- SUBSTITUIDAS COMO AGONISTAS DEL RECEPTOR 5-HT2C

SOLICITANTE: ELI-LILLY AND COMPANY

DIRECCIÓN: Lilly Corporate Center, Indianapolis Indiana 46285 E.U.A.

APODERADO: CARLOS R. OLARTE

BOGOTÁ, agosto 24 de 2006

P2006/000146

OLARTERAI

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-083938- -00000-0000
Fec: 2006-08-24 16:41:47 Dep: 2020 MUECREACIONES
Tra: 11 PATENTEIYII
Eve: 379 FASENACIONALII
Act: 411 PRESENTACION Folios: 1618

Industria y Comercio
SUPERINTENDENCIA

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL 25/09/06

SOLICITUD DE:

(1) [X] Patente de Invención. [ ] Patente de Modelo de Utilidad.

[ ] Capítulo I. [X] Capítulo II.

(2) **SOLICITANTE (71)**

Nombre: ELI-LILLY AND COMPANY
Dirección: Lilly Corporate Center, Indianapolis Indiana 46285 E.U.A.
Nacionalidad o Domicilio: ESTADOUNIDENSE
Lugar de Constitución: ESTADOS UNIDOS DE AMERICA
Teléfono: _____ Fax: _____
E-mail: _____

IDENTIFICACIÓN
C.C. [ ] NIT [ ]
C.E. [ ] Otro [ ]
Cual _____
Número _____

(3) **REPRESENTANTE APODERADO**

Nombre: CARLOS R. OLARTE
Dirección: World Trade Center Torre A, Calle 100 Nº. 8A-37 Piso 10
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IDENTIFICACIÓN
C.C. [X] NIT [ ]
C.E. [ ] Otro [ ]
Cual _____
Número 79.782.747 Btá
TP 74.295

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

Nombre: VER PAGINA ADJUNTA
Dirección: VER PAGINA ADJUNTA
Nacionalidad o Domicilio: VER PAGINA ADJUNTA

(5) **PCT (86)**

Solicitud Internacional No. PCT/US2005/005418 Fecha Febrero 18, 2005

Publicación Internacional No. WO 2005/082859 Fecha Septiembre 9, 2005

(6) **Título (54)** 2, 3, 4, 5-TETRAHIDRO-1H-BENZO[d]AZEPINAS 6-SUBSTITUIDAS COMO AGONISTAS DEL RECEPTOR 5-HT_{2c}

(7) **Clasificación Internacional (51)** C07D 223/16, 401/12, 417/12, 413/12, 403/12, 409/12, 405/12, 413/14, 417/06, 403/06, A61K 31/55, A61P 25/22, 25/24, 25/30, 3/04

(8) **Prioridad** SI [X] NO [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Febrero 25, 2004	60/547.681

(9) **Comprobante de pago No.** 06 – 63,714 **Fecha** Agosto 22, 2006

(10) **ANEX S**

- [x] Comprobante de pago de la tasa de presentación de la solicitud.
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso.
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones.
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).
- [x] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12 x 12.
- [ ] 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.
- [x] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [x] Otros. Búsqueda Internacional

(11) **FIGURA CARACTERÍSTICA:**

(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

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

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NACIONALIDAD: Alemana

9

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-083936- -00000-0000
Fec: 2006-08-24 16:41:47 Dep: 2020 RECREACIONES
Tra: 11 PATENTE(Y)I
Eve: 378 FASENACIONALII
Act 411 PRESENTACION Folios: 1518

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 06 - 63,714
FECHA : AGOSTO 22 DE 2006

C O N S I G N A C I O N

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBECK	CONSIGNACION	BANCO POPULAR	050-00110-6	52202107	10/08/2006	3,382,000.00

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	463,000.00
		TOTAL : $	463,000.00

SON: CUATROCIENTOS SESENTA Y TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Traducción oficial del Inglés por Marlén Neira Castro, resolución 2117 del Ministerio de Justicia de Colombia

APOSTILLA EN PODER DE REPRESENTACIÓN DE

ELI LILLY AND COMPANY

Bilingüe inglés- español otorgado en Indianapolis, Indiana, Estados Unidos el 17 de julio de 2003 y firmado por Peter G. Stringer, Director Ejecutivo y Patentes Internacionales de Ely Lilly & Company.

Todd Rokita — Secretario de Estado

Secretario de Estado de Indiana — Estado de Indiana

APOSTILLA

(Convención de la Haya del 5 de octubre de [illegible])

1. País: Estados Unidos de América- Este documento Públ[illegible]
2. ha sido firmado por Catherine Michel
3. Quien ejerce funciones de Secretario de la Corte del Circuito en y para el condado Johnson
4. Lleva el sello del Secretario de la Corte del Circuito en y para el estado de Indiana

CERTIFICADO

5. En Indianapolis, Indiana — 6. El 22 de julio de 2003
7. Por el Secretario de Estado de Indiana — 8. No. A2003- 11279
9. Gran Sello del Estado de Indiana
10. Firma legible de Todd Rokita- Secretario de Estado de Indiana

* Vigente desde el 1 mayo de 2003, todas las apostillas del Secretario de Estado de Indiana tienen el sello impreso electrónicamente.

The Statehouse, Indianapolis, Indiana 46204, (317) 232-6531, fax (317) 233-3283

CERTIFICACION NOTARIAL

Bilingüe inglés- español, el 17 de julio de 2003 el suscrito notario Catherine Michel certifica que Peter G. Stringer, domiciliado en 7620 Castleton Farms, West Drive, Indianapolis, Indiana - 46256 Estados Unidos ejercía funciones de Director Ejecutivo y Patentes Internacionales de Ely Lilly & Company, con sede en Indianapolis, Indiana, Estados Unidos.

MARLEN NEIRA CASTRO
Traductor e Intérprete Oficial
Inglés - Español - Inglés

El otorgante fundamenta sus certificaciones en este documento: Delegación de Autoridad concerniente a Ciertas Materias de Patentes, suscrito el 20 de enero de 2003: conforme al poder otorgado al Asesor General de la Compañía por el Comité ejecutivo de la Junta Directiva de Eli Lilly and Company.

Firma del notario público Catherine Michel certifica

Sus funciones vencen el 21 de octubre de 2008 - residente en el condado Johnson

Sello de notario público de Indiana

--

Es traducción fiel del inglés, con copia archivo para confrontación. Bogotá 28 de julio-2003.

Marlen Neira C

MARLEN NEIRA CASTRO
Traductor e Intérprete Oficial
Inglés - Español - Inglés
Resolución No. 2117 del 7 Oct 1987



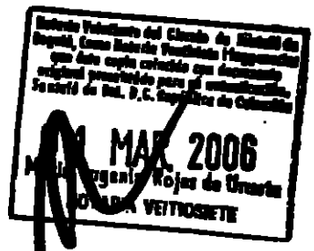
OLARTERAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

WORLD TRADE CENTER – TORRE C
CALLE 100 NO. 8A-55 PISO 10
BOGOTA, COLOMBIA
TELEPHONE: +57-1 638-6200
FAX: +57-1 638-6201

www.olarteraisbeck.com

6



Power of Attorney

Poder

The undersigned,

El suscrito,

ELI LILLY AND COMPANY

domiciled in

domiciliado en

Lilly Corporate Center, Indianapolis, Indiana 46285 US

by means of these presents hereby grants to **Carlos R. Olarte, J. Ian Raisbeck and Ana María Frieri** full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's Patents, Utility Models and Industrial Designs in the Republic of Colombia, to which end it empowers them to take all steps necessary before any administrative or judicial authority of any class for the objects stated, to file petitions, appeals, replies and oppositions, pay taxes and annuities, request testimonies, receive documents and securities, abandon applications and collect refunds. Sufficient power is hereby granted to receive notifications on behalf of the Company, to confer powers on those who are to represent the company judicially and extrajudicially, to answer in court in the matter of all claims and demands that may be presented in connection with the objects stated, giving them likewise power to substitute these presents and revoke such substitutions.

por medio del presente otorga a **Carlos R. Olarte, J. Ian Raisbeck y Ana María Frieri** poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de Patentes, Modelos de Utilidad y Diseños Industriales de la compañía en la República de Colombia, a cuyo efecto los faculta para dar todos los pasos necesarios ante cualquier autoridad administrativa o judicial de cualquier jerarquía para cumplir con lo encomendado, elevar solicitudes, apelaciones, respuestas y oposiciones, pagar impuestos y anualidades, solicitar testimonios, recibir documentos y valores, desistir y percibir. Se concede poder bastante para recibir notificaciones a nombre de la compañía, otorgar poderes a quienes vayan a representar a la compañía judicial y extrajudicialmente, responder en juicio a todas las reclamaciones o demandas que por motivo de lo encomendado se presentaren, dándoles asimismo facultad para sustituir el presente y revocar dichas sustituciones.

Signature/Firma

Date/Fecha: 17 July 2003

City,Country/Ciudad,País: Indianapolis, Indiana, United States of America

SECRETARY OF STATE
STATE OF INDIANA

Todd Rokita
Secretary of State

APOSTILLE

(Convention de la Haye du 5 Octobre 1961)

1 MAR 2006

1. **Country: United States of America**
2. **This public document has been signed by** *Catherine Michel*
3. **acting in the capacity of circuit court clerk in & for** *Johnson* **County**
4. **and bears the seal/stamp of circuit court clerk in & for the State of Indiana**

Certified

5. **at Indianapolis, Indiana**
6. **this** *Twenty-second* **day of** *July, 2003*
7. **by Secretary of State of Indiana**
8. **No. A2003-** *11279*

9. **Seal/Stamp:**

10. Signature:

Todd Rokita

Indiana Secretary of State

*Effective May 1, 2003 all apostilles from the Indiana Secretary of State will have an electronically printed seal.

The Statehouse, Indianapolis, Indiana 46204, (317) 232-6531, Fax (317) 233-3283

OLARTERAISBECK

OLARTE RAISBECK & FRIEDL, LTDA.
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FAX: +57-1 638-6201

www.olarteraisbeck.com

11

Notarial Certification

On this date,
17 July 2003
The undersigned Notary Public certifies:

1. That
Peter G. Stringer
of legal age and domiciled in
7620 Castleton Farms, West Drive, Indianapolis, Indiana 46256 US
signed the foregoing document.

2. That the grantor has executed the foregoing document as Executive Director, International Patents
of ELI LILLY AND COMPANY

3. That ELI LILLY AND COMPANY
having its principal place of business located in
Indianapolis, Indiana, United States of America
is duly incorporated, is currently in existence, and that the purposes for which the Power of Attorney is granted are within the scope of its corporate purposes.

4. That the grantor has the authority to execute the Power of Attorney and that his/her representation is legal.

5. The foundation for my certifications contained in points 2, 3 and 4 was the exhibition of the following authentic document(s):
Delegation of Authority Concerning Certain Patent Matters, executed January 20, 2003; pursuant to the authority granted to the General Counsel of the Company by the executive Committee of the Board of Directors of Eli Lilly and Company

NOTARY PUBLIC (Signature):

NOTARY PUBLIC SEAL INDIANA

Catherine Michel
My Commission Expires October 21, 2008
Resident of Johnson County

Certificación Notarial

En esta fecha,

el Notario Público suscrito certifica:

Notaría Veintidós del Círculo de Bogotá, Carrera 13 No. 13-24 Piso 2 Teléfono 3414000 Fax 3414001 Bogotá D.C. República de Colombia
01 MAR 2006
María Eugenia Rojas de Urueta
NOTARIA VEINTIDOS

1. Que
mayor de edad y domiciliado
suscribió el documento que antece

2. Que el otorgante ha suscrito el
documento en su carácter de

de

4. Que
con sede principal ubicada en

está legalmente constituida, que tiene existencia legal vigente y que los propósitos para los cuales se otorga el poder se encuentra dentro de los que comprenden su objeto social.

4. Que el otorgante tiene la representación para suscribir el poder, y que ésta es legítima.

5. El fundamento de mis certificaciones contenidas en los puntos 2, 3 y 4 fue la exhibición de los (del) siguiente(s) documento(s) auténtico(s):

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
9 September 2005 (09.09.2005)

PCT

(10) International Publication Number
WO 2005/082859 A1

(51) International Patent Classification⁷: C07D 223/16, 401/12, 417/12, 413/12, 403/12, 409/12, 405/12, 413/14, 417/06, 403/06, A61K 31/55, A61P 25/22, 25/24, 25/30, 3/04

(21) International Application Number: PCT/US2005/005418

(22) International Filing Date: 18 February 2005 (18.02.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/547,681 25 February 2004 (25.02.2004) US

(71) Applicant (*for all designated States except US*): ELI LILLY AND COMPANY [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): ALLEN, John, Gordon [US/US]; 5886 North Delaware Street, Indianapolis, Indiana 46220 (US). BRINER, Karin [CH/US]; 7649 Pinesprings East Drive, Indianapolis, Indiana 46256 (US). COHEN, Michael, Philip [US/US]; 8141 Bowline Court, Indianapolis, Indiana 46236 (US). GALKA, Christopher, Stanley [US/US]; 13690 N. Stone Have Drive, Carmel, Indiana 46033 (US). HELLMAN, Sarah, Lynne [US/US]; 7620 Kincoe Lane, Indianapolis, Indiana 46254 (US). MARTINEZ-GRAU, Maria, Angeles [ES/ES]; Lilly S. A., Avenida de la Industria 30, E-28108 Alcobendas (Madrid) (ES). REINHARD, Matthew, Robert [US/US]; 8301 Scarsdale Court, Indianapolis, IN 46256 (US). RODRIGUEZ, Michael, John [US/US]; 7649 Gordonshire Court, Indianapolis, Indiana 46278 (US). ROTHHAAR, Roger, Ryan [US/US]; 5282 West 775 South, Reelsville, In 46171 (US). TIDWELL, Michael, Wade [US/US]; 665 Downing Drive, Greenwood, Indiana 46143 (US). VICTOR, Frantz [US/US]; 4855 North Tuxedo Street, Indianapolis, Indiana 46205 (US). WILLIAMS, Andrew, Caerwyn [GB/GB]; Eli Lilly and Company Limited, Kingsclere Road, Basingstoke Hampshire RG21 6XA (GB). ZHANG, Deyi [US/US]; 1372 Kirklees Drive, Carmel, Indiana 46032 (US). BOYD, Steven, Armen [US/US]; 5665 Saint Vrain Road, Longmont, Colorado 80503-9061 (US). CONWAY, Richard, Gerard [US/US]; 3315 Beech Drive, Carmel, Indiana 46033 (US). DEO, Arundhati, S. [US/US]; 2342 Hillside Avenue, Saint Paul, Minnesota 55108 (US). LEE, Wai-Man [CN/US]; 2128 24th Avenue, Longmont, Colorado 80501 (US). SIEDEM, Christopher, Stephen [US/US]; 4215 Redmond Drive, Longmont, Colorado 80503 (US). SINGH, Ajay [IN/US]; 2028 South Evanston Court, Aurora, Colorado 80014 (US).

(74) Agents: TUCKER, R., Craig et al.; P. O. Box 6288, Indianapolis, Indiana 46206-6288 (US).

(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, 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, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

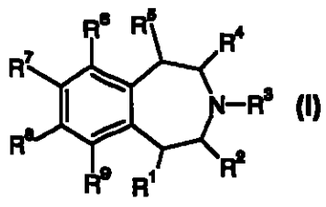
Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA,*

[Continued on next page]

WO 2005/082859 A1

(54) Title: 6-SUBSTITUTED 2,3,4,5-TETRAHYDRO-1H-BENZO[D]AZEPINES AS 5-HT2C RECEPTOR AGONISTS



(I)

(57) Abstract: The present invention provides 6-substituted 2,3,4,5-tetrahydro-1H-benzo[d]azepines of Formula I as selective 5-HT2C receptor agonists for the treatment of 5-HT2C associated disorders including obesity, obsessive/compulsive disorder, depression, and anxiety: I where: R6 is -C=C-R10, -O-R12, -S-R14, or -NR24R25; and other substituents are as defined in the specification.

ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

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6-SUBSTITUTED 2,3,4,5-TETRAHYDRO-1H-BENZO[d]AZEPINES AS 5-HT$_{2C}$ RECEPTOR AGONISTS

The neurotransmitter serotonin (5-hydroxytryptamine, 5-HT) has a rich pharmacology arising from a heterogeneous population of at least seven receptor classes. The serotonin 5-HT$_2$ class is further subdivided into at least three subtypes, designated 5-HT$_{2A}$, 5-HT$_{2B}$, and 5-HT$_{2C}$. The 5-HT$_{2C}$ receptor has been isolated and characterized (Julius, *et al.*, U.S. Patent No. 4,985,352), and transgenic mice lacking the 5-HT$_{2C}$ receptor have been reported to exhibit seizures and an eating disorder resulting in increased consumption of food (Julius *et al.*, U.S. Patent No. 5,698,766). The 5-HT$_{2C}$ receptor has also been linked to various other neurological disorders including obesity (Vickers *et al.*, Psychopharmacology, 167: 274-280 (2003)), hyperphagia (Tecott *et al.*, Nature, 374: 542-546 (1995)), obsessive compulsive disorder (Martin *et al.*, Pharmacol. Biochem. Behav., 71: 615 (2002); Chou-Green *et al.*, Physiology & Behavior, 78: 641-649 (2003)), depression (Leysen, Kelder, Trends in Drug Research II, 29: 49-61 (1998)), anxiety (Curr. Opin. Invest. Drugs 2(4), p. 317 (1993)), substance abuse, sleep disorder (Frank *et al.*, Neuropsychopharmacology 27: 869-873 (2002)), hot flashes (EP 1213017 A2), epilepsy (Upton *et al.*, Eur. J. Pharmacol., 359: 33 (1998); Fitzgerald, Ennis, Annual Reports in Medicinal Chemistry, 37: 21-30 (2002)), and hypogonadism (Curr. Opin. Invest. Drugs 2(4), p. 317 (1993)).

Certain substituted 2,3,4,5-tetrahydro-1H-benzo[d]azepine compounds have been disclosed as useful therapeutics as for example:

US 4,265,890 describes certain substituted 2,3,4,5-tetrahydro-1H-benzo[d]azepine compounds as dopaminergic receptor antagonists for use as antipsychotics and antiemetics, *inter alia*.

EP 0 285 287 describes certain substituted 2,3,4,5-tetrahydro-1H-benzo[d]azepine compounds for use as agents to treat gastrointestinal motility disorders, *inter alia*.

WO 93/03015 and WO 93/04686 describe certain substituted 2,3,4,5-tetrahydro-1H-benzo[d]azepine compounds as alpha-adrenergic receptor antagonists for use as agents to treat hypertension and cardiovascular diseases in which changes in vascular resistance are desirable, *inter alia*.

WO 02/074746 A1 describes certain substituted 2,3,4,5-tetrahydro-1H-benzo[d]azepine compounds as 5-HT_{2C} agonists for the treatment of hypogonadism, obesity, hyperphagia, anxiety, depression, sleep disorder, *inter alia*.

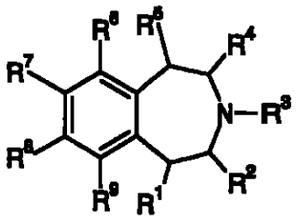
WO 03/006466 A1 describes certain substituted tricyclic hexahydroazepinoindole and indoline compounds as 5-HT ligands and consequently their usefulness for treating diseases wherein modulation of 5-HT activity is desired.

High affinity 5-HT_{2C} receptor agonists would provide useful therapeutics for the treatment of the above mentioned 5-HT_{2C} receptor-associated disorders including obesity, hyperphagia, obsessive/compulsive disorder, depression, anxiety, substance abuse, sleep disorder, hot flashes, and hypogonadism. High affinity 5-HT_{2C} receptor agonists that are also selective for the 5-HT_{2C} receptor, would provide such therapeutic benefit without the undesirable adverse events associated with current therapies. Achieving selectivity for the 5-HT_{2C} receptor, particularly as against the 5-HT_{2A} and 5-HT_{2B} receptors, has proven difficult in designing 5-HT_{2C} agonists. 5-HT_{2A} receptor agonists have been associated with problematic hallucinogenic adverse events. (Nelson *et al.*, Naunyn-Schmiedeberg's Arch. Pharm., 359: 1-6 (1999)). 5-HT_{2B} receptor agonists have been associated with cardiovascular related adverse events, such as valvulopathy. (V. Setola et al., Mol. Pharmacology, 63: 1223-1229 (2003), and *ref. cited therein*).

Previous references to substituted 2,3,4,5-tetrahydro-1H-benzo[d]azepine compounds as potential therapeutics have predominately recited their uses as alpha adrenergic and/or dopaminergic modulators. Adrenergic modulators are often associated with the treatment of cardiovascular diseases (Frishman, Kotob, Journal of Clinical Pharmacology, 39: 7-16 (1999)). Dopaminergic receptors are primary targets in the treatment of schizophrenia and Parkinson's disease (Seeman, Van Tol, Trends in

Pharmacological Sciences, 15: 264-270 (1994)). It will be appreciated by those skilled in the art that selectivity as against these and other physiologically important receptors will generally also be preferred characteristics for therapeutics for the specific treatment of 5-HT_{2C} associated disorders as described above.

The present invention provides selective 5-HT_{2C} agonist compounds of Formula I:



I

where:

R^1 is hydrogen, fluoro, or (C_1-C_3)alkyl;

R^2, R^3, and R^4 are each independently hydrogen, methyl, or ethyl;

R^5 is hydrogen, fluoro, methyl, or ethyl;

R^6 is $-C{\equiv}C-R^{10}$, $-O-R^{12}$, $-S-R^{14}$, or $-NR^{24}R^{25}$;

R^7 is hydrogen, halo, cyano, (C_1-C_6)alkyl optionally substituted with 1 to 6 fluoro substituents, (C_2-C_6)alkenyl optionally substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl, (C_1-C_6)alkoxy optionally substituted with 1 to 6 fluoro substituents, (C_1-C_6)alkylthio optionally substituted with 1 to 6 fluoro substituents, Ph^1-(C_0-C_3)alkyl, Ph^1-(C_0-C_3)alkyl-O-, or Ph^1-(C_0-C_3)alkyl-S-;

R^8 is hydrogen, halo, cyano, or $-SCF_3$;

R^9 is hydrogen, halo, cyano, $-CF_3$, $-SCF_3$, or (C_1-C_3)alkoxy optionally substituted with 1 to 6 fluoro substituents;

R^{10} is $-CF_3$, ethyl substituted with 1 to 5 fluoro substituents, (C_3-C_6) alkyl optionally substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, Ar^1-(C_0-C_3)alkyl, Ph^1-(C_0-C_3)alkyl, or 3-(C_1-C_4)alkyl-2-oxo-imidazolidin-1-yl-(C_1-C_3)alkyl;

R^{12} is Ph^2-(C_1-C_3)alkyl, Ar^2-(C_1-C_3)alkyl, (C_1-C_6)alkyl-S-(C_2-C_6)alkyl, (C_3-C_7)cycloalkyl-S-(C_2-C_6)alkyl, phenyl-S-(C_2-C_6)alkyl, Ph^2-S-(C_2-C_6)alkyl, phenylcarbonyl-(C_1-C_3)alkyl, Ph^2-C(O)-(C_1-C_3)alkyl, (C_1-C_6)alkoxycarbonyl(C_3-C_6)alkyl, (C_3-C_7)cycloalkyl-OC(O)-(C_3-C_6)alkyl, phenyloxycarbonyl-(C_3-C_6)alkyl, Ph^2-OC(O)-(C_3-C_6)alkyl, Ar^2-OC(O)-(C_3-C_6)alkyl, (C_3-C_7)cycloalkyl-NH-C(O)-(C_2-C_4)alkyl-, Ph^1-NH-C(O)-(C_2-C_4)alkyl-, Ar^2-NH-C(O)-(C_2-C_4)alkyl-, or R^{13}-C(O)NH-(C_2-C_4)alkyl;

R^{13} is (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, Ph^1, Ar^2, or (C_1-C_3)alkoxy optionally substituted with 1 to 6 fluoro substituents, Ph^1-NH- or N-linked Het^1;

R^{14} is Ar^2 which is not N-linked to the sulfur atom, Ph^2, R^{15}-L-, tetrahydrofuranyl, tetrahydropyranyl, or phenyl-methyl substituted on the methyl moiety with a substituent selected from the group consisting of (C_1-C_3)-*n*-alkyl substituted with hydroxy, (C_1-C_3)alkyl-O-(C_1-C_2)-*n*-alkyl, (C_1-C_3)alkyl-C(O)-(C_0-C_2)-*n*-alkyl, and (C_1-C_3)alkyl-O-C(O)-(C_0-C_2)-*n*-alkyl,

wherein when R^{14} is Ph^2 or Ar^2, wherein Ar^2 is pyridyl, then R^{14} may also, optionally be substituted with phenyl-CH=CH- or phenyl-C≡C-, said phenyl-CH=CH- or phenyl-C≡C- being optionally further substituted with 1 to 3 substituents independently selected from the group consisting of halo, cyano, -SCF_3, (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, and (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents, and

wherein when Ar^2 is pyridyl, the pyridyl may alternatively, optionally be substituted with $R^{26}R^{29}N$-C(O)-, and optionally further substituted with one methyl, -CF_3, cyano, or -SCF_3 substituent, or with 1 to 2 halo substituents, and

wherein the tetrahydrofuranyl and tetrahydropyranyl may optionally be substituted with an oxo substituent, or with one or two groups independently selected from methyl and -CF_3;

R^{15} is -OR^{16}, cyano, -SCF_3, Ph^2, Ar^2, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, phthalimido, benzothiophenyl optionally substituted at the 2-position with phenyl or benzyl, benzothiazolyl optionally substituted at the 2-position with phenyl or benzyl,

benzothiadiazolyl optionally substituted with phenyl or benzyl, 2-oxo-dihydroindol-1-yl optionally substituted at the 3 position with gem dimethyl or (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, 2-oxo-dihydroindol-5-yl optionally substituted at the 3 position with gem dimethyl or (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, 2-oxo-imidazolidin-1-yl optionally substituted at the 3 position with gem dimethyl or (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, 2-oxo-tetrahydropyrimidinyl optionally substituted at the 3 or 4 position with gem dimethyl or (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, 2-oxo-tetrahydroquinolin-1-yl optionally substituted at the 3 position with gem dimethyl or (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, 2-oxo- dihydrobenzimidazol-1-yl optionally substituted at the 3 position with gem dimethyl or (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, $-NR^{17}R^{18}$, $-C(O)R^{22}$, or a saturated heterocycle selected from the group consisting of pyrrolidinyl, piperidinyl, morpholinyl, and thiomorpholinyl, tetrahydrofuranyl, and tetrahydropyranyl,

wherein Ph^2 and Ar^2 when Ar^2 is pyridyl, may also optionally be substituted with phenyl-CH=CH- or phenyl-C≡C-,

said phenyl-CH=CH- and phenyl-C≡C- being optionally further substituted on the phenyl moiety with 1 to 3 substituents independently selected from the group consisting of halo, cyano, $-SCF_3$, (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, and (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents, and

wherein Ar^2 may alternatively, optionally be substituted with a substituent selected from the group consisting of (C_3-C_7)cycloalkyl-(C_0-C_3)alkyl, Het^1-(C_0-C_3)alkyl, pyridyl-(C_0-C_3)alkyl, and phenyl-(C_0-C_3)alkyl, and optionally further substituted with one methyl, $-CF_3$, cyano, or $-SCF_3$ substituent, or with 1 to 2 halo substituents,

said pyridyl-(C_0-C_3)alkyl and phenyl-(C_0-C_3)alkyl optionally being further substituted with 1-3 substituents independently selected from halo, $-CH_3$, $-OCH_3$, $-CF_3$, $-OCF_3$, -CN, and $-SCF_3$, and

wherein when Ar^2 is pyridyl, the pyridyl may alternatively, optionally be substituted with $R^{28}R^{29}N$-C(O)-, or (C_1-C_6)alkyl-C(O)- optionally substituted with 1 to 6 fluoro substituents, and may be optionally further substituted with one methyl, -CF_3, cyano, or -SCF_3 substituent, or with 1 to 2 halo substituents, and

wherein when Ar^2 is thiazolyl, the thiazolyl may alternatively, optionally be substituted with (C_3-C_7)cycloalkyl-(C_0-C_3)alkyl-NH-, and

wherein the pyrrolidinyl, piperidinyl, morpholinyl, and thiomorpholinyl is substituted with oxo- on a carbon atom adjacent to the ring nitrogen atom, or is N-substituted with a substituent selected from the group consisting of

(C_1-C_6)alkylcarbonyl, (C_1-C_6)alkylsulfonyl,
(C_3-C_7)cycloalkyl(C_0-C_3)alkyl-C(O)-,
(C_3-C_7)cycloalkyl(C_0-C_3)alkyl-S(O)$_2$-, Ph^1-(C_0-C_3)alkyl-C(O)-, and
Ph^1-(C_0-C_3)alkyl-S(O)$_2$-, and

may optionally be further substituted with 1 or 2 methyl or -CF_3 substituents, and when oxo-substituted, may optionally be further N-substituted with a substituent selected from the group consisting of (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, and Ph^1-(C_0-C_3)alkyl, and

wherein tetrahydrofuranyl and tetrahydropyranyl may optionally be substituted with an oxo substituent, and/or with one or two groups independently selected from methyl and –CF_3;

L is branched or unbranched (C_1-C_6)alkylene, except when R^{15} is -$NR^{17}R^{18}$ or Ar^2-N-linked to L, in which case L is branched or unbranched (C_2-C_6)alkylene, and when L is methylene or ethylene, L may optionally be substituted with gem-ethano or with 1 to 2 fluoro substituents, and when R^{15} is Ph^2, Ar^2, or a saturated heterocycle, L may alternatively, optionally be substituted with a substituent selected from the group consisting of hydroxy, cyano, -SCF_3, (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents, (C_1-C_6)alkoxycarbonyl optionally further substituted with 1 to 6 fluoro substituents, (C_1-C_6)alkylcarbonyloxy optionally further substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl-(C_0-C_3)alkyl-O-,

(C_3-C_7)cycloalkyl-(C_0-C_3)alkyl-O-C(O)-, and (C_3-C_7)cycloalkyl-(C_0-C_3)alkyl-C(O)-O-;

R^{16} is hydrogen, (C_1-C_6)alkyl optionally substituted with 1 to 6 fluoro substituents, (C_1-C_6)alkylcarbonyl, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-C(O)-, Ph^1-(C_0-C_3)alkyl, Ph^1-(C_0-C_3)alkyl-C(O)-, Ar^2-(C_0-C_3)alkyl, or Ar^2-(C_0-C_3)alkyl-C(O)-,

R^{17} is (C_1-C_4)alkyl optionally substituted with 1 to 6 fluoro substituents, *t*-butylsulfonyl, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-C(O)-, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-sulfonyl, Ph^1-(C_0-C_3)alkyl, Ph^1-(C_0-C_3)alkyl-C(O)-, Ph^1-(C_0-C_3)alkylsulfonyl, Ar^2-(C_0-C_3)alkyl, Ar^2-(C_0-C_3)alkyl-C(O)-, Ar^2-(C_0-C_3)alkylsulfonyl, $R^{19}OC(O)$-, or $R^{20}R^{21}NC(O)$-;

R^{18} is hydrogen or (C_1-C_4)alkyl optionally substituted with 1 to 6 fluoro substituents, or R^{17} and R^{18}, taken together with the nitrogen atom to which they are attached form Het^1 where Het^1 is substituted with oxo- on a carbon atom adjacent to the ring nitrogen atom, or

R^{17} and R^{18}, taken together with the nitrogen atom to which they are attached, form an aromatic heterocycle selected from the group consisting of pyrolyl, pyrazolyl, imidazolyl, 1,2,3-triazolyl, and 1,2,4-triazolyl,

said aromatic heterocycle optionally being substituted with 1 to 2 halo substituents, or substituted with 1 to 2 (C_1-C_4)alkyl substituents optionally further substituted with 1 to 3 fluoro substituents, or mono-substituted with fluoro, nitro, cyano, $-SCF_3$, or (C_1-C_4)alkoxy optionally further substituted with 1 to 3 fluoro substituents, and optionally further substituted with a (C_1-C_4)alkyl substituent optionally further substituted with 1 to 3 fluoro substituents;

R^{19} is (C_1-C_6)alkyl optionally substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, Ar^2-(C_0-C_3)alkyl, or Ph^1-(C_0-C_3)alkyl,

R^{20} is (C_1-C_6)alkyl optionally substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, Ar^2-(C_0-C_3)alkyl, or Ph^1-(C_0-C_3)alkyl,

R^{21} is hydrogen or (C_1-C_4)alkyl optionally substituted with 1 to 6 fluoro substituents, or R^{20} and R^{21}, taken together with the nitrogen atom to which they are attached, form Het^1;

R^{22} is (C_1-C_6)alkyl optionally substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, R^{23}-O-, Ph^1-(C_0-C_3)alkyl, Ar^2-(C_0-C_3)alkyl, or $R^{32}R^{33}N$-;

R^{23} is (C_1-C_6)alkyl optionally substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, Ph^1-(C_0-C_3)alkyl, or Ar^2-(C_0-C_3)alkyl;

R^{24} is (C_1-C_6)alkoxy(C_2-C_5)alkyl optionally substituted with 1 to 6 fluoro substituents, (C_1-C_6)alkylthio(C_2-C_5)alkyl optionally substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl(C_0-C_1)alkyl-O-(C_1-C_5)alkyl, (C_3-C_7)cycloalkyl(C_0-C_1)alkyl-S-(C_1-C_5)alkyl, phenyl(C_1-C_3) *n*-alkyl, Ph^2-(C_1-C_3)-*n*-alkyl, $Ar^2(C_0-C_3)$ *n*-alkyl, phenyl(C_0-C_1)alkyl-O-(C_1-C_5)alkyl, phenyl(C_0-C_1)alkyl-S-(C_1-C_5)alkyl, Ph^1-(C_0-C_1)alkyl-C(O)NH-(C_2-C_4)alkyl, Ph^1-(C_0-C_1)alkyl-NH-C(O)NH-(C_2-C_4)alkyl, pyridyl-(C_0-C_1)alkyl-C(O)NH-(C_2-C_4)alkyl, pyridyl-(C_0-C_1)alkyl-NH-C(O)NH-(C_2-C_4)alkyl, or $Ar^3(C_1-C_2)$alkyl,

where Ar^3 is a bi-cyclic moiety selected from a group consisting of indanyl, indolyl, dihydrobenzofuranyl, benzofuranyl, benzothiophenyl, benzoxazolyl, benzothiazolyl, benzo[1,3]dioxolyl, naphthyl, dihydrobenzopyranyl, quinolinyl, isoquinolinyl, and benzo[1,2,3]thiadiazolyl,

said Ar^3 optionally being substituted with (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, phenyl(C_0-C_1)alkyl optionally further substituted with 1 to 6 fluoro substituents, or substituted with (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, or substituted with 1-3 substituents independently selected from the group consisting of halo, oxo, methyl, and $-CF_3$,

said phenyl(C_1-C_3) *n*-alkyl, Ph^2-(C_1-C_3) *n*-alkyl, or $Ar^2(C_0-C_3)$ *n*-alkyl optionally being substituted on the *n*-alkyl moiety when present with (C_1-C_3)alkyl, dimethyl, gem-ethano, 1 to 2 fluoro substituents, or (C_1-C_6)alkyl-C(O)-,

said $Ar^2(C_0-C_3)$ *n*-alkyl being alternatively optionally substituted with a substituent selected from the group consisting of (C_3-C_7)cycloalkyl-(C_0-C_3)alkyl, Het^1-(C_0-C_3)alkyl, pyridyl-(C_0-C_3)alkyl, phenyl-(C_0-C_3)alkyl, pyridyl-(C_0-C_3)alkyl-NH-, phenyl-(C_0-C_3)alkyl-NH-, (C_1-C_6)alkyl-S-, and

(C_3-C_7)cycloalkyl-(C_0-C_3)alkyl-S-, and optionally further substituted with one methyl, -CF_3, cyano, or -SCF_3 substituent, or with 1 to 2 halo substituents,

said pyridyl-(C_0-C_3)alkyl and phenyl-(C_0-C_3)alkyl optionally being further substituted with 1-3 substituents independently selected from halo, -CH_3, -OCH_3, -CF_3, -OCF_3, -CN, and -SCF_3, and

said Ph^2-(C_1-C_3) *n*-alkyl and Ar^2(C_0-C_3) *n*-alkyl where Ar^2 is pyridyl, also optionally being substituted on the phenyl or Ar^2 moiety, respectively, with phenyl-CH=CH- or phenyl-C≡C-,

said phenyl-CH=CH- or phenyl-C≡C- being optionally further substituted with 1 to 3 substituents independently selected from the group consisting of halo, cyano, -SCF_3, (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, and (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents, and

said Ar^2(C_0-C_3) *n*-alkyl where Ar^2 is pyridyl, alternatively, optionally being substituted with (C_1-C_6)alkyl-C(O)- or $R^{28}R^{29}$N-C(O)-, and optionally further substituted with one methyl, -CF_3, cyano, or -SCF_3 substituent, or with 1 to 2 halo substituents,

said phenyl(C_0-C_1)alkyl-O-(C_1-C_3)alkyl, or phenyl(C_0-C_1)alkyl-S-(C_1-C_3)alkyl optionally being substituted on the phenyl moiety with (C_1-C_2)-$S(O)_2$-, or with 1 to 5 independently selected halo substituents, or with 1 to 3 substituents independently selected from the group consisting of halo, cyano, –SCF_3, (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, and (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents, and

said pyridyl-(C_0-C_1)alkyl-C(O)NH-(C_2-C_4)alkyl and pyridyl-(C_0-C_1)alkyl-NH-C(O)NH-(C_2-C_4)alkyl optionally being substituted on the pyridyl moiety with methyl, -CF_3, or 1 to 3 halo substituents;

R^{25} is hydrogen, (C_1-C_3)alkyl optionally substituted with 1 to 6 fluoro substituents, or allyl;

R^{26} is hydrogen, (C_1-C_6)alkyl optionally substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl;

R^{27} is hydrogen or (C_1-C_4)alkyl optionally substituted with 1 to 6 fluoro substituents, or R^{26} and R^{27}, taken together with the nitrogen atom to which they are attached, form Het^1;

R^{28} is (C_1-C_8)alkyl optionally substituted with 1 to 6 fluoro substituents, (C_3-C_8)cycloalkyl(C_0-C_3)alkyl, tetrahydropyran-3-yl(C_0-C_3)alkyl, tetrahydropyran-4-yl(C_0-C_3)alkyl, tetrahydrofuranyl(C_0-C_3)alkyl, Ph^1-(C_0-C_2) *n*-alkyl, or Ar^2-(C_0-C_2) *n*-alkyl,

said Ph^1-(C_0-C_2) *n*-alkyl and Ar^2-(C_0-C_2) *n*-alkyl optionally being substituted on the alkyl moiety when present with (C_1-C_3)alkyl, dimethyl, or gem-ethano;

R^{29} is hydrogen or (C_1-C_3)alkyl;

R^{30} is hydrogen, (C_1-C_6)alkyl optionally substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, Ph^1-(C_0-C_3)alkyl, or $Ar^2(C_0-C_3)$alkyl,

R^{31} is hydrogen or (C_1-C_6)alkyl optionally substituted with 1 to 6 fluoro substituents, or R^{30} and R^{31}, taken together with the nitrogen atom to which they are attached, form Het^1,

said Het^1 also optionally being substituted with phenyl optionally further substituted with 1 to 3 halo substituents;

R^{32} and R^{33} are each independently hydrogen or (C_1-C_6)alkyl optionally substituted with 1 to 6 fluoro substituents, or R^{32} and R^{33}, taken together with the nitrogen atom to which they are attached, form Hst^1, or R^{32} is $Ph^1(C_0-C_1)$alkyl provided that R^{33} is hydrogen;

Ar^1 is an aromatic heterocycle substituent selected from the group consisting of furanyl, thiophenyl, thiazolyl, oxazolyl, isoxazolyl, pyridyl, and pyridazinyl, any of which may optionally be substituted with 1 to 3 substituents independently selected from the group consisting of halo, (C_1-C_3)alkyl, (C_1-C_3)alkoxy, $-CF_3$, $-O-CF_3$, nitro, cyano, and trifluoromethylthio;

Ar^2 is an aromatic heterocycle substituent selected from the group consisting of pyrrolyl, pyrazolyl, imidazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, furanyl, oxazolyl, isoxazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, thiophenyl, thiazolyl, isothiazolyl, 1,2,3-thiadiazolyl, 1,3,4-thiadiazolyl, pyridyl, pyridazinyl, and

benzimidazolyl, any of which may optionally be substituted with 1 to 3 substituents independently selected from the group consisting of halo, cyano, $-SCF_3$, (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, and (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents, and wherein pyridyl and pyridazinyl may also optionally be substituted with (C_1-C_6)alkylamino optionally further substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, or (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-amino;

Het^1 is a saturated, nitrogen-containing heterocycle substituent selected from the group consisting of azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl, morpholinyl, thiomorpholinyl, homomorpholinyl, and homothiomorpholinyl, any of which may optionally be substituted with (C_1-C_6)alkyl or with 2 methyl substituents;

Het^2 is a saturated, oxygen-containing heterocycle substituent selected from the group consisting of tetrahydrofuranyl and tetrahydropyranyl, any of which may optionally be substituted with (C_1-C_6)alkyl or with 2 methyl substituents;

Ph^1 is phenyl optionally substituted with 1 to 5 independently selected halo substituents, or with 1 to 3 substituents independently selected from the group consisting of halo, cyano, $-SCF_3$, (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, and (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents;

Ph^2 is phenyl substituted with:

a) 1 to 5 independently selected halo substituents; or

b) 1 to 3 substituents independently selected from the group consisting of halo, cyano, $-SCF_3$, nitro, hydroxy, (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, and (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents; or

c) 0, 1, or 2 substituents independently selected from the group consisting of halo, cyano, $-SCF_3$, methyl, $-CF_3$, methoxy, $-OCF_3$, nitro, and hydroxy, together with one substituent selected from the group consisting of

i) (C_1-C_{10})alkyl optionally further substituted with 1 to 6 fluoro substituents or mono-substituted with hydroxy, (C_1-C_6)alkoxy, (C_3-C_7)cycloalkyl(C_0-C_3)alkyloxy, Het^2-(C_0-C_3)alkyloxy, Ph^1-(C_0-C_3)alkyloxy,

ii) (C_1-C_{10})alkoxy-(C_0-C_3)alkyl optionally further substituted with 1 to 6 fluoro substituents, and optionally further substituted with hydroxy,

iii) (C_1-C_6)alkyl-C(O)-(C_0-C_5)alkyl optionally further substituted with 1 to 6 fluoro substituents,

iv) carboxy,

v) (C_1-C_6)alkoxycarbonyl optionally further substituted with 1 to 6 fluoro substituents,

vi) (C_1-C_6)alkyl-C(O)-(C_0-C_3)-O- optionally further substituted with 1 to 6 fluoro substituents,

vii) (C_1-C_6)alkylthio-(C_0-C_3)alkyl optionally further substituted with 1 to 6 fluoro substituents,

viii) (C_1-C_6)alkylsulfinyl-(C_0-C_3)alkyl optionally further substituted with 1 to 6 fluoro substituents,

ix) (C_1-C_6)alkylsulfonyl-(C_0-C_3)alkyl optionally further substituted with 1 to 6 fluoro substituents,

x) (C_1-C_6)alkylsulfonyl-(C_0-C_3)alkyl-O- optionally further substituted with 1 to 6 fluoro substituents,

xi) (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, optionally further substituted on the cycloalkyl with 1 to 4 substituents selected from methyl and fluoro,

xii) (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-O-, optionally further substituted on the cycloalkyl with 1 to 4 substituents selected from methyl and fluoro,

xiii) (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-C(O)-,

xiv) (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-O-C(O)-,

xv) (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-S-,

xvi) (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-S(O)-,

xvii) (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-$S(O)_2$-,

xviii) Ph^1-(C_0-C_3)alkyl, optionally substituted on the alkyl moiety with 1 to 2 fluoro substituents,

xix) Ph^1-(C_0-C_3)alkyl-O-, optionally substituted on the alkyl moiety with 1 to 2 fluoro substituents

xx) Ph^1-(C_0-C_3)alkyl-C(O)-,

xxi) Ph^1-(C_0-C_3)alkyl-O-C(O)-,
xxii) Ph^1-(C_0-C_3)alkyl-C(O)-(C_0-C_3)alkyl-O-,
xxiii) Ph^1-(C_0-C_3)alkylthio,
xxiv) Ph^1-(C_0-C_3)alkylsulfinyl,
xxv) Ph^1-(C_0-C_3)alkylsulfonyl,
xxvi) Ar^2(C_0-C_3)alkyl,
xxvii) Ar^2(C_0-C_3)alkyl-O-
xxviii) Ar^2-(C_0-C_3)alkyl-S-,
xxix) Ar^2(C_0-C_3)alkyl-C(O)-,
xxx) Ar^2(C_0-C_3)alkyl-C(S)-,
xxxi) Ar^2-(C_0-C_3)alkylsulfinyl,
xxxii) Ar^2-(C_0-C_3)alkylsulfonyl,
xxxiii) Het^1(C_0-C_3)alkyl-C(O)- optionally substituted on the Het^1 moiety with Ph^1,
xxxiv) Het^1(C_0-C_3)alkyl-C(S)- optionally substituted on the Het^1 moiety with Ph^1,
xxxv) N-linked Het^1-C(O)-(C_0-C_3)alkyl-O-,
xxxvi) Het^2-(C_0-C_3)alkyloxy,
xxxvii) $R^{26}R^{27}N$-,
xxxviii) $R^{28}R^{29}$-N-(C_1-C_3)alkoxy,
xxxix) $R^{28}R^{29}N$-C(O)-,
xl) $R^{28}R^{29}N$-C(O)-(C_1-C_3)alkyl-O-,
xli) $R^{28}R^{29}N$-C(S)-,
xlii) $R^{30}R^{31}N$-$S(O)_2$-,
xliii) HON=C(CH_3)-, and
xliv) HON=C(Ph^1)-,

or a pharmaceutically acceptable salt thereof, subject to the following provisos:

a) no more than two of R^1, R^2, R^3, R^4, and R^5 may be other than hydrogen;
b) when R^2 is methyl, then R^1, R^3, R^4, and R^5 are each hydrogen;
c) when R^3 is methyl, then R^2 and R^4 are each hydrogen;

d) when R^3 is methyl, R^7 and R^8 are each –OH, and R^1, R^2, R^4, R^5, and R^9 are each hydrogen, then R^6 is other than cyclohexylthio, furanylthio, or phenylthio; and

e) When R^{12} is Ar^2-(C_1-C_3)alkyl, then R^7 is other than hydrogen or R^9 is other than chloro.

This invention also provides pharmaceutical compositions which comprise a compound of Formula I, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier, diluent, or excipient.

In another aspect of the present invention, there is provided a method for increasing activation of the 5-HT_{2C} receptor in mammals comprising administering to a mammal in need of such activation an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

The present invention also provides a method for treating obesity in mammals comprising administering to a mammal in need of such treatment an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

The present invention also provides a method for treating obsessive/compulsive disorder in mammals comprising administering to a mammal in need of such treatment an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

Furthermore, the present invention provides a method for treating depression in mammals comprising administering to a mammal in need of such treatment an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

Furthermore, the present invention provides a method for treating anxiety in mammals comprising administering to a mammal in need of such treatment an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

In preferred embodiments of the above methods of treatment utilizing a compound of Formula I, or a pharmaceutically acceptable salt thereof, the mammal is a human.

In another aspect of the present invention, there is provided a compound of Formula I for use in selectively increasing activation of the 5-HT_{2C} receptor and/or for use in treating a variety of disorders associated with decreased activation of 5-HT_{2C} receptors. Preferred embodiments of this aspect of the invention include a compound of Formula I for use in the treatment of obesity, hyperphagia, obsessive/compulsive disorder, depression, anxiety, substance abuse, sleep disorder, hot flashes, and/or hypogonadism. Particularly preferred embodiments of this aspect of the invention include the treatment of obesity, obsessive/compulsive disorder, depression, and/or anxiety.

In another aspect of the present invention, there is provided the use of one or more compounds of Formula I in the manufacture of a medicament for the activation of 5-HT_{2C} receptors in a mammal. In preferred embodiments of this aspect of the invention, there is provided the use of one or more compounds of Formula I in the manufacture of a medicament for the treatment of obesity, hyperphagia, obsessive/compulsive disorder, depression, anxiety, substance abuse, sleep disorder, hot flashes, and/or hypogonadism. Particularly preferred embodiments of this aspect of the invention include the use of one or more compounds of Formula I in the manufacture of medicaments for the treatment of obesity, obsessive/compulsive disorder, depression, and/or anxiety.

Additionally, the present invention provides a pharmaceutical formulation adapted for the treatment of obesity, or for the treatment of obsessive/compulsive disorder, or for the treatment of depression, or for the treatment of anxiety, each of which comprise a compound of Formula I in association with a pharmaceutically acceptable carrier, diluent or excipient.

In those instances where the disorders which can be treated by 5-HT_{2C} agonists are known by established and accepted classifications, their classifications can be found in various sources. For example, at present, the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV™) (1994, American Psychiatric

Association, Washington, D.C.), provides a diagnostic tool for identifying many of the disorders described herein. Also, the International Classification of Diseases, Tenth Revision (ICD-10), provides classifications for many of the disorders described herein. The skilled artisan will recognize that there are alternative nomenclatures, nosologies, and classification systems for disorders described herein, including those as described in the DSM-IV and ICD-10, and that terminology and classification systems evolve with medical scientific progress.

The general chemical terms used throughout have their usual meanings. For example, the term "alkyl" refers to a branched or unbranched saturated hydrocarbon group. The term "*n*-alkyl" refers to an unbranched alkyl group. By way of illustration, but without limitation, the term "(C_1-C_2)alkyl" refers to methyl and ethyl. The term "(C_1-C_3) *n*-alkyl" refers to methyl, ethyl, and propyl. The term "(C_1-C_3)alkyl" refers to methyl, ethyl, propyl, and isopropyl. The term "(C_1-C_4) *n*-alkyl" refers to methyl, ethyl, *n*-propyl, and *n*-butyl. The term "(C_1-C_4)alkyl" refers to methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, *sec*-butyl, and *tert*-butyl. The term "(C_1-C_6)alkyl" refers to all branched and unbranched alkyl groups having from one to six carbon atoms. The term "(C_3-C_6)alkyl" refers to all branched and unbranched alkyl groups having from three to six carbon atoms. The term "(C_2-C_6)alkyl" refers to all branched and unbranched alkyl groups having from two to six carbon atoms.

(C_x-C_y)alkyl may also be used in conjunction with other substituents to indicate a branched or unbranched saturated hydrocarbon linker for the substituent, where x and y indicate the range of carbon atoms permitted in the linker moiety. By way of illustration, but without limitation, -(C_0-C_1)alkyl refers to a single bond or a methylene linker moiety; -(C_0-C_2)alkyl refers to a single bond, methylene, methyl-methylene, or ethylene linker moiety; -(C_0-C_3)alkyl further includes trimethylene, alpha- or beta-methyl ethylene, or ethyl methylene. -(C_1-C_2)alkyl, -(C_1-C_3)alkyl, -(C_1-C_4)alkyl, and -(C_1-C_6)alkyl refer to branched or unbranched alkylene linkers having from 1 to 2, 3, 4, or 6 carbons, respectively.

The term "alkenyl" refers to a branched or unbranched unsaturated hydrocarbon group. By way of illustration, but without limitation, the term "(C_2-C_6)alkenyl" refers to a branched or unbranched hydrocarbon group having from 2 to 6 carbon atoms and 1 or more carbon-carbon double bonds. Allyl means a propyl-2-en-1-yl moiety (CH_2=CH-CH_2-).

The term "(C_3-C_7)cycloalkyl" refers to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. Cycloalkylalkyl refers to a cycloalkyl moiety linked through a branched or unbranched alkylene linker, as for example, but without limitation, -CH_2-, -CH_2CH_2-, -CH(CH_3)-, -$CH_2CH_2CH_2$-, -CH_2CH(CH_3)-, -CH(CH_3)CH_2-, -CH(CH_2CH_3)-, and the like. (C_3-C_7)cycloalkyl(C_0-$C_{1,2\text{ or }3}$)alkyl, refers to cycloalkyls linked through a single bond (i.e. C_0-alkyl) or an alkylene linker. Each alkyl, cycloalkyl, and cycloalkylalkyl group may be optionally substituted as provided for herein.

The terms "alkoxy", "phenyloxy", "sulfonyloxy", and "carbonyloxy" refer to an alkyl group, phenyl group, sulfonyl group, or carbonyl group, respectively, that is bonded through an oxygen atom.

The terms "alkylthio", "trifluoromethylthio", "cycloalkylthio" ("cyclohexylthio"), "phenylthio", and "furanylthio" refer to an alkyl group, trifluoromethyl group, cycloalkyl (cyclohexyl) group, phenyl group, or furanyl group, respectively, that is bonded through a sulfur atom.

The terms "alkylcarbonyl", "alkoxycarbonyl", "phenylcarbonyl", and "phenyloxycarbonyl", refer to an alkyl, alkoxy, phenyl, or phenyloxy group bonded through a carbonyl moiety.

The term "alkylcarbonyloxy" refers to an alkylcarbonyl group bonded through an oxygen atom.

The terms "(C_1-C_6)alkylsulfinyl", "Ph^1-(C_0-C_3)alkylsulfinyl", and "Ar^2-(C_0-C_3)alkylsulfinyl", refer to an alkyl, Ph^1-(C_0-C_3)alkyl, or Ar^2-(C_0-C_3)alkyl, respectively, group bonded through a sulfinyl moiety (-SO-).

The terms "alkylsulfonyl" (*t*-butylsulfonyl), "(C_3-C_7)cycloalkylsulfonyl", "phenylsulfonyl", "Ph^1-(C_0-C_3)alkylsulfonyl", and "Ar^2-(C_0-C_3)alkylsulfonyl", refer to an alkyl (*t*-butyl), (C_3-C_7)cycloalkyl, phenyl, Ph^1-(C_0-C_3)alkyl, or Ar^2-(C_0-C_3)alkyl group bonded through a sulfonyl moiety ($-SO_2-$).

The term "phenylamino" refers to a phenyl group bonded through a nitrogen atom.

The term "N-linked" means that the referenced moiety is linked through its nitrogen atom, by way of illustration, but without limitation, N-linked Het^1 means the Het^1 moiety is linked through a nitrogen atom in the ring of the Het^1 moiety, and N-linked Ar^2 means the Ar^2 moiety is linked through a nitrogen atom in the ring of the Ar^2 moiety.

The term "halo" refers to fluoro, chloro, bromo, or iodo. Preferred halo groups are fluoro, chloro, and bromo. More preferred halo groups are fluoro and chloro.

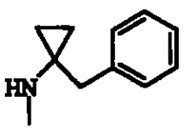
The term "heterocycle" is taken to mean a saturated or unsaturated 4 to 7 membered ring containing from 1 to 3 heteroatoms selected from nitrogen, oxygen and sulfur, said ring optionally being benzofused. Exemplary saturated heterocycles, for the purposes of the present invention, include azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl, tetrahydrofuranyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, piperazinyl, and the like. Exemplary unsaturated heterocycles include, but are not limited to, pyrrolyl, pyrazolyl, imidazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, furanyl, oxazolyl, isoxazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, thiophenyl, thiazolyl, isothiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, pyridyl, pyridazinyl, and the like. Exemplary benzofused heterocyclic rings include, but are not limited to, indolyl, dihydroindolyl, indazolyl, benzisoxazolyl, benzimidazolyl, benzofuranyl, dihydrobenzofuranyl, benzoxazolyl, benzo[1,3]dioxolyl, benzothiophenyl, benzothiazolyl, quinolinyl, isoquinolinyl, benzopyranyl, dihydrobenzopyranyl, cinnolinyl, quinazolinyl

and the like, all of which may be optionally substituted as provided for herein, which also includes optionally substituted on the benzene ring when the heterocycle is benzofused.

In one embodiment, preferred heterocycles include pyrrolidinyl, piperidinyl, homopiperidinyl, tetrahydrofuranyl, tetrahydropyranyl, pyrrolyl, pyrazolyl, imidazolyl, furanyl, isoxazolyl, 1,2,4-oxadiazolyl, thiophenyl, thiazolyl, 1,2,3-thiadiazolyl, pyridyl, pyridazinyl, indolyl, dihydroindolyl, benzimidazolyl, benzofuranyl, dihydrobenzofuranyl, benzoxazolyl, benzo[1,3]dioxolyl, benzothiophenyl, benzothiazolyl, quinolinyl, isoquinolinyl, and benzopyranyl, all of which may be optionally substituted as provided for herein.

In yet another embodiment, preferred heterocycles include pyridyl, pyridazinyl, and thiophenyl.

The terms "gem-", "geminal", or "geminate" refer to two identical substituents bonded to a common carbon atom, as for example, but without limitation, gem-methyl, meaning two methyl groups bound to a common carbon atom, as for instance in a 3,3-dimethyltetrahydrobenzofuranyl group. For the purposes of this application, gem-ethano means an ethylene substituent wherein both carbons are bound to the same carbon atom of the substituted group to form a cyclopropyl moiety, as for example, but without limitation, the ethano substituent on the 2-phenyl-(1,1-ethano)ethylamino group below:



It is to be understood that when a basic definition of a group lists optionally allowable substituents, and in another place that group is said to also optionally be substituted with other recited substituents, then those other recited substituents are intended to be added to the list of optionally allowable substituents listed in the basic definition of the group. Conversely, if in another place that group is said to be alternatively, optionally substituted with other recited substituents, then those other recited substituents are intended to replace the list of optionally allowable substituents

recited in the basic definition of the substituent. For example, but without limitation, Ar^2 has a basic definition that recites that any of the listed heteroaromatic groups may "optionally be substituted with 1 to 3 substituents independently selected from the group consisting of halo, cyano, $-SCF_3$, (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, and (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents, and wherein pyridyl and pyridazinyl may also optionally be substituted with (C_1-C_6)alkylamino optionally further substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, or (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-amino." This is to be understood to mean that any of the listed heteroaromatic groups may optionally be substituted with [1 to 3 substituents independently selected from the group consisting of halo, cyano, $-SCF_3$, (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, and (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents], and that when Ar^2 is selected to be pyridyl or pyridazinyl, the list of substituents selectable for the 1 to 3 substituents is expanded to also include [(C_1-C_6)alkylamino optionally further substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, and (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-amino]. Likewise, in the definition of R^{14}, the terminology "wherein . . . Ar^2, wherein Ar^2 is pyridyl, then R^{14} may also, optionally be substituted with phenyl-CH=CH- or phenyl-C≡C- . . ." is understood to mean that the list of substituents selectable for the 1 to 3 substituents optionally allowed on Ar^2 = pyridyl is again expanded to also include [phenyl-CH=CH- or phenyl-C≡C- . . .]. Conversely, later in the definition of R^{14}, the terminology "wherein when Ar^2 is pyridyl, the pyridyl may alternatively, optionally be substituted with $R^{28}R^{29}N$-C(O)- and optionally further substituted with one methyl, $-CF_3$, cyano, or $-SCF_3$ substituent, or with 1 to 2 halo substituents", is understood to mean that when R^{14} is selected to be Ar^2 = pyridyl, then the list of 1 to 3 independently selected substituents optionally allowable in the basic definition of Ar^2 may be superceded by "$R^{28}R^{29}N$-C(O)- and optionally further substituted with one methyl, $-CF_3$, cyano, or $-SCF_3$ substituent, or with 1 to 2 halo substituents."

The term "amino protecting group" as used in this specification refers to a substituent commonly employed to block or protect the amino functionality while reacting other functional groups on the compound. Examples of such amino protecting groups

include the formyl group, the trityl group, the acetyl group, the trichloroacetyl group, the trifluoroacetyl group, the chloroacetyl, bromoacetyl, and iodoacetyl groups, carbamoyl-type blocking groups such as benzyloxycarbonyl, 9-fluorenylmethoxycarbonyl ("FMOC"), *t*-butoxycarbonyl (*t*-BOC), and like amino protecting groups. The species of amino protecting group employed is not critical so long as the derivatized amino group is stable to the conditions of subsequent reactions on other positions of the molecule and can be removed at the appropriate point without disrupting the remainder of the molecule. The selection and use (addition and subsequent removal) of amino protecting groups is well known within the ordinary skill of the art. Further examples of groups referred to by the above terms are described by T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis", 3rd edition, John Wiley and Sons, New York, NY, 1999, chapter 7, hereafter referred to as "*Greene*".

The term "pharmaceutical" or "pharmaceutically acceptable" when used herein as an adjective, means substantially non-toxic and substantially non-deleterious to the recipient.

By "pharmaceutical composition" it is further meant that the carrier, solvent, excipients and/or salt must be compatible with the active ingredient of the composition (e.g. a compound of Formula I). It is understood by those of ordinary skill in this art that the terms "pharmaceutical formulation" and "pharmaceutical composition" are generally interchangeable, and they are so used for the purposes of this application.

The term "effective amount" means an amount of a compound of Formula I which is capable of activating 5-HT_{2C} receptors and/or elicit a given pharmacological effect.

The term "suitable solvent" refers to any solvent, or mixture of solvents, inert to the ongoing reaction that sufficiently solubilizes the reactants to afford a medium within which to effect the desired reaction.

It is understood that compounds of the present invention may exist as stereoisomers. As such, all enantiomers, diastereomers, and mixtures thereof, are included within the scope of the present invention. Where specific stereochemistries are

identified in this application, the Cahn-Prelog-Ingold designations of (R)- and (S)- and the cis and trans designation of relative stereochemistry are used to refer to specific isomers and relative stereochemistry. Known optical rotations are designated by (+) and (-) for dextrorotatary and levorotatary, respectively. Where a chiral compound is resolved into its isomers, but absolute configurations or optical rotations are not determined, the isomers are arbitrarily designated as isomer 1, isomer 2, etc. While all enantiomers, diastereomers, and mixtures thereof, are contemplated within the present invention, preferred embodiments are single enantiomers and single diastereomers.

It is generally understood by those skilled in this art, that compounds intended for use in pharmaceutical compositions are routinely, though not necessarily, converted to a salt form in efforts to optimize such characteristics as the handling properties, stability, pharmacokinetic, and/or bioavailability, etc. Methods for converting a compound to a given salt form are well known in the art (see for example, Berge, S.M, Bighley, L.D., and Monkhouse, D.C., *J. Pharm. Sci.*, 66:1, (1977)). In that the compounds of the present invention are amines and therefore basic in nature, they readily react with a wide variety of pharmaceutically acceptable organic and inorganic acids to form pharmaceutically acceptable acid addition salts therewith. Such salts are also embodiments of this invention.

Typical inorganic acids used to form such salts include hydrochloric, hydrobromic, hydroiodic, nitric, sulfuric, phosphoric, hypophosphoric, metaphosphoric, pyrophosphoric acid, and the like. Salts derived from organic acids, such as aliphatic mono and dicarboxylic acids, phenyl substituted alkanoic acids, hydroxyalkanoic and hydroxyalkandioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, may also be used. Such pharmaceutically acceptable salts thus include chloride, bromide, iodide, nitrate, acetate, phenylacetate, trifluoroacetate, acrylate, ascorbate, benzoate, chlorobenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, methylbenzoate, o-acetoxybenzoate, isobutyrate, phenylbutyrate, α-hydroxybutyrate, butyne-1,4-dicarboxylate, hexyne-1,4-dicarboxylate, caprate, caprylate, cinnamate, citrate, formate, fumarate, glycolate, heptanoate, hippurate, lactate, malate, maleate, hydroxymaleate, malonate, mandelate, nicotinate, isonicotinate, oxalate, phthalate, terephthalate,

propiolate, propionate, phenylpropionate, salicylate, sebacate, succinate, suberate, benzenesulfonate, p-bromobenzenesulfonate, chlorobenzenesulfonate, ethylsulfonate, 2-hydroxyethylsulfonate, methylsulfonate (mesylate), naphthalene-1-sulfonate, naphthalene-2-sulfonate, naphthalene-1,5-sulfonate, p-toluenesulfonate, xylenesulfonate, tartrate, and the like.

It is well known that such compounds can form salts in various molar ratios with the acid to provide, for example, the hemi-acid, mono-acid, di-acid salt, etc. Where in the salt formation procedure, the acid is added in a specific stoichiometric ratio, unless otherwise analyzed to confirm, the salt is presumed, but not known, to form in that molar ratio. Terms such as "$(acid)_x$" are understood to mean that the molar ratio of the salt formed is not known and can not be presumed, as for example, but without limitation, $(HCl)_x$ and $(methanesulfonic\ acid)_x$.

Abbreviations used herein are defined as follows:

"2B-3 ethanol" means ethanol denatured with toluene.

"AIBN" means 2,2'-azobisisobutyronitrile.

"Anal. Calc'd" or "Anal. Calcd" means calculated elemental analysis.

"APCI" means atmospheric pressure chemical ionization.

"bp" means boiling point.

"BINAP" means *rac*-2,2'-bis(diphenylphosphino)-1,1'binaphthyl.

"Boc" or "*t*-Boc" means *tert*-butoxycarbonyl.

"Brine" means a saturated aqueous sodium chloride solution.

"CV" means calorific value of oxygen.

"DBU" means 1,8-diazabicyclo[5.4.0]undec-7-ene.

"DCE" means 1,2-dichloroethane.

"DCM" means dichloromethane (i.e. methylene chloride, CH_2Cl_2).

"DIBAL-H" means diisobutylaluminum hydride.

"DIEA" means *N,N*-diisopropylethylamine.

"DMAP" means 4-(dimethylamino)pyridine.

"DME" means 1,2-dimethoxyethane.

"DMEA" means *N,N*-dimethylethylamine.

"DMF" means *N,N*-dimethylformamide.

"DMSO" means dimethylsulfoxide.

"DOI" means (±)-1-(2,5-dimethoxy-4-[^{125}I]-iodophenyl)-2-aminopropane.

"EDC" means 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride.

"EDTA" means ethylenediaminetetraacetic acid.

"EE" means energy expenditure.

"EtOAc" means ethyl acetate.

"GC-MS" means gas chromatography – mass spectrometry.

"GDP" means guanosine diphosphate.

"GTP" means guanosine triphosphate.

"GTPγ[^{35}S]" means guanosine triphosphate having the terminal phosphate substituted with ^{35}S in place of an oxygen.

"HATU" means O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate.

"HMPA" means hexamethylphosphoramide.

"HOBT" means 1-hydroxybenzotriazole hydrate.

"HPLC" means high-pressure liquid chromatography.

"HRMS" means high-resolution mass spectrometry.

"ISPA" means immunoadsorption scintillation proximity assay.

"*m*-CPBA" means *meta*-chloroperoxybenzoic acid.

"mp" means melting point.

"Ms" in a chemical structure means the methanesulfonyl moiety ($-SO_2CH_3$).

"MS (ES+)" means mass spectroscopy using electrospray ionization.

"MTBE" means methyl *t*-butyl ether.

"NBS" means *N*-bromosuccinimide.

"NMP" means 1-methyl-2-pyrrolidinone.

"NMR" means nuclear magnetic resonance.

"Pd/C" means palladium on activated carbon.

"RQ" means respiratory quotient.

"SCX chromatography" means chromatography on an SCX column or cartridge.

"SCX column" or "SCX cartridge", as used herein, refers to a Varian Bond Elute® silica based strong cation exchange resin column or disposable cartridge or equivalent.

"Sudan III" means 1- [(4-phenylazo)phenylazo]-2-naphthalenol.

"Tf" in a chemical structure means the trifluoromethanesulfonyl moiety ($-SO_2CF_3$).

"TFA" means trifluoroacetic acid.

"THF" means tetrahydrofuran.

"TLC" means thin layer chromatography.

While all of the compounds of the present invention are useful as 5-HT_{2C} agonists, certain classes are preferred, as for example, compounds having any of the following enumerated selections of substituents: Compounds wherein

1) R^7 is halo;
2) R^7 is chloro;
3) R^7 is (C_1–C_6)alkyl optionally substituted with 1 to 6 fluoro substituents;
4) R^7 is (C_1–C_3)alkyl optionally substituted with 1 to 6 fluoro substituents;
5) R^7 is $-CF_3$;
6) R^7 is (C_3–C_6)alkenyl optionally substituted with 1 to 6 fluoro substituents;
7) R^7 is (C_3–C_6)alkenyl;
8) R^7 is cyano;
9) R^{1-5} are each hydrogen;
10) R^4 is methyl or ethyl;
11) R^4 is methyl;
12) R^3 is methyl;
13) R^8 is hydrogen;
14) R^9 is (C_1–C_3)alkoxy;
15) R^9 is methoxy;
16) R^9 is halo;
17) R^9 is chloro;
18) R^6 is $-C{\equiv}C-R^{10}$;
19) R^{10} is Ph^1-(C_0–C_3)alkyl;
20) R^{10} is Ph^1-(C_1–C_2)alkyl;

21) R^{10} is Phenyl(C_0–C_3)alkyl;

22) R^{10} is (C_3–C_7)cycloalkyl(C_0–C_3)alkyl;

23) R^{10} is (C_3–C_7)cycloalkylmethyl;

24) R^{10} is (C_4–C_6)alkyl;

25) R^{10} is branched (C_4–C_6)alkyl;

26) R^{10} is (C_1–C_6)alkyl substituted with 2-6 fluoro substituents;

27) R^{10} is Ar^1-(C_0–C_3)alkyl;

28) R^{10} is Ar^1-(C_1–C_2)alkyl;

29) R^6 is –O-R^{12};

30) R^{12} is Ph^2-(C_0–C_3)alkyl;

31) R^{12} is Ph^2-(C_1–C_2)alkyl;

32) R^{12} is Ph^2-(C_1–C_2)alkyl and Ph^2 is substituted with 1-3 halo substituents;

33) R^{12} is Ph^2-(C_1–C_2)alkyl and Ph^2 is substituted with 1-3 fluoro substituents;

34) R^{12} is Ph^2-(C_1–C_2)alkyl and Ph^2 is substituted with cyano;

35) R^{12} is Ph^2-(C_1–C_2)alkyl and Ph^2 is substituted with $R^{30}R^{31}N$-$S(O)_2$-;

36) R^{12} is Ph^2-(C_1–C_2)alkyl, Ph^2 is substituted with $R^{30}R^{31}N$-$S(O)_2$-, R^{30} is (C_1-C_3)alkyl optionally further substituted with 1-3 fluoro substituents and R^{31} is hydrogen;

37) R^{12} is Ar^2-(C_0–C_3)alkyl;

38) R^{12} is Ar^2-(C_1–C_2)alkyl;

39) R^{12} is Ar^2-(C_1–C_2)alkyl and Ar^2 is pyridyl, thiazolyl, oxazolyl, or pyrazolyl, each optionally substituted with methyl;

40) R^{12} is benzazolyl-(C_1–C_3)alkyl;

41) R^{12} is Ph^2-C(O)-(C_1–C_3)alkyl,

42) R^{12} is Ph^2-C(O)-(C_1–C_3)alkyl and Ph^2 is substituted with 1 to 3 halo substituents;

43) R^{12} is Ph^2-C(O)-(C_1–C_3)alkyl and Ph^2 is substituted with 1 to 3 halofluoro substituents;

44) R^{12} is Ph^1-$S(O)_2$–;

45) R^{12} is (C_1–C_6)alkyl-O-C(O)-(C_3–C_6)alkyl;

46) R^{12} is (C_1–C_3)alkyl-O-C(O)-(C_3–C_6)alkyl;

47) R^{12} is R^{13}-C(O)NH-(C_2–C_4)alkyl;

48) R^{12} is R^{13}-C(O)NH-(C_2–C_4)alkyl and R^{13} is Ph^1;

49) R^{12} is R^{13}-C(O)NH-(C_2–C_4)alkyl, R^{13} is Ph^1; substituted with 1 to 3 halo substituents;

50) R^{12} is R^{13}-C(O)NH-(C_2–C_4)alkyl and R^{13} is (C_3–C_7)cycloalkyl;

51) R^{12} is R^{13}-C(O)NH-(C_2–C_4)alkyl and R^{13} is pyridyl;

52) R^{12} is R^{13}-C(O)NH-(C_2–C_4)alkyl and R^{13} is (C_1–C_3)alkoxy;

53) R^{12} is R^{13}-C(O)NH-(C_2–C_4)alkyl and R^{13} is (C_3–C_7)cycloalkyl;

54) R^6 is –S-R^{14};

55) R^6 is –S-R^{14} and R^{14} is Ph^2;

56) R^6 is –S-R^{14}, R^{14} is Ph^2 substituted with 1 to 3 halo substituents;

57) R^6 is –S-R^{14}, R^{14} is Ph^2 substituted with cyano;

58) R^6 is –S-R^{14}, R^{14} is Ph^2; substituted with cyano and 1 to 2 halo substituents;

59) R^6 is –S-R^{14} and R^{14} is Ar^2;

60) R^6 is –S-R^{14}, R^{14} is Ar^2, and Ar^2 is optionally substituted pyridyl or pyridazinyl;

61) R^6 is –S-R^{14}, R^{14} is Ar^2, and Ar^2 is optionally substituted thiophenyl, thiazolyl, isothiazolyl, 1,2,3-thiadiazolyl, 1,3,4-thiadiazolyl;

62) R^6 is –S-R^{14} and R^{14} is tetrahydrofuranyl or tetrahydropyranyl;

63) R^6 is –S-R^{14} and R^{14} is tetrahydrofuranyl or tetrahydropyranyl and the tetrahydrofuranyl or tetrahydropyranyl is substituted with oxo on a carbon adjacent to the ring oxygen;

64) R^6 is –S-R^{14} and R^{14} is R^{15}-L-;

65) L is (C_1–C_2)alkylene;

66) L is branched (C_2–C_3)alkylene;

67) L is methyl-methylene;

68) L is di-methyl-methylene;

69) L is methyl-ethylene;

70) L is gem-di-methyl-ethylene;

71) L is gem-ethano-ethylene;

72) R^{15} is Ph^2;

73) R^{15} is Ph^2 substituted with 1 to 3 halo substituents;

74) R^{15} is Ph^2 substituted with cyano;

75) R^{15} is Ph^2 substituted with $(C_1–C_6)$alkoxy;

76) R^{15} is Ph^2 substituted with $(C_1–C_6)$alkoxy optionally further substituted with 1 to 3 fluoro substituents;

77) R^{15} is Ph^2 substituted with $(C_1–C_6)$alkoxy$(C_1–C_1)$alkyl;

78) R^{15} is Ph^2 substituted with $(C_1–C_6)$alkoxy$(C_1–C_1)$alkyl further substituted with 1 to 3 fluoro substituents;

79) R^{15} is Ph^2 substituted with $(C_1–C_6)$alkylthio;

80) R^{15} is Ph^2 substituted with $(C_1–C_6)$alkylthio optionally further substituted with 1 to 3 fluoro substituents;

81) R^{15} is Ph^2 substituted with $(C_1–C_6)$alkylthio$(C_1–C_1)$alkyl;

82) R^{15} is Ph^2 substituted with $(C_1–C_6)$alkylthio$(C_1–C_1)$alkyl further substituted with 1 to 3 fluoro substituents;

83) R^{15} is Ph^2 substituted with $(C_3–C_7)$cycloalkyl$(C_0–C_1)$alkyl;

84) R^{15} is Ph^2 substituted with $(C_1–C_6)$alkylsulfonyl$(C_0–C_1)$alkyl optionally further substituted with 1 to 3 fluoro substituents;

85) R^{15} is Ph^2 substituted with $(C_1–C_6)$alkylsulfinyl$(C_0–C_1)$alkyl optionally further substituted with 1 to 3 fluoro substituents;

86) R^{15} is Ph^2 substituted with Ph^1-$(C_0–C_1)$alkyl-sulfonyl;

87) R^{15} is Ph^2 substituted with Ph^1-$(C_0–C_1)$alkyl;

88) R^{15} is Ph^2 substituted with $R^{26}R^{27}N$-;

89) R^{15} is Ph^2 substituted with Het^1;

90) R^{15} is Ph^2 substituted with $(C_1–C_6)$alkyl-C(O)- optionally further substituted with 1 to 3 fluoro substituents;

91) R^{15} is Ph^2 substituted with $(C_1–C_6)$alkyl—O-C(O)- optionally further substituted with 1 to 3 fluoro substituents;

92) R^{15} is Ph^2 substituted with Ph^1;

93) R^{15} is Ph^2 substituted with $Ph^1(C_0–C_3)$alkyl-O-;

94) R^{15} is Ph^2 substituted with $Ph^1(C_0–C_3)$alkyl-C(O)-;

95) R^{15} is Ph^2 substituted with $Ph^1(C_0–C_3)$alkyl-C(O)-;

96) R^{15} is Ph^2 substituted with $Ar^2(C_0–C_3)$alkyl-C(O)-;

97) R^{15} is Ph^2 substituted with $Ar^2(C_0–C_3)$alkyl-C(O)- and Ar^2 is pyrazolyl optionally further substituted as provided for in Ar^2;

98) R^{15} is Ph^2 substituted with $R^{28}R^{29}N$-C(O)-;

99) R^{15} is Ph^2 substituted with $R^{28}R^{29}N$-C(O)- and R^{28} is $(C_1–C_6)$alkyl;

100) R^{15} is Ph^2 substituted with $R^{28}R^{29}N$-C(O)- and R^{28} is (C_3-C_7)cycloalkyl(C_0-C_2)alkyl;

101) R^{15} is Ph^2 substituted with $R^{28}R^{29}N$-C(O)- and R^{28} is Ph^1-(C_0-C_2)-*n*-alkyl optionally substituted on the alkyl moiety when present with (C_1-C_3)alkyl, dimethyl, or gem-ethano;

102) R^{15} is Ph^2 substituted with $R^{28}R^{29}N$-C(O)- and R^{28} is Ar^2-(C_0-C_2)-*n*-alkyl optionally substituted on the alkyl moiety when present with (C_1-C_3)alkyl, dimethyl, or gem-ethano;

103) R^{15} is Ph^2 substituted with Het^1-C(O)-;

104) R^{15} is Ph^2 substituted with Het^1-C(O)- further substituted with Ph^1;

105) R^{15} is Ar^2;

106) R^{15} is Ar^2 further substituted with methyl;

107) R^{15} is Ar^2 further substituted with $(C_3–C_7)$cycloalkyl$(C_0–C_2)$alkyl, Het^1, pyridyl, or phenyl optionally further substituted with methyl, $-CF_3$, cyano, $-SCF_3$, or with 1 to 3 halo substituents;

108) R^{15} is pyrrolyl, pyrazolyl, imidazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, furanyl, oxazolyl, isoxazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, thiophenyl, thiazolyl, isothiazolyl, 1,2,3-thiadiazolyl, or 1,3,4-thiadiazolyl, any of which may optionally be substituted with 1 to 3 substituents selected from the group consisting of halo, cyano, $–SCF_3$, (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro, and (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro.

109) R^{15} is pyridyl optionally further substituted as provided for in Ar^2;

110) R^{15} is tetrahydrofuranyl or tetrahydropyranyl, either optionally being substituted with an oxo substituent, or with one or two groups selected independently from methyl and $–CF_3$;

111) R^{15} is tetrahydrofuranyl or tetrahydropyranyl, being substituted with an oxo substituent, and optionally being further substituted with one or two groups selected independently from methyl and $–CF_3$;

112) R^{15}–L- is pyrid-2-yl-methyl;

113) R^{15}–L- is pyrid-3-yl-methyl;

114) R^{15}–L- is pyrid-2-yl-CH(CH_3)-;

115) R^{15}–L- is pyrid-3-yl-CH(CH_3)-;

116) R^{15} is pyridazinyl optionally further substituted as provided for in Ar^2;

117) R^{15}–L- is pyridazin-2-yl-methyl;

118) R^{15}–L- is pyridazin-3-yl-methyl;

119) R^{15}–L- is pyridazin-2-yl-CH(CH_3)-;

120) R^{15}–L- is pyridazin-3-yl-CH(CH_3)-;

121) R^{15} is pyridyl further substituted with (C_3–C_7)cycloalkyl(C_0–C_2)alkyl, Het^1, pyridyl, or phenyl optionally further substituted with methyl, -CF_3, cyano, -SCF_3, or with 1 to 3 halo substituents;

122) R^{15} is pyridazinyl further substituted with (C_3–C_7)cycloalkyl(C_0–C_2)alkyl, Het^1, pyridyl, or phenyl optionally further substituted with methyl, -CF_3, cyano, –SCF_3, or with 1 to 3 halo substituents;

123) R^{15} is R^{22}-C(O)-;

124) R^{15} is R^{22}-C(O)- and R^{22} is (C_1-C_6)alkyl optionally substituted with 1 to 6 fluoro substituents;

125) R^{15} is R^{22}-C(O)- and R^{22} is (C_1-C_6)alkoxy optionally substituted with 1 to 6 fluoro substituents;

126) R^{15} is R^{22}-C(O)- and R^{22} is (C_3-C_7)cycloalkyl(C_0-C_3)alkyl;

127) R^{15} is R^{22}-C(O)- and R^{22} is (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-O-;

128) R^{15} is R^{22}-C(O)- and R^{22} is Ph^1-(C_0-C_3)alkyl;

129) R^{15} is R^{22}-C(O)- and R^{22} is Ph^1-(C_0-C_3)alkyl-O-;

130) R^{15} is R^{22}-C(O)- and R^{22} is Ar^2-(C_0-C_3)alkyl;

131) R^{15} is R^{22}-C(O)- and R^{22} is Ar^2-(C_0-C_3)alkyl-O-;

132) R^{15} is R^{22}-C(O)- and R^{22} is $R^{32}R^{33}N$-;

133) R^{15} is phthalimido;

134) R^{15} is $R^{17}R^{16}N$-;

135) R^{15} is $R^{17}R^{16}N$- and R^{17} is (C_1-C_3)alkoxy-C(O)-;

136) R^{15} is $R^{17}R^{16}N$- and R^{17} is (C_3-C_7)cycloalkyl(C_0-C_2)-C(O)-;

137) R^{15} is $R^{17}R^{16}N$- and R^{17} is Ph^1-(C_0-C_2)-C(O)-;

138) R^{15} is $R^{17}R^{16}N$- and R^{17} is Ar^2-(C_0-C_2)-C(O)-;

139) R^{15} is $R^{16}O$-;

140) R^{15} is $R^{16}O$- and R^{16} is (C_1-C_6)alkyl-C(O)-;

141) R^{15} is $R^{16}O$- and R^{16} is (C_3-C_7)cycloalkyl(C_0-C_2)-C(O)-;

142) R^6 is $R^{24}R^{25}N$- and R^{24} is (C_1-C_6)alkoxy(C_2-C_3)alkyl optionally substituted with 1 to 6 fluoro substituents;

143) R^6 is $R^{24}R^{25}N$- and R^{24} is (C_1-C_6)alkylthio(C_2-C_3)alkyl optionally substituted with 1 to 6 fluoro substituents;

144) R^6 is $R^{24}R^{25}N$- and R^{24} is (C_3-C_7)cycloalkyl(C_0-C_1)alkyl-O-(C_1-C_3)alkyl;

145) R^6 is $R^{24}R^{25}N$- and R^{24} is (C_3-C_7)cycloalkyl(C_0-C_1)alkyl-S-(C_1-C_3)alkyl;

146) R^6 is $R^{24}R^{25}N$- and R^{24} is phenyl(C_1-C_3) *n*-alkyl optionally substituted on the *n*-alkyl moiety when present with (C_1-C_3)alkyl, dimethyl, or gem-ethano;

147) R^6 is $R^{24}R^{25}N$- and R^{24} is Ph^2-(C_1-C_3) *n*-alkyl optionally substituted on the *n*-alkyl moiety when present with (C_1-C_3)alkyl, dimethyl, or gem-ethano;

148) R^6 is $R^{24}R^{25}N$- and R^{24} is $Ar^2(C_0-C_3)$ *n*-alkyl optionally substituted on the *n*-alkyl moiety when present with (C_1-C_3)alkyl, dimethyl, or gem-ethano;

149) R^6 is $R^{24}R^{25}N$- and R^{24} is $Ar^2(C_0-C_3)$ *n*-alkyl optionally substituted on the *n*-alkyl moiety when present with (C_1-C_3)alkyl, dimethyl, or gem-ethano, wherein Ar^2 contains a nitrogen atom, and Ar^2 is substituted;

150) R^6 is $R^{24}R^{25}N$- and R^{24} is $Ar^2(C_0-C_3)$ *n*-alkyl optionally substituted on the *n*-alkyl moiety when present with (C_1-C_3)alkyl, dimethyl, or gem-ethano, wherein Ar^2 contains a nitrogen atom, and Ar^2 is substituted with (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro, (C_1-C_6)alkylamino optionally further substituted with 1 to 6 fluoro, or (C_3-C_7)cycloalkyl(C_0-C_2)alkyl optionally further substituted with 1 to 6 fluoro;

151) R^6 is $R^{24}R^{25}N$- and R^{24} is $Ar^2(C_0-C_3)$ *n*-alkyl optionally substituted on the *n*-alkyl moiety when present with (C_1-C_3)alkyl, dimethyl, or gem-ethano, and wherein Ar^2 is pyridyl or pyridazinyl and is substituted with (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro, (C_1-C_6)alkylamino optionally further substituted with 1 to 6 fluoro, or (C_3-C_7)cycloalkyl(C_0-C_2)alkyl optionally further substituted with 1 to 6 fluoro;

152) R^6 is $R^{24}R^{25}N$- and R^{24} is $Ar^2(C_0-C_3)$ *n*-alkyl optionally substituted on the *n*-alkyl moiety when present with (C_1-C_3)alkyl, dimethyl, or gem-ethano, and wherein Ar^2 is pyridyl substituted with $R^{28}R^{29}N$-C(O)- and R^{28} is (C_3-C_7)cycloalkyl(C_0-C_2)alkyl or Ph^1 and R^{29} is hydrogen;

153) R^6 is $R^{24}R^{25}N$- and R^{24} is $Ar^2(C_0-C_3)$ *n*-alkyl, wherein Ar^2 is pyridyl substituted with $R^{28}R^{29}N$-C(O)- and R^{28} is (C_3-C_7)cycloalkyl or phenyl optionally substituted with 1 to 3 halo, preferably fluoro, and R^{29} is hydrogen;

154) R^6 is $R^{24}R^{25}N$- and R^{24} is Ph^1-(C_0-C_1)alkyl-O-(C_1-C_5)alkyl;

155) R^6 is $R^{24}R^{25}N$- and R^{24} is Ph^1-(C_0-C_1)alkyl-S-(C_1-C_5)alkyl;

156) R^6 is $R^{24}R^{25}N$- and R^{24} is Ph^1-(C_0-C_1)alkyl-C(O)NH-(C_2-C_4)alkyl;

157) R^6 is $R^{24}R^{25}N$- and R^{24} is Ph^1-(C_0-C_1)alkyl-NH-C(O)NH-(C_2-C_4)alkyl;

158) R^6 is $R^{24}R^{25}N$- and R^{24} is pyridyl-(C_0-C_1)alkyl-C(O)NH-(C_2-C_4)alkyl optionally substituted on the pyridyl moiety with methyl, $-CF_3$, or 1 to 3 halo substituents;

159) R^6 is $R^{24}R^{25}N$- and R^{24} is pyridyl-(C_0-C_1)alkyl-NH-C(O)NH-(C_2-C_4)alkyl optionally substituted on the pyridyl moiety with methyl, $-CF_3$, or 1 to 3 halo substituents;

160) R^6 is $R^{24}R^{25}N$- and R^{24} is Ar^3-(C_1-C_2)alkyl;

161) R^6 is $R^{24}R^{25}N$- and R^{24} is Ar^3-methyl;

It will be understood that the above classes may be combined to form additional preferred classes. Exemplary combinations include, but are not limited to:

162) Any one of preferred embodiments 19) through 161) (the preferred selections for R^6), combined with any one of preferred embodiments 1) through 9) (the preferred selections for R^7);

163) Any one of preferred embodiments 19) through 161) (the preferred selections for R^6), wherein R^7 is halogen;

164) Any one of preferred embodiments 19) through 161) (the preferred selections for R^6), wherein R^7 is chloro;

165) A preferred combination according to 162), 163), or 164), wherein R^{1-5}, and R^8 are each hydrogen;

166) A preferred combination according to 162), 163), or 164), wherein R^{1-5}, R^8 and R^9, are each hydrogen.

167) Any one of preferred embodiments 37), 38), or 39), wherein R^7 is other than hydrogen;

168) Any one of preferred embodiments 37), 38), or 39), wherein R^9 is hydrogen;

169) Any one of preferred embodiments 37), 38), or 39), wherein R^7 is other than hydrogen and R^9 is hydrogen;

170) Any one of preferred embodiments 37), 38), or 39), wherein R^7 is chloro and R^9 is hydrogen;

171) compounds of formula (I) wherein R^6 is $-C{\equiv}C-R^{10}$ and wherein R^{10} is selected from the values defined in any one of embodiments 19) to 28);

172) compounds of formula (I) wherein R^6 is $-O-R^{12}$ and wherein R^{12} is selected from the values defined in any one of embodiments 30) to 53);

173) compounds of formula (I) wherein R^6 is $-S-R^{14}$ and wherein R^{14} is selected from the values defined in any one of embodiments 55) to 63) or 64) wherein L is selected from the values of 65) to 71) and R^{15} is selected from the values defined in any one of embodiments 72) to 141);

174) compounds of formula (I) wherein R^6 is $R^{24}R^{25}N-$ and wherein R^{24} is selected from the values defined in any one of embodiments 142) to 161);

175) compounds according to embodiment 172) wherein R^{12} is selected from the values defined in any one of embodiments 37), 38) or 39);

176) compounds of formula (I) wherein R^7 is other than hydrogen;

177) compounds according to any one of embodiments 171) or 174) wherein R^7 is other than hydrogen;

178) compounds according to any one of embodiments 171) or 174) wherein R^7 is chloro;

179) compounds according to any one of embodiments 171) or 174) wherein R^9 is hydrogen;

180) compounds according to any one of embodiments 171) or 174) wherein R^9 is $(C_1–C_3)$alkoxy;

181) compounds according to any one of embodiments 171) or 174) wherein R^9 is methoxy;

182) compounds according to any one of embodiments 171) or 174) wherein R^7 is choro and R^9 is hydrogen;

183) compounds according to any one of embodiments 171) or 174) wherein R^7 is choro and R^9 is $(C_1–C_3)$alkoxy;

184) compounds according to any one of embodiments 171) or 174) wherein R^7 is choro and R^9 is methoxy;

185) compounds according to any one of embodiments 171) or 185) wherein R^9 is hydrogen;

186) compounds according to any one of embodiments 171) or 185) wherein R^9 is $(C_1–C_3)$alkoxy;

187) compounds according to any one of embodiments 171) or 185) wherein R^9 is methoxy;

188) compounds according to any one of embodiments 171) or 187) wherein R^{1-5} are each hydrogen;

Generally, when R^6 is $–S-R^{14}$, then R^{15}-L- is the more preferred R^{14}. When R^{14} or R^{15} is substituted Ar^2, para-substitution is preferred. When L is present, particularly preferred are methylene, and methyl-methylene. Particularly preferred R^{15}-L- is when R^{15} is Ph^2 and L is methylene. Also particularly preferred is when R^{15} is Ph^2 and L is methyl-methylene. Also particularly preferred is when R^{15} is Ar^2 and L is methylene. Also particularly preferred is when R^{15} is Ar^2 and L is methyl-methylene.

Also generally, when R^6 is $-NR^{24}R^{25}$, then Ph^2-(C_1-C_3)-*n*-alkyl is particularly preferred over phenyl(C_1-C_3)-*n*-alkyl.

Preferred compounds of formula (I) are those wherein

R^6 is $–C\equiv C-R^{10}$ and wherein R^{10} is selected from the values defined in any one of embodiments 19) to 28); or

R^6 is $–O-R^{12}$ and wherein R^{12} is selected from the values defined in any one of embodiments 30) to 53); or

R^6 is $-S-R^{14}$ and wherein R^{14} is selected from the values defined in any one of embodiments 55) to 63) or embodiment 64) wherein L is selected from

the values defined in any one of embodiments 65) to 71) and R^{15} is selected from the values defined in any one of embodiments 72) to 111) and 121 to 141), or R^{15}-L- is selected from the values defined in any one of embodiments 112) to 120); or

R^6 is $R^{24}R^{25}N$- and wherein R^{24} is selected from the values defined in any one of embodiments 143) to 161).

Particularly preferred compounds of formula (I) are those wherein R^6 is –O-R^{12} and wherein R^{12} is selected from the values defined in any one of embodiments 37), 38) or 39).

Further preferred compounds of formula (I) are those wherein R^7 is other than hydrogen. In particular, R^7 is preferably selected from the values defined in any one of embodiments 1) to 8). More preferably, R^7 is selected from halo (especially chloro), (C_1-C_3)alkyl optionally substituted with 1 to 6 fluoro substituents (especially methyl, ethyl, *n*-propyl or CF_3), and cyano.

Particularly preferred compounds of formula (I) are those wherein R^7 is halogen, and in particular wherein R^7 is chloro.

Preferred compounds of formula (I) are those wherein R^9 is (C_1-C_3)alkoxy, preferably methoxy, or halo, preferably chloro.

Also preferred are those compounds of formula (I) wherein R^9 is hydrogen.

Particularly preferred compounds of formula (I) are those wherein R^7 is other than hydrogen and R^9 is hydrogen, and most especially wherein R^7 is chloro and R^9 is hydrogen.

Further preferred compounds of formula (I) are those wherein R^1 is hydrogen.

Also preferred are those compounds of formula (I) wherein R^2 is hydrogen.

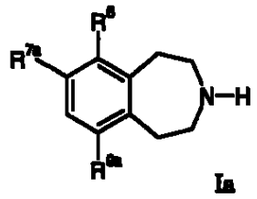
Also preferred are those compounds of formula (I) wherein R^3 is hydrogen or methyl, and especially wherein R^3 is hydrogen.

Another preferred class of compounds of formula (I) is that wherein R^4 is hydrogen, methyl or ethyl, particularly wherein R^4 is hydrogen or methyl, and especially wherein R^4 is hydrogen.

Further preferred are those compounds of formula wherein R^5 is hydrogen.

Also preferred are those compounds of formula (I) wherein R^8 is hydrogen.

One favored group of compounds of the present invention is that represented by formula (Ia), and pharmaceutically acceptable salts thereof:



Ia

wherein

R^{7a} is halogen, and especially chloro;

R^{9a} is hydrogen, halogen or (C_1-C_3)alkoxy, particularly hydrogen, chloro or methoxy, and especially hydrogen; and

R^6 is as defined in relation to formula (I).

Specific preferred compounds of the present invention are those described in the Examples herein, including the free bases and the pharmaceutically acceptable salts thereof.

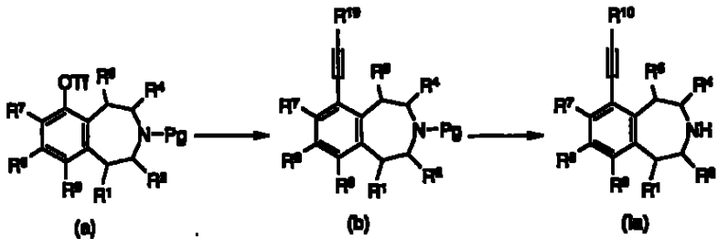
It will be appreciated that the preferred definitions of the various substituents recited herein may be taken alone or in combination and, unless otherwise stated, apply to

the generic formula (I) for compounds of the present invention, as well as to the preferred class of compounds represented by formula (Ia).

The compounds of the invention can be prepared according to the following synthetic schemes by methods well known and appreciated in the art. Suitable reaction conditions for the steps of these schemes are well known in the art and appropriate substitutions of solvents and co-reagents are within the skill of the art. Likewise, it will be appreciated by those skilled in the art that synthetic intermediates may by isolated and/or purified by various well known techniques as needed or desired, and that frequently, it will be possible to use various intermediates directly in subsequent synthetic steps with little or no purification. Furthermore, the skilled artisan will appreciate that in some circumstances, the order in which moieties are introduced is not critical. The particular order of steps required to produce the compounds of Formula I is dependent upon the particular compound being synthesized, the starting compound, and the relative liability of the substituted moieties as is well appreciated by those of ordinary skill in the art. All substituents, unless otherwise indicated, are as previously defined, and all reagents are well known and appreciated in the art.

Compounds of Formula I where R^6 is an acetylene-linked substituent may be prepared as illustrated in Scheme I where Pg is a suitable protecting group for a secondary amine such as, but not limited to, 2,2,2-trifluoroacetyl or *tert*-butoxycarbonyl, and variables R^1, R^2, R^4, R^5, R^7, R^8, R^9 and R^{10} are as previously defined.

Scheme I



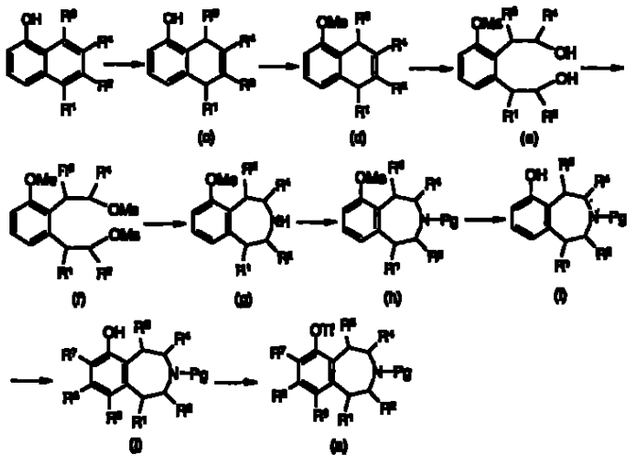
Mix the 6-triflate of the 2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepines (a) with an appropriately substituted acetylene, a suitable palladium/copper catalyst mixture in a

solvent, typically DMF, using triethylamine as base, and heat to afford the desired compound (b). Deprotection reaction and the standard extractive and chromatographic techniques afford the desired compound (Ia).

The appropriate 6-triflate of 2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepines (a) may be prepared as described in Scheme II. Compound (a) may be prepared from 1-naphthol. 1-Naphthol can be converted to 5-hydroxy-1,4-dihydronaphthalene (c) by Birch reduction using ammonia and lithium metal at low temperature. Methylation of the 6-hydroxy group affords the compound (d). Ozonolysis of (d) and subsequent reduction with sodium borohydride provide the diol (e). After converting the two hydroxyl groups into two good leaving groups, for example methanesulfonates, cyclize the compound (f) to the 6-methoxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepines (g) with aqueous ammonia under pressure. Protect the ring nitrogen with a variety of alkyl halides, acid chlorides or anhydrides such as trifluoroacetic anhydride to give compound (h). Subsequently convert the methyl ether (h) to the phenol (i) with BBr_3 in dichloromethane or other methods well known in the literature [see for example, Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley and sons, Chapter III, New York (1999)].

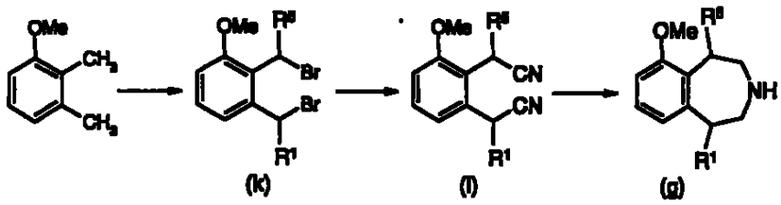
Functionalization of the aromatic ring to introduce substituents R^7, R^8 and R^9 are well known in the art and very depending on the substitution desired. Subsequent trifluoromethanesulfonylation of the 6-hydroxy (j) affords the desired 2,3,4,5-tetrahydro-*1H*-benzo[d]azepines (a).

Scheme II



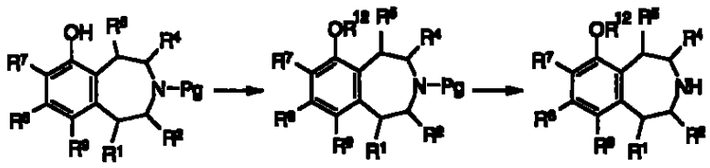
Alternately, compound (g) could be prepared from 1,2-bis(cyanomethyl)-3-methoxybenzene (l), previously described in the literature (*J. Med. Chem.* 1984, 27, 918-921), as shown in Scheme III below.

Scheme III



Compounds of Formula I where R^6 is an oxygen-linked substituent may be prepared as illustrated in Scheme IV where Pg is a suitable protecting group for secondary amine, such as 2,2,2-trifluoroacetyl or tert-butoxycarbonyl, and variables R^7, R^9 and R^{12} are as previously defined.

Scheme IV



(l) (m) (Ib)

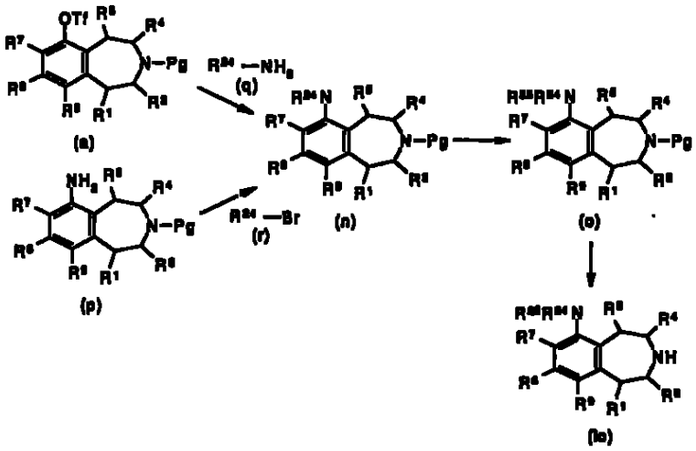
Compound (m) can be prepared by treating 6-hydroxy-2,3,4,5-tetrahydro-*1H*-benzo[d]azepines (j) with an appropriate alkylation reagent, such as an alkyl halide or sulfonate, and a base in a suitable solvent, typically acetone, ethanol or acetonitrile, followed by he standard extractive and chromatographic techniques. Deprotection of the ring nitrogen gives the compound (Ib). Alternately, compound (m) can be obtained by Mitsunobu reaction with an appropriate alcohol, a phosphine reagent such as triphenylphosphine, and diethyl azodicarboxylate (DEAD) or 1,1'-(azodicarbonyl)-dipiperidine in an anhydrous solvent, for example THF.

Compounds of Formula Ic where R^6 is a nitrogen-linked substituent may be prepared as illustrated in the Scheme V. The 6-triflate protected 2,3,4,5-tetrahydro-*1H*-benzo[d]azepines (a) can be converted to the compounds (n), under Buchwald conditions, by treatment with an appropriate amine (q) in the presence of an effective palladium catalyst, and a base in a suitable solvent, typically toluene or 1,4-dioxane under an inert atmosphere. Introduction of a second substituent R^{25}, if needed, may be performed. Standard work-up and chromatographic techniques followed by deprotection, give the compound (Ic).

Alternately 6-amino-2,3,4,5-tetrahydro-*1H*-benzo[d]azepines (p) can be transformed to the desired compounds (n) by reaction with an appropriate bromide (r), and an appropriate base in a suitable solvent.

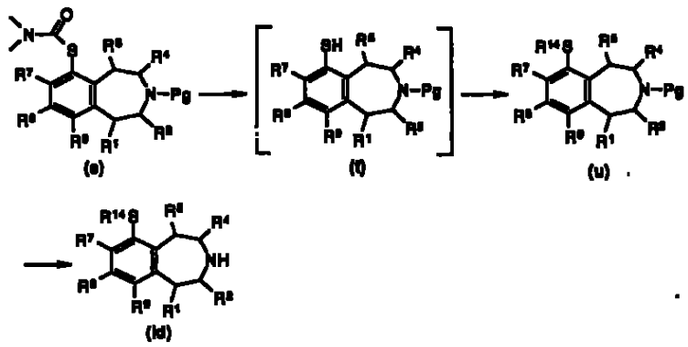
Bromides (r) are either commercially available or may be prepared by methods well known to the skilled artisan. Amines (q) are either commercially available or may be prepared by methods well known to the skilled artisan.

Scheme V



Compounds of Formula I where the R^6 is a sulfur-linked substituent may be prepared as illustrated in the Scheme VI.

Scheme VI



Heat the appropriately substituted 3-(tert-butoxycarbonyl-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[d]azepine (s) with an appropriate base in a suitable solvent, such as methanol, to obtain the intermediate thiol (t). Isolate the intermediate thiol (t), if required, and treat it with an appropriate electrophile (halide or alkyl sulfonate). Isolate the compound (u) by standard extractive and chromatographic techniques and deprotect to afford the desired compound (Id).

The requisite halides or alkyl sulfonates are either commercially available or may be prepared by methods well known to the skilled artisan.

The skilled artisan will also appreciate that not all of the substituents in the compounds of Formula I will tolerate certain reaction conditions employed to synthesize the compounds. These moieties may be introduced at a convenient point in the synthesis, or may be protected and then deprotected as necessary or desired, as is well known in the art. The skilled artisan will appreciate that the protecting groups may be removed at any convenient point in the synthesis of the compounds of the present invention. Methods for introducing and removing protecting groups used in this invention are well known in the art; see, for example, Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley and sons, New York (1999).

The following Preparations and Examples are illustrative of methods useful for the synthesis of the compounds of the present invention. Exemplified compounds are also particularly preferred compounds of the present invention.

General Procedure 1-1

Dissolve the appropriately substituted 3-(2,2,2- trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine in ammonia/methanol solution (1.0–7.0 M). Stir for 1-16 h at ambient temperature unless otherwise specified. Remove the volatiles *in vacuo*. Purify by chromatography on silica gel eluting with 1-20% 2M ammonia/methanol in DCM, or by SCX chromatography eluting with 1.0-7.0 M ammonia in methanol.

General Procedure 1-2

Dissolve the appropriately substituted 3-(2,2,2- trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.0 equiv.) in methanol. Add a 0.5 M aqueous solution of potassium carbonate (4.0 equiv.) and stir at ambient temperature for 6 h. Concentrate *in vacuo* and partition the residue between water and DCM. Extract the aqueous phase twice with DCM. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo*. If needed, purify by chromatography on silica gel eluting with 1-20% 2M ammonia/methanol in DCM, or by SCX chromatography eluting with 1.0-7.0 M ammonia in methanol.

General Procedure 1-3

Dissolve the appropriately substituted 3-(2,2,2- trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.0 equiv.) in methanol or ethanol (0.1 to 2M solution) and add from 10-50% by volume of a 1.0-5.0 N aqueous solution of sodium hydroxide or lithium hydroxide. Stir the reaction mixture at ambient temperature for 0.25-16 h and concentrate *in vacuo*. Partition the residue between EtOAc or DCM and water. Separate and dry the organic fraction over Na_2SO_4, filter, and concentrate *in vacuo*. Purify by SCX chromatography, followed by chromatography on silica gel eluting with 1-20% 2M ammonia/methanol in DCM or reverse phase HPLC.

General Procedure 1-4

Dissolve the appropriately substituted 3-*tert*-butoxycarbonyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine in 4M hydrogen chloride in dioxane or 1M hydrogen chloride in ethyl ether and stir the mixture for 2-16 h at ambient temperature unless otherwise specified. Remove the solvent *in vacuo*. If a solid is obtained, wash the solid with ether and filter under vacuum to afford the desired hydrochloride salt. If an oil is obtained, dissolve the oil in the minimal volume of DCM, methanol or EtOAc and add ether to precipitate out the solid. Remove the solvent *in vacuo*, wash the solid with ether and filter. Dry the solid *in vacuo* or under a stream of nitrogen.

General Procedure 1-5

Dissolve the appropriately substituted 3-*tert*-butoxycarbonyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine in a mixture of trifluoroacetic acid/DCM (from 1:0 to 1:10 ratio) and stir the reaction for 1-16 h at ambient temperature. Concentrate *in vacuo* and either subject the residue to SCX chromatography or partition the residue between saturated aqueous $NaHCO_3$ and DCM or EtOAc. Dry the organic layer over Na_2SO_4 and concentrate *in vacuo*. Purify by either chromatography on silica gel (eluting with 1-20% 2M ammonia/methanol in DCM) or reverse phase HPLC.

General Procedure 1-6

Add acetyl chloride (40 equiv.) to cold methanol (0 °C) and stir for 5 min. Then add a solution of the appropriately substituted 7-chloro-3-(*tert*-butoxycarbonyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1 equiv.) in methanol. Stir the reaction at ambient temperature for 12 h. Remove the solvent *in vacuo*, basify with saturated aqueous $NaHCO_3$ and extract three times with DCM. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel, eluting with 1-20% 2M ammonia/methanol in DCM.

General Procedure 2-1

Dissolve the purified free base (1 equiv.) in acetone, ether or methanol and add a solution of succinic acid (1 equiv.) in a minimal volume of acetone or methanol. Stir for 1 h at ambient temperature. Concentrate to an oil, add a minimal volume of DCM and

ethyl ether to precipitate out the salt. Alternatively, to precipitate out the salt, allow the reaction mixture to stand 1-16 h at ambient temperature, 4 °C or –10 °C and add ether or hexane. Filter and wash the solid with ether or hexane to obtain the succinate salt. Alternatively, evaporate the solvent *in vacuo*, wash the solid with ether and filter or decant the solvent to obtain the succinate as a solid. Dry the solid *in vacuo* or under a stream of nitrogen.

General Procedure 2-2

Dissolve the purified free base (1 equiv.) in a minimal volume of acetone, dioxane, methanol or DCM and add an excess of 4M hydrogen chloride in dioxane or a 1M solution of hydrogen chloride in ethyl ether. Stir for 1 h and evaporate the solvent to obtain the salt as a solid. Alternatively, allow the reaction mixture to stand 1 to 16 h at ambient temperature and add ether or hexane to precipitate out the salt. Filter and wash the solid with ether or hexane to obtain the salt as a solid. Alternatively, evaporate the solvent *in vacuo*, wash the solid with ether, filter or decant the solvent to obtain the hydrochloride salt as a solid. Dry the solid *in vacuo* or under a stream of nitrogen.

General Procedure 2-3

Dissolve the purified free base in methanol, add a solution of ammonium chloride (1 equiv.) in methanol and stir for 1 h. Slowly remove the volatiles *in vacuo*. Dissolve the residue in methanol and remove most of the solvent *in vacuo*. Add anhydrous ethyl ether or EtOAc to precipitate out the hydrochloride salt. Collect the solid, wash the solid with ether and then dry the solid *in vacuo* or under a stream of nitrogen.

General Procedure 2-4

Dissolve the purified free base (1.0 equiv.) in methanol. Add a 0.5 M solution of methanesulfonic acid in methanol (2.0 equiv). Mix well, stir for 1 h, then remove the solvent *in vacuo*. Dissolve the residue into a minimal volume of DCM. Add ethyl ether to precipitate out the solid. Remove the solvent *in vacuo* to form a foam. Dry *in vacuo* or under a stream of nitrogen to obtain the methanosulfonic acid salt.

General Procedure 2-5

Dissolve the purified free base (1 equiv.) in a minimal volume of acetone and add a solution of oxalic acid (1 equiv.) in a minimal volume of acetone. Allow the mixture to stand 10 min to 16 h at ambient temperature to -10°C, and/or add ether or hexane to precipitate out the solid. Filter and wash the solid with ether or hexane to obtain the oxalic acid salt as a solid. Dry the solid *in vacuo* or under a stream of nitrogen.

General Procedure 2-6

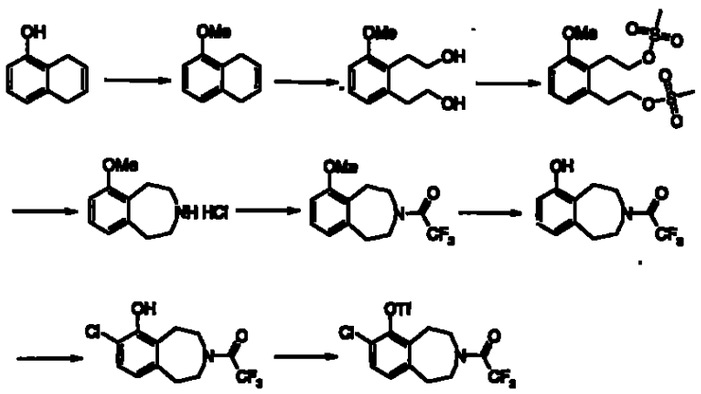
Dissolve the purified free base (1 equiv.) in a minimal volume of cyclohexane, isohexane, chloroform, dichloromethane, methanol or a mixture thereof and add a solution of (*L*)-tartaric acid in isopropanol or methanol. If a solid precipitate out, filter and wash the solid with ether, cyclohexane, isohexane or EtOAc. If no solid formation is observed, remove all the volatiles *in vacuo* to form a foam. Dry *in vacuo* or under a stream of nitrogen to obtain the tartaric acid salt.

General Procedure 3

Dissolve the appropriately substituted 3-*tert*-butoxycarbonyl-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine or 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1 equiv.), $PdCl_2(PPh_3)_2$ (0.1 equiv.), tetrabutyl ammonium iodide (3 equiv.), and copper(I) iodide (0.3 equiv.) in triethylamine/DMF (1:5). Stir the mixture for 5 min at ambient temperature, add the appropriately substituted acetylene (2 equiv.) and heat at 70 °C for 2-16 h in a sealed tube. Cool the reaction mixture to ambient temperature, dilute with EtOAc/hexane (1:1) and wash with water. Dry the organic fraction over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc mixtures.

Preparation 1

7-Chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine



5-Methoxy-1,4-dihydronaphthalene: Add powdered potassium carbonate (193.1 g, 1.397 mol) to a solution of 5-hydroxy-1,4-dihydronaphthalene [68.08 g, 90% potency based on ^{1}H-NMR, 0.4657 mol, from Societa Italiana Medicinale Scandicci, s.r.l., Reggello (Firenze), Italy] in ethanol (700 mL). Cool the solution to 0°C with ice/water and add dimethyl sulfate (88.1 g, 66.1 mL, 0.699 mol) dropwise, maintaining the temperature between 5°C and 10°C. Then heat the reaction mixture to 40°C until the TLC (10:1 hexane/EtOAc) shows the absence of starting material (about 2 h). Filter off the solids by vacuum filtration and remove the solvent *in vacuo*. Dilute the residual brown oil with diethyl ether (500 mL), wash with 10% aqueous NH_4OH (500 mL), water (500 mL), brine (500 mL), dry the organic layer over Na_2SO_4, filter and concentrate *in vacuo* to give the crude product as a brown oil (73 g). Purify the crude product by short path distillation under vacuum (bp 120-130°C/ 5 Torr) to give the desired intermediate as a clear oil (69.0 g, 92.5% potency corrected) (contains some 1,2,3,4-tetrahydro-5-methoxynaphthalene as an impurity). ^{1}H NMR (300 MHz, $CDCl_3$), δ7.15 (t, 1H, J = 7.9), 6.72 (dd, 2H, J = 15.7, 7.9), 5.93-5.88 (m, 2H), 3.83 (s, 3H), 3.42-3.39 (m, 2H), 3.30-3.28 (m, 2 H); R_f = 0.58 eluting with 10:1 hexane/EtOAc.

2,3-Bis-(2-hydroxyethyl)-1-methoxybenzene: Charge a four-neck 5 L flask equipped with an over-head mechanical stirrer, reflux condenser, thermocouple, and gas dispersion apparatus with 5-methoxy-1,4-dihydronaphthalene (264.54 g, 89.5% potency based on ^{1}H-NMR, 1.478 mol) in DCM (1.3 L) and 2B-3 ethanol (1 L). Add sudan III (10 mg) to give a faint red color. Cool the solution to -65°C or lower, then pass O_3 through the

solution until the solution turns a light yellow color and the TLC (10:1 hexane/EtOAc, $KMnO_4$ stain) shows the absence of the starting material (about 30 h). Transfer the solution via cannula into a slurry of $NaBH_4$ (97.8 g, 2.59 mol) in 2B-3 ethanol (500 mL) cooled in ice/water. It is important that the temperature be maintained at or above 0°C, as for example between 0°C and 10°C, throughout the transfer to ensure the ozonide is completely reduced to the diol. After the transfer is complete, warm the solution to ambient temperature and stir for about 30 min. Cool the slurry to 0°C with ice/water then slowly add acetone (540 mL, 7.4 mol) to remove excess $NaBH_4$. After all the solids dissolve, remove the solvent *in vacuo*. Dissolve the yellow solid in DCM (1 L) and water (1 L), separate the layers and extract the aqueous layer with DCM (750 mL). Wash the combined organic layers with brine (1.5 L), add toluene (750 mL) and remove the solvent *in vacuo*. Dissolve the solid in DCM (500 mL) with heating, then add toluene (750 mL) and concentrate the solution *in vacuo* to give the desired intermediate as a light yellow solid (283.7 g, 89% potency corrected, mp 82-83°C) (contains 1,2,3,4-tetrahydro-5-methoxynaphthalene as an impurity (8.6%)). Further purify the product by vacuum drying overnight at 75°C, 5 Torr, to remove all but trace amount of the 1,2,3,4-tetrahydro-5-methoxynaphthalene impurity. ^1H NMR (300 MHz, $CDCl_3$), δ 7.16 (dd, 1H, J = 8.2, 7.6), 6.83 (s, 1H, J = 7.0), 6.76 (s, 1H, J = 8.2), 3.85-3.77 (m, 7H), 3.01-2.91 (m, 4H), 2.35 (s, 2H); ^{13}C NMR (300 MHz, DMSO-d_6), δ 157.5, 138.9, 126.5, 125.2, 122.0, 108.4, 62.1, 60.5, 55.3, 36.1, 29.6; IR (KBr): 3006, 2960, 2886, 2829, 1583, 1461, 1440, 1264, 1091, 1041 cm^{-1}; MS (ES+) *m/z* 178 $(M+H)^+$; Anal. Calc'd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22; N, 0. Found: C, 67.26, H, 8.10, N, 0.21; R_f = 0.23 eluting with 95:5 DCM/methanol.

2,3-Bis-(2-methanesulfonyloxyethyl)-1-methoxybenzene: To a slurry of 2,3-bis-(2-hydroxyethyl)-1-methoxybenzene (50.6 g, 0.258 mol, 1 equiv.) and triethylamine (78.3 g, 0.774 mol, 3 equiv.) in DCM (500 mL) at 0°C, add dropwise a solution of methanesulfonyl chloride (65.0 g, 0.567 mol, 2.2 equiv.) in DCM (100 mL) over 45 min. The addition is exothermic and the methanesulfonyl chloride is added at a rate to keep the temperature below 10°C. After the addition is complete, warm the reaction to ambient temperature. Wash the solution with water (2 x 500 mL), and then brine (750 mL). Dry

the organic layer over Na_2SO_4, filter and concentrate *in vacuo* to obtain the desired intermediate as a dark yellow oil (87.4 g, 96.2%), which is used in the next reaction without further purification. An analytical sample is obtained by flash column chromatography eluting with 100% diethyl ether. ^{1}H NMR (300 MHz, $CDCl_3$), δ 7.20 (t, 1H, J = 7.9), 6.82 (s, 1H, J = 7.2), 6.80 (s, 1H, J = 8.2), 4.41-4.34 (m, 4H), 3.83 (s, 3H), 3.16-3.09 (m, 4H), 2.91 (s, 3H), 2.87 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$), δ 158.07, 136.55, 128.26, 123.34, 122.39, 109.24, 69.88, 69.08, 55.55, 37.35, 37.14, 32.57, 26.47; ^{13}C NMR (300 MHz, DMSO-d_6), δ 157.58, 136.79, 127.81, 122.91, 122.00, 109.33, 70.19, 68.88, 55.55, 36.49, 36.47, 31.56, 25.72; IR (KBr): 1586.8, 1469.4, 1358.51, 1267.3, 1173.9, 1105.4, 972.4, 954.6, 914.3 cm^{-1}; MS (ES+) *m/z* 257 $(M+H)^+$; Anal. Calc'd. for $C_{13}H_{20}O_7S_2$: C, 44.31; H, 5.72; N, 0. Found: C, 44.22, H, 5.68, N, 0.13; R_f= 0.72 eluting with 95:5 DCM/methanol.

6-Methoxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Dissolve 2,3-bis-(2-methanesulfonyloxyethyl)-1-methoxybenzene (474.4 g, 1.346 mol) in acetonitrile (7 L) and split the mixture into two equal lots. In two separate runs, add concentrated aqueous NH_4OH (3.5 L) and charge the solution to a pressure vessel (PARR apparatus). Heat the solution in a closed reactor to 100°C over 20 min (internal pressure reaches about 100 psi), and maintain at 100°C until the reaction is complete (about 1 h, HPLC monitored). Cool the reaction mixture to ambient temperature. Combine the two lots and remove the solvent *in vacuo*. Dissolve the residue in MTBE (3.5 L) and water (3.5 L). Adjust the pH to 6.5 using 2M aqueous NaOH or 1M aqueous HCl as appropriate (typically the pH is about pH=5.1 and the adjustment requires about 50 mL 2M aqueous NaOH). Discard the organic layer, adjust the aqueous layer to pH=13 using 50% NaOH (about 150 mL). Extract with MTBE (2 x 3.5 L), wash the combined organic layers with brine (3.5 L), dry over Na_2SO_4, filter and concentrate *in vacuo* to give the title compound as a crude yellow oil that solidifies upon standing (179.3 g). Use the material for the next step without further purification. Prepare an analytical sample by purification by two Kugelrohr distillations to give a clear oil that solidifies upon standing, mp 44.3-45.0°C. ^{13}C NMR (300 MHz, DMSO-d_6) □ 156.1, 144.4, 130.3, 126.2, 121.5, 108.9, 55.5, 48.2, 47.9, 39.9,

29.1; MS (ES+) *m/z* 163 $(M+H)^+$; Anal. Calc'd for $C_{11}H_{13}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.28, H, 8.62, N, 7.86.

6-Methoxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride: Dissolve crude 6-methoxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (35.1 g, 0.198 mol) in 2B-3 ethanol (250 mL), heat the solution to reflux and add 2M HCl in ethanol (108.9 mL, 0.218 mol, 1.1 equiv.). Slowly add heptane (700 mL) over 10 min, then remove the heating mantle and cool the solution to ambient temperature, and finally continue the cooling with an ice/water mixture. Collect the resulting solid by vacuum filtration and wash with cold ethanol:heptane (1:2) (3 x 100 mL), air-dry for 15 min under vacuum, then further dry the product in a vacuum oven at 60°C for 1 h to give the desired intermediate as a white granular solid (35.53 g, 63%): mp 246.6-246.9°C; ^{1}H NMR (300 MHz, DMSO-d_6), δ 9.82 (broad s, 1H), 7.12 (dd, 1H, J = 7.6, 7.9), 6.88 (d, 1H J = 8.2), 6.78 (d, 1H, J = 7.3), 3.75 (s, 3H), 3.20-3.00 (m, 8H); ^{13}C NMR (300 MHz, DMSO-d_6), δ 156.2, 141.3, 127.4, 127.2, 121.6, 109.7, 55.7, 44.9, 44.7, 31.6, 21.7; MS (ES+) *m/z* 178 $(M+H)^+$; Anal. Calc'd for $C_{11}H_{13}ClNO$: C, 62.12; H, 7.11; N, 6.59. Found: C, 61.95, H, 7.64, N, 6.58.

6-Methoxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: To a slurry of 6-methoxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine hydrochloride (35.3 g, 0.165 mol, 1 equiv.) and triethylamine (69.1 mL, 0.496 mol, 3 equiv.) in DCM (300 mL) cooled at 0°C with ice/water, add dropwise a solution of trifluoroacetic anhydride (25.7 mL, 0.182 mol, 1.1 equiv.) in DCM (40 mL) over 30 min, but at a rate that maintains the temperature below 10°C. After the addition is complete, warm the reaction mixture to ambient temperature and stir until the reaction is complete (verify by TLC using 9:1 CH_2Cl_2:methanol, about 2 h.). Wash the solution with water (2 x 350 mL), and then brine (350 mL), dry the organic layer over Na_2SO_4, filter and concentrate *in vacuo* to give desired intermediate as a yellow oil that solidifies upon standing (44.9 g, 96%). Use the material without further purification in the next step. Prepare an analytical sample by chromatography on silica gel eluting with 40% diethyl ether in hexane, mp 74-76°C. ^{1}H NMR (300 MHz, $CDCl_3$), δ 7.16-7.11 (m, 1H), 6.81-6.74 (m, 2H), 3.81 (s, 3H), 3.79-3.64 (m, 4H), 3.11-3.07 (m, 2H), 2.99-2.95 (m, 2H); ^{1}H NMR (300 MHz, DMSO-d_6), δ 7.13

(dd, 1H, J = 1.5, 7.0), 7.08 (d, 1H, J = 1.5), 6.88-6.74 (m, 1H), 3.75 (s, 3H), 3.67-3.61 (m, 4H), 3.04-2.92 (m, 4H); ^{13}C NMR (300 MHz, DMSO-d_6), δ 156.43. 156.38, 155.06, 155.00, 154.60, 154.54, 154.14, 154.08, 141.31, 141.04, 127.44, 127.18, 127.05, 127.01, 122.27, 121.94, 121.90, 118.46, 114.64, 110.80, 109.52, 109.41, 55.63, 55.61, 47.11, 47.07, 46.67, 46.63, 45.61, 45.16, 35.90, 34.65, 26.18, 24.91; Anal. Calc'd for $C_{13}H_{14}F_3NO_2$: C, 57.14; H, 5.16; N, 5.13. Found: C, 57.17, H, 5.27, N, 5.08.

6-Hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: To a 1M solution of BBr_3 (1.1 L, 1.6 equiv.), cooled at 0°C with an ice-water bath, add 6-methoxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (187 g, 0.684 mol) in DCM (200 mL) over 1 h., while maintaining the temperature between 0°C and 10°C. Warm the reaction mixture to ambient temperature and stir until HPLC indicates completion of the reaction (about 2 h.). Cool the solution to 0°C and transfer it via cannula into an ice/water solution (1.2 L), thereby precipitating the product as a white solid. Add EtOAc (2 L) to dissolve most of the precipitate, separate the layers and concentrate the organic layer *in vacuo*. Extract the aqueous layer three times with EtOAc (2 x 2 L, 1 x 1 L). Wash the combined organic layers with water (2 L), and then brine (2 L), dry over Na_2SO_4, filter and concentrate *in vacuo* to give the desired intermediate as a light yellow solid (166.3 g, 94%). Use the product for the next step without further purification. Prepare an analytical sample by chromatography on silica gel eluting with 40% diethyl ether in hexane: mp 183.0-185.2°C. ^{1}H NMR (300 MHz, DMSO-d_6), δ 9.39 (s, 1H), 6.94-6.88 (m, 1H), 6.72-6.68 (m, 1H), 6.61-6.57 (m, 1H), 3.67-3.32 (m, 4H), 2.99-2.86 (m, 4H); ^{13}C NMR (300 MHz, DMSO-d_6), δ 154.50, 141.47, 141.18, 126.77, 126.64, 125.77, 125.33, 120.38, 120.32, 118.49, 114.67, 113.64, 113.47, 47.31, 47.27, 47.00, 46.96, 45.83, 45.49, 36.17, 34.93, 26.46, 25.18, 20.66, 14.00; MS (ES+) *m/z* 260 $(M+H)^+$; Anal. Calc'd. for $C_{12}H_{12}F_3NO_2$: C, 55.60; H, 4.67; N, 5.40. Found: C, 55.51, H, 4.71, N, 5.29.

7-Chloro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Heat a mixture of 6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (120 g, 0.4629 mol) and toluene (14.4 L) to 70°C for 45 min until most

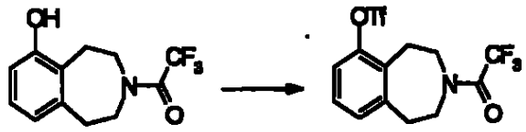
of the starting material is dissolved. Add diisobutylamine (1.197 g, 1.62 mL, 9.26 mmol) followed by addition of sulfuryl chloride (62.48 g, 37.19 mL, 0.463 mol) in toluene (360 mL) over 20 min. Stir the reaction mixture for 50 min and then add additional sulfuryl chloride (4.536 g, 2.70 mL, 0.0336 mol) neat and stir the reaction mixture for 15 min at 70°C. Cool the reaction mixture to 24°C over 30 min and then add 1N hydrochloric acid (2.00 L). Separate, wash the organic layer with saturated aqueous $NaHCO_3$ (2.00 L), brine (2.00 L) and then dry over Na2SO4. Filter and remove the solvent with a rotary evaporator at 70°C until about 672.5 g remains using the minimum effective vacuum in order to maintain a vapor phase sufficient to prevent drying above the solvent line and self-seeding, thus preventing crystallization under these conditions. Using toluene heated to 70°C, transfer the light-yellow solution to a preheated (70°C) 3-neck flask equipped with a mechanical stirrer. Lower the temperature to 58°C over 1 h. If available, seed the solution with crystals of 7-chloro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine from a prior synthesis to enhance crystallization. After 30 min, reduce the temperature further to 55°C and observe the initiation of the crystallization process. Hold the temperature at 55°C for 2 h. followed by 4 h. at 45°C, then turn off the heat allowing the mixture to slowly reach 24°C (ambient temperature). After stirring for 8 h. with the heat off, cool the mixture to 0°C for 2 h. followed by 2 h. at -10°C. Collect the resulting dense, white, granular crystals by vacuum filtration at -10°C. Rinse the crystals twice with cold (-10°C) toluene and vacuum dry at 50°C, 5 Torr, for 12 h., to obtain the desired intermediate as a white solid (120.7 g, 99.5% purity, 88.8%): mp 133-134°C. MS (ES+) *m/z* 294 $(M+H)^+$. Anal. Calc'd for $C_{12}H_{11}ClF_3NO_2$: C, 49.08; H, 3.78; N, 4.77; Cl, 12.07. Found: C, 49.01; H, 3.63; N, 4.72; Cl, 12.32.

7-Chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Cool a solution of 7-chloro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (60 g, 0.204 mol), triethylamine (62.6 mL, 0.448 mol, 2.2 equiv.), and DCM (590 mL) in an ice bath and add dropwise trifluoromethanesulfonic anhydride (43.5 mL, 0.258 mol, 1.26 equiv.) over 70 min. Remove the ice bath and stir the reaction mixture for 2 h. Wash the reaction mixture sequentially with water (500 mL), 1N aqueous HCl (500 mL), water (500 mL), and brine (500 mL). Dry the organic layer over Na_2SO_4 and concentrate *in vacuo* to give the crude

product as a brown solid (90 g). Dissolve the solid in warm toluene (200 mL). Further purify by plug filtration chromatography over silica gel (500 g) eluting sequentially with hexane (1 L), hexane/EtOAc (9:1, 1L), hexane/EtOAc (4:1, 1L), and hexane/EtOAc (7:3, 9L). Pool the eluents and evaporate the solvent to obtain the product as a yellow tan solid (86.3 g). Dissolve the solid in warm EtOAc (86 mL) and then add hexane (700 mL). If available, seed the solution with crystals of 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine from a prior synthesis to enhance crystallization. Allow the mixture to stand at ambient temperature for 30 min. Cool the mixture at about -10°C for 2 h., filter, rinse the crystals with cold (-10°C) hexane/EtOAc, and air-dry on the filter under vacuum to obtain the title compound as a first crop of crystals (73.54 g). Concentrate the mother liquor to obtain a solid (12.7 g). Recrystallize the solid in a mixture of EtOAc/hexane (15 mL:121 mL) to obtain additional title compound (7.65 g, total yield: 81.19 g, 93%).

Preparation 2

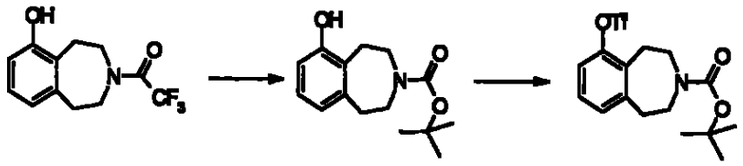
3-(2,2,2-Trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine



Cool a solution of 6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (2 g, 7.72 mmol), triethylamine (1.4 mL, 10.1 mmol) and DCM (50 mL) in a cryogenic bath set at –30 °C and add dropwise trifluoromethanesulfonic anhydride (1.7 mL, 10.1 mmol) over 20 min. Stir at –30°C for 2 h and then warm to ambient temperature overnight. Wash the reaction mixture sequentially with water (100 mL), 1N aqueous HCl (100 mL), water (200 mL), and brine (200 mL). Dry the organic layer over Na_2SO_4 and concentrate *in vacuo* to give the title compound as a colorless to light yellow oil (2.7 g, 89%) that was used without purification. Obtain an analytical sample by chromatography on silica gel eluting with hexane/EtOAc (9:1) to give the title compound as an off-white waxy solid. GC-MS *m/z*: 391 (M^+).

Preparation 3

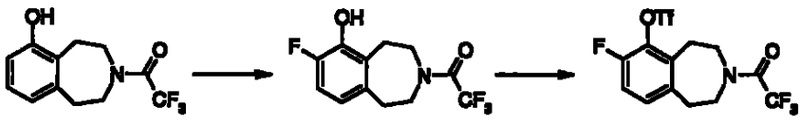
3-*tert*-Butoxycarbonyl-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine



Dissolve 6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (5 g, 19.3 mmol) in 7N ammonia in methanol (50 mL) and stir at ambient temperature for 16 h. Concentrate the reaction mixture to an oil and use without further purification. Dissolve the residue in a solvent mixture consisting of methanol (20 mL), DCM (10 mL) and water (100 mL), and add potassium carbonate (5 g) and di-*tert*-butyl-dicarbonate (5.05 g, 23.2 mmol). Stir the reaction mixture at ambient temperature for 16 h and concentrate *in vacuo*. Extract the aqueous phase with DCM, dry over Na_2SO_4, filter and concentrate. Use the residue without further purification. Dissolve the material in a mixture of DCM (300 mL) and pyridine (30 mL) and cool in an ice bath. Add dropwise to the stirred solution trifluoromethanesulfonic anhydride (5.84 mL, 34.7 mmol) and stir the reaction mixture for 2 h at ambient temperature. Dilute the reaction mixture with DCM (400 mL) and wash with 2.5N aqueous HCl. Dry the organic fraction over Na_2SO_4, filter and concentrate to give the title compound as a yellow solid (6.1 g, 80%). MS (ES+) *m/z*: 396 $(M+H)^+$.

Preparation 4

7-Fluoro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine

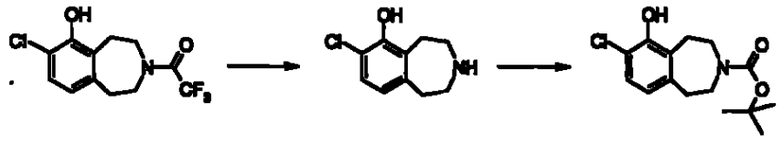


Add *N*-fluoro-4,6-bis(trifluoromethyl)-pyridinium 2-sulfonate (3.02 g, 9.6 mmol) to a stirred mixture of 6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (2.5 g, 9.6 mmol) and hexafluoro-2-propanol (10 mL) in DCM (150

mL). Stir at ambient temperature for 16 h. Concentrate the reaction mixture and partition the residue between EtOAc and 1N aqueous HCl. Wash the organic fraction with saturated aqueous $NaHCO_3$, brine, dry over Na_2SO_4, filter and concentrate. Purify by chromatography on silica gel eluting with hexane/EtOAc (20:1, 10:1, 6:1, 5:1 and 3:1) to give 7-fluoro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a white solid (1.8 g, 68%). Dissolve 7-fluoro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.5 g, 5.41 mmol) in a mixture of DCM (20 mL) and pyridine (2 mL) and cool in an ice bath. Add dropwise to the stirred solution a mixture of trifluoromethanesulfonic anhydride (1.64 mL, 9.74 mmol) in DCM and stir the reaction for 1.5 h at ambient temperature. Dilute the reaction with DCM (300 mL) and wash with 2.5N aqueous HCl. Dry the organic fraction over Na_2SO_4, filter and concentrate to give the title product as a white solid (2.2 g, 99%). MS (ES+) *m/z*: 410 $(M+H)^+$.

Preparation 5

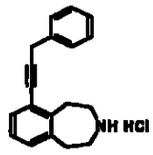
3-*tert*-Butoxycarbonyl-7-chloro-6-hydroxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine



Dissolve 7-chloro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (3 g, 10.2 mmol) in 7 N ammonia in methanol (50 mL) and stir at ambient temperature for 16 h. Concentrate the reaction mixture to an oil and use without further purification. Dissolve the residue in a solvent mixture consisting of DCM (25 mL) and saturated aqueous potassium carbonate solution (25 mL) and add di-*tert*-butyl-dicarbonate (2.2 g, 10.2 mmol). Stir the reaction mixture at ambient temperature for 4 h, concentrate *in vacuo* and extract the aqueous residue with DCM. Dry the organic fraction over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with EtOAc/hexane (1:5) to give the title compound as a white solid (2.3 g, 76%). MS (ES-) *m/z*: 296 $(M-H)^-$.

Example 1

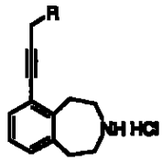
6-(3-Phenyl-prop-1-ynyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the General Procedure 3 to couple 3-*tert*-butoxycarbonyl-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.6 g, 1.5 mmol) with 3-phenyl-1-propyne (0.38 mL, 3 mmol). Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 40:1 and 20:1) to give 3-*tert*-butoxycarbonyl-6-(3-phenyl-prop-1-ynyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an orange oil (400 mg, 74%).

Use a method similar to the General Procedure 1-5 to deprotect 3-*tert*-butoxycarbonyl-6-(3-phenyl-prop-1-ynyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (68 mg, 0.19 mmol). Purify by chromatography on silica gel eluting with DCM/2*M* ammonia in methanol (1:0, 20:1 and 10:1) to obtain the free base of the title compound. Use a method similar to the General Procedure 2-2 to give the title compound as a tan solid (48 mg, 85%). MS (ES+) *m/z*: 262 $(M+H)^+$.

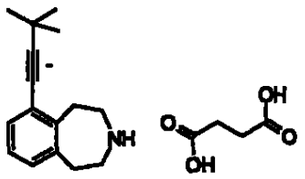
Examples 2–4 may be prepared essentially as described in Example 1 by using 3-*tert*-butoxycarbonyl-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate alkyne. Overall yields and MS (ES+) data are shown in the Table below.



Ex.	R	Compound	Yield (%)	MS (ES+) *m/z*
2	Benzyl	6-(4-Phenyl-but-1-ynyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	60	276 $(M+H)^+$
3	Cyclopentyl	6-(3-Cyclopentyl-prop-1-ynyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	73	254 $(M+H)^+$
4	Cyclohexyl	6-(3-Cyclohexyl-prop-1-ynyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	79	268 $(M+H)^+$

Example 5

6-(3,3-Dimethyl-but-1-ynyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

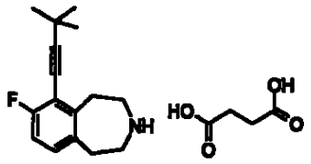


Use a method similar to the General Procedure 3 to couple 3-*tert*-butoxycarbonyl-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.5 g, 1.3 mmol) with 3,3-dimethyl-1-butyne (0.311 mL, 2.5 mmol). Purify by chromatography on silica gel eluting with hexane/EtOAc (10:1) to give 3-*tert*-butoxycarbonyl-6-(3,3-dimethyl-but-1-ynyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow oil (304 mg, 74%).

Use a method similar to the General Procedure 1-5 to deprotect 3-*tert*-butoxycarbonyl-6-(3,3-dimethyl-but-1-ynyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (1:0, 50:1, 20:1, 15:1 and 10:1) to obtain the free base of the title compound. Use a method similar to the General Procedure 2-1 to give the title compound as a tan solid (171 mg, 53%). MS (ES+) *m/z*: 228 $(M+H)^+$.

Example 6

6-(3,3-Dimethyl-but-1-ynyl)-7-fluoro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Use a method similar to the General Procedure 3 to couple 7-fluoro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1 g, 2.4 mmol) with 3,3-dimethyl-1-butyne (0.599 mL, 4.9 mmol). Purify by chromatography on silica gel eluting with hexane/EtOAc (10:1) to give 6-(3,3-dimethyl-but-1-ynyl)-7-fluoro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow oil (700 mg, 84%).

Use a method similar to the General Procedure 1-3 to deprotect 6-(3,3-dimethyl-but-1-ynyl)-7-fluoro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Purify by SCX chromatography followed by chromatography on silica gel eluting with DCM/2M ammonia in methanol (1:0, 50:1, 20:1, 15:1 and 10:1) to obtain the free base of the title compound. Use a method similar to the General Procedure 2-1 to give the title compound as a white solid (589 mg, 83%). MS (ES+) *m/z*: 246 $(M+H)^+$.

General Procedure 4-1

Add 7-chloro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1 equiv.), the appropriate alkylating agent (1.2 equiv.), ground K_2CO_3 (3 equiv.) and KI (0.1 equiv.) to a proper solvent (acetone, ethanol or acetonitrile) and heat to reflux for 6 to 16 h unless otherwise specified. Cool the reaction mixture to ambient temperature, quench with 1N aqueous HCl and extract the aqueous layer three times with EtOAc. Combine the organic fractions, wash with saturated aqueous $NaHCO_3$, brine, dry over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc mixtures.

General Procedure 4-2

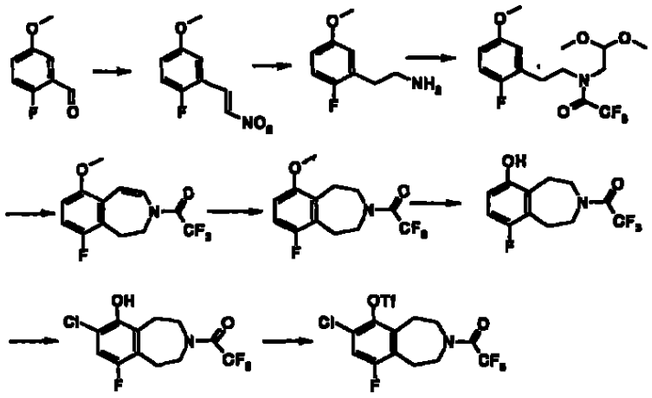
Add 7-chloro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1 equiv.), the appropriate alcohol (1.1 equiv.), triphenylphosphine (1.2 equiv.) and diethyl azodicarboxylate (1.1 equiv.) sequentially to anhydrous THF. Stir the mixture at ambient temperature under nitrogen. Re-add triphenylphosphine (1.2 equiv.) and diethyl azodicarboxylate (1.1 equiv.) if the reaction is not completed (monitored by TLC). Dilute the mixture with EtOAc, wash with saturated aqueous $NaHCO_3$, brine, dry over Na_2SO_4 and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc mixtures.

General Procedure 4-3

Add 7-chloro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1 equiv.), the appropriate alcohol (1.2-1.5 equiv.) and triphenylphosphine (1.5 equiv.) sequentially to anhydrous THF. Stir the mixture at 0°C under nitrogen for 10 min. Add 1,1'-(azodicarbonyl)dipiperidine (1.5 equiv.) and let the mixture warm to ambient temperature over 16 h. Dilute with ether, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc mixtures.

Preparation 6

7-Chloro-9-fluoro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine



1-Fluoro-4-methoxy-2-(2-nitro-vinyl)-benzene: Heat 2-fluoro-5-methoxybenzaldehyde (15 g, 97.4 mmol) with nitromethane (32 mL, 584 mmol) and ammonium acetate (30 g, 390 mmol) in acetic acid (136 mL) under reflux for 30 min. Evaporate the solvent and dissolve the residue in ether. Wash the organic fraction with water, saturated aqueous $NaHCO_3$ and evaporate to give the desired intermediate (18.7 g, 97%). GC-MS *m/z*: 197 $(M)^+$.

2-(2-Fluoro-5-methoxyphenyl)-ethylamine: Cautiously add sulfuric acid (14.7 mL, 265 mmol) dropwise at 0°C to lithium aluminum hydride (1M solution in THF, 565 mL) with efficient stirring. Warm the mixture to ambient temperature for 20 min and then cool back to 0°C. Add a solution of 1-fluoro-4-methoxy-2-(2-nitro-vinyl)-benzene (18.7 g, 95 mmol) in THF (150 mL) by cannula and stir 2.5 h at ambient temperature. Cool the mixture to 0°C, cautiously add water (4.6 mL) followed by 2N aqueous NaOH (4.6 mL) and water (6.5 mL). Remove the precipitate by filtration and evaporate the filtrate to give the desired intermediate (16 g, 100 %). MS (ES+) *m/z*: 170 $(M+H)^+$.

N-(2,2-Dimethoxy-ethyl)-2,2,2-trifluoro-*N*-[2-(2-fluoro-5-methoxy-phenyl)-ethyl]-acetamide: Dissolve 2-(2-fluoro-5-methoxyphenyl)-ethylamine (16 g, 95 mmol) and dimethoxy acetaldehyde (60 % aqueous, 21.5 mL, 142 mmol) in methanol (500 mL). After 1.5 h, cautiously add sodium borohydride (5.39 g, 142 mmol) at 0°C and then stir at ambient temperature for 3 h. Add acetone and evaporate the mixture. Dissolve the residue in DCM (250 mL), cool to 0°C and add triethylamine (26.5 mL, 190 mmol) and trifluoroacetic anhydride (20.1 mL, 142 mmol). After 30 min, wash the mixture with 1N aqueous HCl (4 x 100 mL), brine and saturated aqueous $NaHCO_3$. Dry the organic layer over Na_2SO_4 and concentrate *in vacuo*. Purify by chromatography on silica gel to give the desired intermediate (19.7 g, 59%). MS (ES+) *m/z*: 322 $(M\text{-}OMe)^+$.

9-Fluoro-6-methoxy-3-(2,2,2-trifluoroacetyl)-2,3-dihydro-1*H*-benzo[*d*]azepine: Dissolve *N*-(2,2-dimethoxy-ethyl)-2,2,2-trifluoro-*N*-[2-(2-fluoro-5-methoxy-phenyl)-ethyl]-acetamide (5 g, 14.2 mmol) in chlorobenzene (100 mL). Add polyphosphoric acid (5 g) and P_2O_5 (2.5 g) and heat at 80°C for 2 h. Add water to the hot mixture, cool to

room temperature and extract with DCM. Dry the organic extracts over Na_2SO_4 and concentrate *in vacuo* to obtain the desired intermediate (3.0 g, 73%). MS (ES+) *m/z*: 290 $(M+H)^+$.

9-Fluoro-6-methoxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Dissolve 9-fluoro-6-methoxy-3-(2,2,2-trifluoroacetyl)-2,3-dihydro-1*H*-benzo[*d*]azepine (9.4 g, 32.4 mmol) with 10 % Pd/C (dry basis, Degussa type, 1.4 g, 0.65 mmol) in EtOAc/ethanol (1:1, 200 mL) and stir at ambient temperature under a balloon of hydrogen for 4.5 h. Filter the mixture through a pad of silica gel and evaporate the filtrate to obtain the desired intermediate (8.6 g, 91%). MS (ES+) *m/z*: 292 $(M+H)^+$.

9-Fluoro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Dissolve 9-fluoro-6-methoxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (8.1 g, 27.7 mmol) in DCM (250 mL), cool to 0°C and add boron tribromide (5.24 mL, 55.5 mmol). Stir at ambient temperature for 1.5 h, wash the mixture with brine, dry the organic layer over Na_2SO_4 and concentrate *in vacuo* to obtain the desired intermediate (7.6 g, 99%). MS (ES+) *m/z*: 278 $(M+H)^+$.

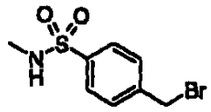
7-Chloro-9-fluoro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Dissolve 9-fluoro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.0 g, 3.6 mmol) in toluene (36 mL) with diisopropylamine (41 µL, 0.29 mmol). Warm to 60°C and add dropwise a solution of sulfuryl chloride (0.32 mL, 3.97 mmol) in toluene (10 mL). After 2 h, wash the mixture with brine, dry the organic layer over Na_2SO_4 and evaporate onto silica gel. Purify by chromatography on silica gel eluting with EtOAc/hexane (0:1 to 1:0) to obtain the desired intermediate (1.0 g, 92%). MS (ES+) *m/z*: 312 $(M+H)^+$.

7-Chloro-9-fluoro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Cool a solution of 7-chloro-9-fluoro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (2.5 g, 8.0 mmol), pyridine (3.25 mL, 40.2 mmol) and DCM (80 mL) at 0 °C and add dropwise

trifluoromethanesulfonic anhydride (2.43 mL, 14.5 mmol) over 20 min. Stir at room temperature for 1 h. Wash the reaction mixture sequentially with 1N aqueous HCl, saturated $NaHCO_3$ solution and brine. Dry the organic fraction over Na_2SO_4 and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (gradient from 19:1 to 1:1) to obtain the title compound (3.1 g, 87%).

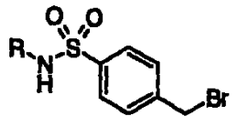
Preparation 7

4-Bromomethyl-*N*-methyl-benzenesulfonamide



Mix 4-(bromomethyl)benzenesulfonyl chloride (2.7 g, 10 mmol), anhydrous potassium carbonate (1.4 g, 10 mmol) and anhydrous THF (60 mL) under nitrogen. Cool the mixture in an ice bath, add dropwise a 2M solution of methylamine in THF, and stir at this temperature for 30 min. Remove the ice bath and stir at ambient temperature for 16 h. Dilute with EtOAc then wash with 1N aqueous HCl. Separate the organic layer, dry over Na_2SO_4 and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 4:1, 7:3 and 13:7) to obtain the title compound (1.5 g, 71%). MS (ES+) *m/z*: 266 $(M+H)^+$.

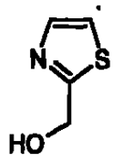
The compounds of Preparations 8-9 may be prepared essentially as described in Preparation 7 by using 4-(bromomethyl)benzenesulfonyl chloride and the appropriate amine. Yields and MS (ES+) data are shown in the Table below.



Prep.	NH-R	Compound	Yield (%)	MS (ES+) *m/z*
8	NH-CH_2CH_3	4-Bromomethyl-*N*-ethyl-benzenesulfonamide	43	278 $(M+H)^+$
9	NH-CH_2CH_2F	4-Bromomethyl-*N*-(2-fluoroethyl)-benzenesulfonamide	39	296 $(M+H)^+$

Preparation 10

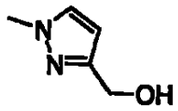
Thiazol-2-yl-methanol



Mix under nitrogen 2-thiazolecarboxaldehyde (1.1 g, 10 mmol) and ethanol (30 mL). Add sodium borohydride (416 mg, 11 mmol) at 0°C. Stir and warm the mixture slowly to ambient temperature for 12 h. Quench with saturated aqueous ammonium chloride and concentrate *in vacuo*. Dilute the residue with EtOAc and wash with brine. Dry the organic fraction over Na_2SO_4 and concentrate *in vacuo* to obtain the title compound as an oil (1.0 g, 87%). MS (ES+) *m/z*: 116 $(M+H)^+$.

Preparation 11

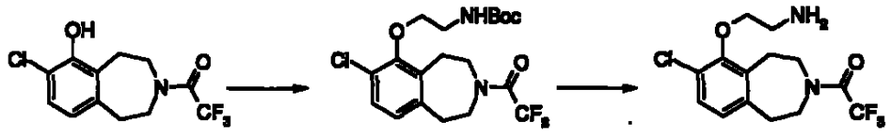
(1-Methyl-1*H*-pyrazol-3-yl)-methanol



Dissolve 3-dimethoxymethyl-1-methylpyrazole (1.562 g, 10 mmol) in acetone (100 mL), add *p*-toluenesulfonic acid (190 mg, 1.0 mmol) and stir at ambient temperature for 12 h. Remove volatiles *in vacuo*, dissolve the residue in EtOAc, wash with saturated aqueous $NaHCO_3$, dry over Na_2SO_4, filter and concentrate *in vacuo* to afford an oil. Dissolve the oil in methanol (15 mL), add sodium borohydride (567 mg, 15 mmol) and stir the reaction mixture at ambient temperature for 12 h. Remove volatiles *in vacuo*, dissolve the residue in EtOAc, wash with saturated aqueous $NaHCO_3$, dry over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with EtOAc/hexane (6:1) to give the title compound as an oil (530 mg, 47%).

Preparation 12

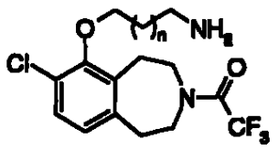
6-(2-Amino-ethoxy)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine

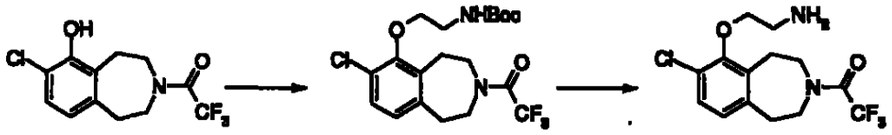


6-(2-*tert*-Butoxycarbonylamino-ethoxy)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Use a method similar to the General Procedure 4-3, using 7-chloro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (277 mg, 0.94 mmol) and *N*-(*tert*-butoxycarbonyl)ethanolamine (244 mg, 1.51 mmol) to give, after chromatography on silica gel eluting with hexane/EtOAc (1:0 and 3:1), the desired intermediate (392 mg, 95%). MS (ES+) *m/z*: 337 $(M+H\text{-}Boc)^+$.

6-(2-Amino-ethoxy)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Dissolve 6-(2-*tert*-butoxycarbonylamino-ethoxy)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (997 mg, 2.28 mmol) in 4M hydrogen chloride in dioxane (15 mL) and stir at ambient temperature for 30 min. Concentrate to obtain the hydrochloride salt. Dissolve the salt in DCM and wash with saturated aqueous $NaHCO_3$. Extract the basic aqueous layer with DCM. Dry the combined organic extracts over $MgSO_4$, and concentrate *in vacuo* to afford the title compound (731 mg, 95%). MS (ES+) *m/z*: 337 $(M+H)^+$.

The compounds of Preparations 13-14 may be prepared essentially as described in Preparation 12 by using 7-chloro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate alcohol. Overall yields and MS (ES+) data are shown in the Table below.

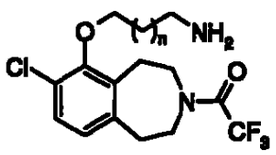




6-(2-*tert* Butoxycarbonylamino-ethoxy)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Use a method similar to the General Procedure 4-3, using 7-chloro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (277 mg, 0.94 mmol) and *N*-(*tert*-butoxycarbonyl)ethanolamine (244 mg, 1.51 mmol) to give, after chromatography on silica gel eluting with hexane/EtOAc (1:0 and 3:1), the desired intermediate (392 mg, 95%). MS (ES+) *m/z*: 337 $(M+H\text{-}Boc)^+$.

6-(2-Amino-ethoxy)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Dissolve 6-(2-*tert*-butoxycarbonylamino-ethoxy)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (997 mg, 2.28 mmol) in 4M hydrogen chloride in dioxane (15 mL) and stir at ambient temperature for 30 min. Concentrate to obtain the hydrochloride salt. Dissolve the salt in DCM and wash with saturated aqueous $NaHCO_3$. Extract the basic aqueous layer with DCM. Dry the combined organic extracts over $MgSO_4$, and concentrate *in vacuo* to afford the title compound (731 mg, 95%). MS (ES+) *m/z*: 337 $(M+H)^+$.

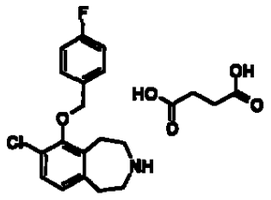
The compounds of Preparations 13-14 may be prepared essentially as described in Preparation 12 by using 7-chloro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate alcohol. Overall yields and MS (ES+) data are shown in the Table below.



Prep.	n	Compound	Yield (%)	MS (ES+) m/z
13	1	6-(3-Amino-propoxy)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine	94	351 $(M+H)^+$
14	2	6-(4-Amino-butoxy)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine	89	365 $(M+H)^+$

Example 7

7-Chloro-6-(4-fluorobenzyloxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



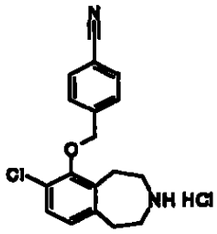
Prepare a slurry of sodium hydride (60% in mineral oil; 99 mg, 2.5 mmol) in DMF (4 mL) and heat to 65° C. Add a solution of 3-*tert*-butoxycarbonyl-7-chloro-6-hydroxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (250 mg, 0.84 mmol) in DMF (5 mL) dropwise and stir for 1 h. Add a solution of 4-fluorobenzyl bromide (191 mg, 1.0 mmol) in DMF (1 mL), stir at 65°C for 1.5 h and cool to ambient temperature. Add water (1 mL) and concentrate the mixture to an oily residue. Partition the residue between EtOAc/hexane (1:1) and water. Dry the organic layer over Na_2SO_4, filter and concentrate *in vacuo*. Dissolve the residue in DCM, wash with 2N aqueous NaOH, dry the organic layer over Na_2SO_4, filter, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (20:1, 10:1 and 7:1) to give 3-*tert*-butoxycarbonyl-7-chloro-6-(4-fluorobenzyloxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil.

Use a method similar to General Procedure 1-5 to deprotect 3-*tert*-butoxycarbonyl-7-chloro-6-(4-fluorobenzyloxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Purify by SCX chromatography followed by chromatography on silica gel eluting with DCM/2M ammonia in methanol (1:0, 50:1, 20:1, 15:1 and 10:1) to give the free base of

the title compound. Use a method similar to the General Procedure 2-1 to give the title compound as a white solid (178 mg, 50%). MS (ES+) *m/z*: 306 $(M+H)^+$.

Example 8

7-Chloro-6-(4-cyanobenzyloxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

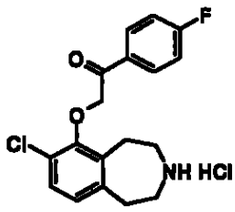


Combine 3-*tert*-butoxycarbonyl-7-chloro-6-hydroxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (200 mg, 0.67 mmol), potassium carbonate (111 mg, 0.8 mmol), and 4-cyanobenzyl bromide (263 mg, 1.34 mmol) in DMSO (5 mL) and heat the stirred mixture to 100° C for 24 h. Cool to ambient temperature and partition the mixture between water and EtOAc/hexane (1:1). Wash the organic layer with brine and dry over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (5:1) to give 3-*tert*-butoxycarbonyl-7-chloro-6-(4-cyanobenzyloxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil.

Use a method similar to the General Procedure 1-5 to deprotect 3-*tert*-butoxycarbonyl-7-chloro-6-(4-cyanobenzyloxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Purify by SCX chromatography to give the free base of the title compound. Use a method similar to the General Procedure 2-2 to give the title compound as an off-white solid (66 mg, 27%). MS (ES+) *m/z*: 313 $(M+H)^+$.

Example 9

7-Chloro-6-[2-(4-fluorophenyl)-2-oxo-ethoxy)]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

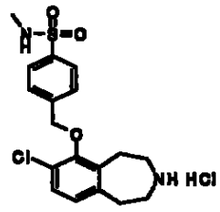


Use a method similar to the General Procedure 4-1, using 7-chloro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (294 mg, 1.0 mmol) and 2-bromo-4'-fluoroacetophenone (260 mg, 1.2 mmol) to give, after purification by chromatography on silica gel eluting with hexane/EtOAc (7:1), 7-chloro-6-[2-(4-fluorophenyl)-2-oxo-ethoxy)]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a solid (402 mg, 93%). MS (ES+) *m/z*: 430 $(M+H)^+$.

Use a method similar to the General Procedure 1-1 to deprotect 7-chloro-6-[2-(4-fluorophenyl)-2-oxo-ethoxy)]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (402 mg, 0.93 mmol). Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (96:4) to give the free base of the title compound (278 mg, 89%). MS (ES+) *m/z*: 334 $(M+H)^+$. Use a method similar to the General Procedure 2-3 to give the title compound.

Example 10

7-Chloro-6-(4-methylsulfamoyl-benzyloxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

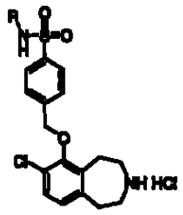


Dissolve under nitrogen 7-chloro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (200 mg, 0.68 mmol) in acetone (30 mL). Add powdered anhydrous potassium carbonate (276 mg, 2.0 mmol) and powdered potassium iodide (11.3 mg, 0.068 mmol) followed by 4-bromomethyl-*N*-methyl-benzenesulfonamide (528 mg,

2.0 mmol). Stir the reaction mixture at ambient temperature for 12 h. Concentrate *in vacuo*, dilute with EtOAc and wash twice with 1N aqueous HCl. Separate the organic layer, dry over Na_2SO_4 and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0 and 4:1) to obtain 7-chloro-6-(4-methylsulfamoyl-benzyloxy)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (201 mg, 60%).

Use a method similar to the General Procedure 1-1 to deprotect 7-chloro-6-(4-methylsulfamoyl-benzyloxy)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (196 mg, 0.41 mmol). Purify by SCX column to give the free base of the title compound (110 mg, 70%). MS (ES+) *m/z*: 381 $(M+H)^+$. Use a method similar to the General Procedure 2-2 to obtain the title compound.

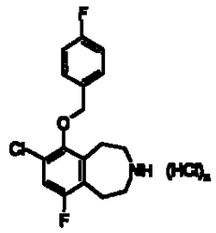
Examples 11-12 may be prepared essentially as described in Example 10 by using 7-chloro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate bromide. MS (ES+) data are shown in the Table below.



Ex.	NH-R	Compound	MS (ES+) *m/z*
11	NH-CH_2-CH_3	7-Chloro-6-(4-ethylsulfamoyl-benzyloxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	395 $(M+H)^+$
12	NH-CH_2-CH_2F	7-Chloro-6-[4-(2-fluoroethylsulfamoyl)-benzyloxy]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	413 $(M+H)^+$

Example 13 Allan 1

7-Chloro-9-fluoro-6-(4-fluorobenzyloxy)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

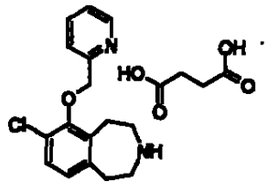


Dissolve 7-chloro-9-fluoro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.25 g, 0.8 mmol) in DMF (8 mL), add potassium carbonate (0.56 g, 4.0 mmol) and 4-fluorobenzyl bromide (0.46 mL, 2.4 mmol). After 14 h at 90 °C, dilute with ether and wash with brine. Dry the organic layer over Na_2SO_4 and evaporate onto silica gel. Purify by chromatography on silica gel eluting with EtOAc/hexane (0:1 to 1:0) to obtain 7-chloro-9-fluoro-6-(4-fluorobenzyloxy)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine.

Use a method similar to the General Procedure 1-1, using 7-chloro-9-fluoro-6-(4-fluorobenzyloxy)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine, to give the free base of the title compound. Use a method similar to the General Procedure 2-2 to obtain the title compound (275 mg, 95%). HRMS calc'd for $C_{17}H_{17}NOF_2Cl$ 324.0902, found 324.0957.

Example 14

7-Chloro-6-(pyridin-2-ylmethoxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



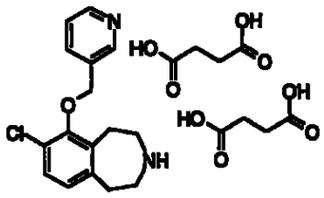
Prepare a slurry of sodium hydride (60% in mineral oil, 168 mg, 4.2 mmol) in DMF (4 mL) and heat to 65° C. Add dropwise a solution of 3-*tert*-butoxycarbonyl-7-chloro-6-hydroxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (250 mg, 0.84 mmol) in DMF (5 mL) and stir for 1 h. Add a solution of 2-(bromomethyl)-pyridine hydrobromide (256

mg, 1 mmol) in DMF (1 mL), stir at 65° C for 0.5 h and cool to ambient temperature. Add water (1 mL) and concentrate the reaction mixture to an oily residue. Partition the residue between EtOAc/hexane (1:1) and water. Dry the organic layer over Na_2SO_4, filter and concentrate. Purify by chromatography on silica gel eluting with hexane/EtOAc (10:1, 5:1 and 3:1) to give 3-*tert*-butoxycarbonyl-7-chloro-6-(pyridin-2-ylmethoxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil.

Use a method similar to the General Procedure 1-5 to deprotect 3-*tert*-butoxycarbonyl-7-chloro-6-(pyridin-2-ylmethoxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Purify by SCX chromatography to give the free base of the title compound. Use a method similar to the General Procedure 2-1 to give the title compound as a white solid (228 mg, 67%). MS (ES+) *m/z*: 289 $(M+H)^+$.

Example 15

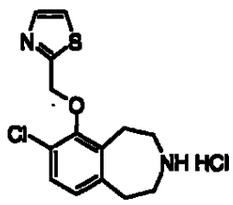
7-Chloro-6-(pyridin-3-ylmethoxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Disuccinate



Use a method similar to the Example 14, using 3-*tert*-butoxycarbonyl-7-chloro-6-hydroxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (250 mg, 0.84 mmol) and 3-(bromomethyl)-pyridine hydrobromide (256 mg, 1 mmol) to give the free base of the title compound. Use a method similar to the General Procedure 2-1 with two equivalents of succinic acid to give the title compound as a white solid (354 mg, 80%). MS (ES+) *m/z*: 289 $(M+H)^+$.

Example 16

7-Chloro-6-(thiazol-2-ylmethoxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

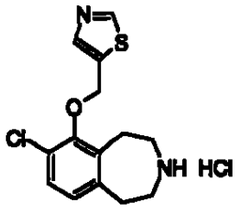


Use a method similar to the General Procedure 4-2, using 7-chloro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and thiazol-2-yl-methanol (86.2 mg, 0.75 mmol) to give, after chromatography on silica gel eluting with hexane/EtOAc (9:1 and 7:3), 7-chloro-6-(thiazol-2-ylmethoxy)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (163 mg, 61%). MS (ES+) *m/z* 391 $(M+H)^+$.

Use a method similar to the General Procedure 1-1 to deprotect 7-chloro-6-(thiazol-2-ylmethoxy)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (94:6) to obtain the free base of the title compound (99 mg, 81%). MS (ES+) *m/z*: 295 $(M+H)^+$. Use a method similar to the General Procedure 2-2 to give the title compound.

Example 17

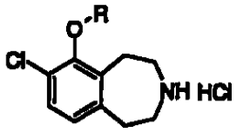
7-Chloro-6-(thiazol-5-ylmethoxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

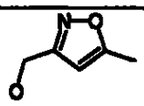
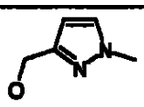


Use a method similar to the General Procedure 4-2, using 7-chloro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (294 mg, 1.0 mmol) and 5-hydroxymethylthiazole (127 mg, 1.1 mmol) to give, after chromatography on silica gel eluting with EtOAc/hexane (1:3), 7-chloro-6-(thiazol-5-ylmethoxy)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (350 mg, 89%). MS (ES+) *m/z*: 391 $(M+H)^+$.

Use a method similar to the General Procedure 1-1 to deprotect 7-chloro-6-(thiazol-5-ylmethoxy)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (350 mg, 0.90 mmol). Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (95:5) to give the free base of the title compound (203 mg, 76%). MS (ES+) *m/z*: 295 $(M+H)^+$. Use a method similar to the General Procedure 2-2 to give the title compound.

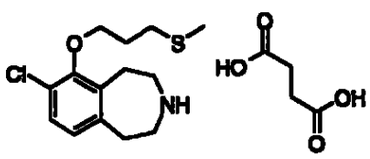
Examples 18-19 may be prepared essentially as described in Example 17 by using 7-chloro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate alcohol. Overall yields and MS (ES+) data are shown in the Table below.



Ex.	O-R	Compound	Yield (%)	MS (ES+) *m/z*
18		7-Chloro-6-(5-methyl-isoxazol-3-ylmethoxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	47	293 $(M+H)^+$
19		7-Chloro-6-(1-methyl-1*H*-pyrazol-3-ylmethoxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	39	292 $(M+H)^+$

Example 20

7-Chloro-6-(3-methylthio-propoxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

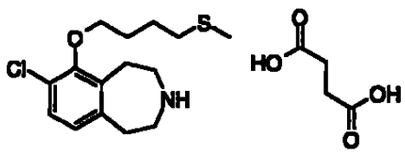


Use a method similar to the General Procedure 4-2, using 7-chloro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 3-(methylthio)-1-propanol (191 mg, 1.8 mmol) to give, after chromatography on silica gel eluting with EtOAc/hexane (1:8), 7-chloro-6-(3-methylthio-propoxy)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (65 mg, 14%).

Use a method similar to the General Procedure 1-1 to deprotect 7-chloro-6-(3-methylthio-propoxy)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (65 mg, 0.17 mmol). Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (94:6) to give the free base of the title compound (25 mg, 51%). MS (ES+) *m/z*: 286 $(M+1)^+$. Use a method similar to the General Procedure 2-1 to give the title compound.

Example 21

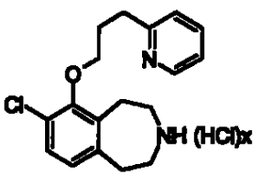
7-Chloro-6-(4-methylthio-butoxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Use a method similar to the Example 20, using 7-chloro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 4-(methylthio)-1-butanol to give the title compound. MS (ES+) *m/z*: 300 $(M+1)^+$.

Example 22

7-Chloro-6-(3-pyridin-2-yl-propoxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

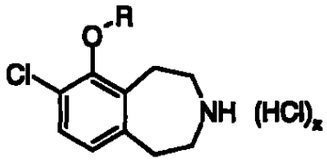


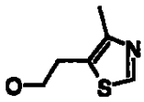
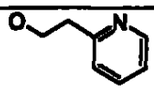
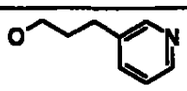
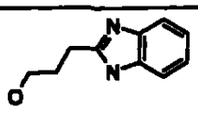
Use a method similar to the General Procedure 4-3, using 7-chloro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (50 mg, 0.17 mmol) and 3-(2-pyridyl)-1-propanol (35 mg, 0.255 mmol) to give, after reverse phase HPLC (10-95% of solvent B in 12.8 min, 25 mL/min; solvent A: water, 0.1% trifluoroacetic acid; solvent B: acetonitrile, 0.1% trifluoroacetic acid; column: YMC SH-341-5, S-5□m, 12 nm, 100 x

20 mm), 7-chloro-6-(3-pyridin-2-yl-propoxy)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine.

Use a method similar to the General Procedure 1-1, using 7-chloro-6-(3-pyridin-2-yl-propoxy)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine to give the free base of the title compound. Use a method similar to the General Procedure 2-2 to give the title compound as a solid (26 mg, 39%). MS (ES+) *m/z*: 317 $(M+H)^+$.

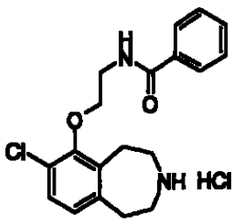
Examples 23-26 may be prepared essentially as described in Example 22 by using 7-chloro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate alcohol. Overall yields and MS (ES+) data are shown in the Table below.



Ex.	O-R	Compound	Yield (%)	MS (ES+) *m/z*
23		7-Chloro-6-[2-(4-methyl-thiazol-5-yl)-ethoxy]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	83	323 $(M+H)^+$
24		7-Chloro-6-(2-pyridin-2-yl-ethoxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	83	303 $(M+H)^+$
25		7-Chloro-6-(3-pyridin-3-yl-propoxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	83	317 $(M+H)^+$
26		6-[3-(1*H*-Benzimidazol-2-yl)-propoxy]-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	8	356 $(M+H)^+$

Example 27

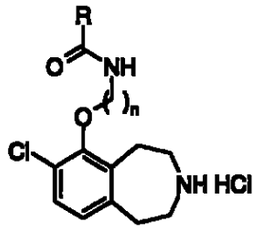
6-(2-Benzoylamino-ethoxy)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

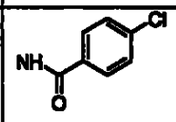
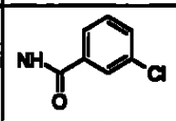
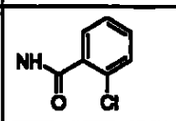
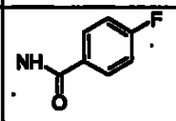
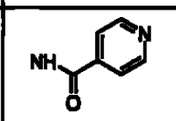
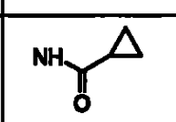
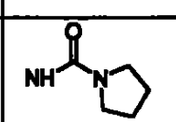
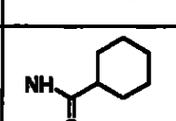


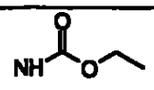
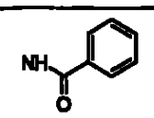
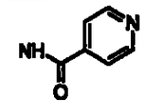
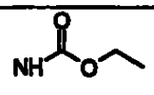
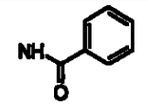
Combine benzoyl chloride (19.3 mg, 0.137 mmol), PS-morpholine (109 mg, 0.272 mmol), 6-(2-amino-ethoxy)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (46 mg, 0.137 mmol) in DCM (1.5 mL) and stir at ambient temperature for 16 h. Filter the resin, wash with DCM and concentrate *in vacuo*. Purify by reverse phase HPLC (10-95% of solvent B in 12.8 min, 25 mL/min; solvent A: water, 0.1% trifluoroacetic acid; solvent B: acetonitrile, 0.1% trifluoroacetic acid; column: YMC SH-341-5, S-5μm, 12 nm, 100 x 20 mm) to give 6-(2-benzoylamino-ethoxy)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine.

Use a method similar to the General Procedure 1-1, using 6-(2-benzoylamino-ethoxy)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine to give the free base of the title compound. Use a method similar to the General Procedure 2-2 to give the title compound as a solid (51 mg, 98%). MS (ES+) *m/z*: 345 $(M+H)^+$.

Examples 28-40 may be prepared essentially as described in Example 27, using 6-(2-amino-ethoxy)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine or 6-(3-amino-propoxy)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine or 6-(4-amino-butoxy)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate acyl chloride. Overall yields and MS (ES+) data are shown in the Table below.

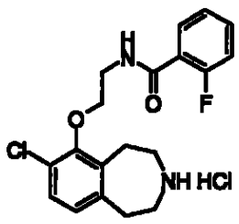


Ex.	NH-CO-R	n	Compound	Yield (%)	MS (ES+) m/z
28		2	7-Chloro-6-[2-(4-chlorobenzoylamino)-ethoxy]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	46	380 $(M+H)^+$
29		2	7-Chloro-6-[2-(3-chlorobenzoylamino)-ethoxy]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	63	380 $(M+H)^+$
30		2	7-Chloro-6-[2-(2-chlorobenzoylamino)-ethoxy]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	18	380 $(M+H)^+$
31		2	7-Chloro-6-[2-(4-fluorobenzoylamino)-ethoxy]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	18	363 $(M+H)^+$
32		2	7-Chloro-6-{2-[(pyridine-4-carbonyl)-amino]-ethoxy}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	4	346 $(M+H)^+$
33		2	7-Chloro-6-[2-(cyclopropanecarbonyl-amino)-ethoxy]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	47	309 $(M+H)^+$
34		2	7-Chloro-6-{2-[(pyrrolidine-1-carbonyl)-amino]-ethoxy}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	6	338 $(M+H)^+$
35		2	7-Chloro-6-[2-(cyclohexanecarbonyl-amino)-ethoxy]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	40	351 $(M+H)^+$

Ex.	NH-CO-R	n	Compound	Yield (%)	MS (ES+) m/z
36		3	7-Chloro-6-(3-ethoxycarbonylamino-propoxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	63	327 $(M+H)^+$
37		3	6-(3-Benzoylamino-propoxy)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	72	359 $(M+H)^+$
38		3	7-Chloro-6-{3-[(pyridine-4-carbonyl)-amino]-propoxy}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	12	360 $(M+H)^+$
39		4	7-Chloro-6-(4-ethoxycarbonylamino-butoxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	49	341 $(M+H)^+$
40		4	6-(4-Benzoylamino-butoxy)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	56	373 $(M+H)^+$

Example 41

7-Chloro-6-[2-(2-fluorobenzoylamino)-ethoxy]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



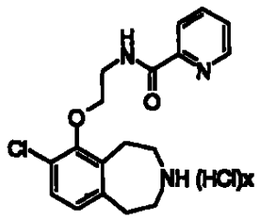
Dissolve 6-(2-amino-ethoxy)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (100 mg, 0.297 mmol) in DCM (5 mL). Add 2-fluorobenzoyl chloride (39 µL, 0.326 mmol), triethylamine (62 µL, 0.445 mmol) and stir at ambient temperature for 72 h under nitrogen atmosphere. Dilute with DCM, add 1M aqueous HCl and extract the aqueous phase with DCM. Dry the combined organic extracts over $MgSO_4$ and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with

hexane/EtOAc (7:3 and 2:1) to give 7-chloro-6-[2-(2-fluorobenzoylamino)-ethoxy]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (111 mg, 82%).

Use a method similar to the General Procedure 1-1, using 7-chloro-6-[2-(2-fluorobenzoylamino)-ethoxy]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine to give the free base of the title compound. Use a method similar to the General Procedure 2-2 to give the title compound as a solid (112 mg, 95%). *MS* (ES+) *m/z*: 363 $(M+H)^+$.

Example 42

7-Chloro-6-{2-[(pyridine-2-carbonyl)-amino]-ethoxy}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



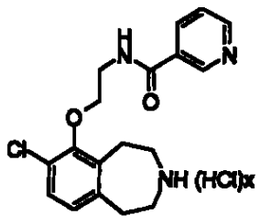
Combine picolinic acid (40 mg, 0.327 mmol), EDC (57 mg, 0.297 mmol) and HOBT (40 mg, 0.297 mmol) in DCM (3 mL). Stir for 10 min at ambient temperature. Add 6-(2-amino-ethoxy)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (100 mg, 0.297 mmol). Stir for 16 h at ambient temperature. Dilute with DCM, add water and extract the aqueous layer with DCM. Wash the combined organic extracts with 1M aqueous NaOH and brine. Dry the organic layer over $MgSO_4$ and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (3:2) to give 7-chloro-6-{2-[(pyridine-2-carbonyl)-amino]-ethoxy}-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (94 mg, 74%).

Use a method similar to the General Procedure 1-1, using 7-chloro-6-{2-[(pyridine-2-carbonyl)-amino]-ethoxy}-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine to give the free base of the title compound. Use a method similar to the

General Procedure 2-2 to give the title compound as a solid (81 mg, 72%). MS (ES+) *m/z*: 346 $(M+H)^+$.

Example 43

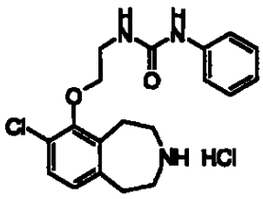
7-Chloro-6-{2-[(pyridine-3-carbonyl)-amino]-ethoxy}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to Example 42, using nicotinic acid (40 mg, 0.327 mmol) and 6-(2-amino-ethoxy)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (100 mg, 0.297 mmol) to give the title compound as a solid (105 mg, 93%). MS (ES+) m/z: 346 $(M+H)^+$.

Example 44

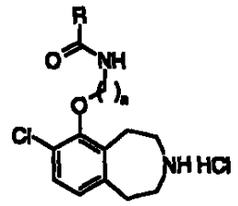
7-Chloro-6-[2-(3-phenyl-ureido)-ethoxy]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

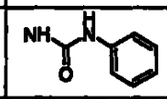
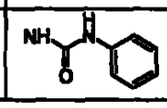


Combine phenyl isocyanate (16.3 mg, 0.137 mmol), 6-(2-amino-ethoxy)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (46 mg, 0.137 mmol) in DCM (1.5 mL) and stir at ambient temperature for 16 h. Concentrate *in vacuo*. Purify by reverse phase HPLC (10-95% of solvent B in 12.8 min, 25 mL/min; solvent A: water, 0.1% trifluoroacetic acid; solvent B: acetonitrile, 0.1% trifluoroacetic acid; column: YMC SH-341-5, S-5µm, 12 nn, 100 x 20 mm) to give 7-chloro-6-[2-(3-phenyl-ureido)-ethoxy]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine.

Use a method similar to the General Procedure 1-1, using 7-chloro-6-[2-(3-phenyl-ureido)-ethoxy]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine to give the free base of the title compound. Use a method similar to the General Procedure 2-2 to give the title compound as a solid (8 mg, 15%). MS (ES+) *m/z*: 360 $(M+H)^+$.

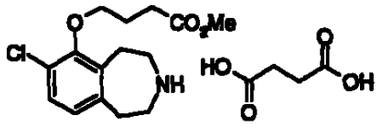
Examples 45-46 may be prepared essentially as described in Example 44 by using phenyl isocyanate and the appropriate 6-(3-amino-propoxy)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine or 6-(4-amino-butoxy)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Overall yields and MS (ES+) data are shown in the Table below.



Ex.	NH-CO-R	n	Compound	Yield (%).	MS (ES+) *m/z*.
45		3	7-Chloro-6-[3-(3-phenyl-ureido)-propoxy]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	36	374 $(M+H)^+$
46		4	7-Chloro-6-[4-(3-phenyl-ureido)-butoxy]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	28	388 $(M+H)^+$

Example 48

7-Chloro-6-(3-methoxycarbonyl-propyloxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Add methyl 4-bromobutyrate (1.9 mL, 10.4 mmol) to a mixture of 3-*tert*-butoxycarbonyl-7-chloro-6-hydroxy-2,3,4,5-tetrahydro-benzo[*d*]azepine (310 mg, 1.0 mmol), DBU (0.23 mL, 1.6 mmol) and DMF (10 mL) at ambient temperature under nitrogen. Stir the reaction mixture for 16 h. Dilute with hexane/EtOAc (1:1, 60 mL), wash the mixture with 10% aqueous NaCl (4 x 25 mL), dry the organic layer over Na_2SO_4 and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (19:1 to 2:3) to obtain 3-*tert*-butoxycarbonyl-7-chloro-6-(3-methoxycarbonyl-propyloxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (303 mg, 73%). MS (ES+) *m/z*: 398 $(M+H)^+$.

Use a method similar to the General Procedure 1-5 to deprotect 3-*tert*-butoxycarbonyl-7-chloro-6-(3-methoxycarbonyl-propyloxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (295 mg, 0.74 mmol). Purify by SCX chromatography followed by chromatography on silica gel eluting with DCM/2M ammonia in methanol (99:1 to 90:10) to give the free base of the title compound. Use a method similar to the General Procedure 2-1 to give the title compound (160 mg, 52%). MS (ES+) *m/z*: 298 $(M+H)^+$.

General Procedure 5-1

Dissolve the appropriately substituted 3-(2,2,2-trifluoroacetyl)-6-trifluoromethane-sulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1 equiv.), palladium(II) acetate (0.1-0.4 equiv.), BINAP (0.2-0.8 equiv.; BINAP/catalyst ratio 2:1) and cesium carbonate (1.4-3.0 equiv.) in toluene (0.2-0.05 *M* solution). Add the amine (1-3 equiv.), degas the mixture with vacuum/nitrogen or argon purge and heat at 80-110°C for 4-16 h. Cool the mixture to ambient temperature, dilute with EtOAc, filter through a pad of silica gel or through Celite® washing with EtOAc or ether, and evaporate the solvent to obtain the crude mixture. Alternatively, partition the reaction mixture between brine or saturated aqueous $NaHCO_3$ and EtOAc, ether or DCM, dry the organic layer over Na_2SO_4, and concentrate to obtain the crude mixture. Purify the crude mixture by chromatography on silica gel eluting with hexane/EtOAc mixtures and further SCX chromatography if needed.

General Procedure 5-2

Dissolve the appropriately substituted 3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1 equiv.), tris(dibenzylideneacetone)dipalladium(0) (0.1-0.5 equiv.), BINAP (0.2-1.0 equiv.; BINAP/catalyst ratio 2:1) and cesium carbonate (1.4 equiv.) in toluene (0.05-0.5 M solution). Degas under vacuum and fill three times with nitrogen. Add the appropriately substituted amine (1.0-5.0 equiv.) and heat the mixture to 80-100°C for 2-16 h in a sealed flask under a nitrogen atmosphere. Cool the reaction flask to ambient temperature, dilute the mixture with EtOAc or DCM, filter through Celite® and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc mixtures and further SCX chromatography if needed.

General Procedure 5-3

Add the appropriately substituted 3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1 equiv.), the appropriate amine (1.2-3.0 equiv.), palladium(II) acetate (0.2-0.4 equiv.), tris(dibenzylideneacetone)dipalladium(0) (0.1-0.2 equiv.), BINAP (0.6-1.2 equiv.; BINAP/catalysts ratio 2:1), cesium carbonate (2-2.5 equiv.) and toluene or 1,4-dioxane (0.05-0.2 M solution) to a flask, degas and fill three times with nitrogen. Heat the mixture at 80-100°C for 10-16 h. Dilute the mixture with EtOAc, wash with saturated aqueous $NaHCO_3$ and brine, dry over Na_2SO_4, filter and concentrate *in vacuo* to give the crude mixture. Alternatively remove the volatiles from the reaction mixture to give directly the crude mixture, or filter the reaction mixture through Celite® and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc mixtures and further SCX chromatography if needed.

General Procedure 5-4

Combine 6-amino-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*] azepine, the appropriate bromide (1.0-2.0 equiv.), potassium or cesium carbonate (1.0-2.0 equiv.) and toluene, DMF or acetonitrile in a sealed tube and heat at

50-150°C for 3-72 h. Cool to ambient temperature and evaporate the solvent *in vacuo* to obtain the crude mixture. Alternatively, partition the reaction mixture between diethyl ether/brine (1:1), dry the organic layer over anhydrous Na_2SO_4 and concentrate to obtain the crude mixture. Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 9:1, 4:1, 7:3 and 3:2).

General Procedure 6-1

Dissolve 4-(*tert*-butoxycarbonylamino-methyl)-benzoic acid (1 equiv.), HATU (1 equiv.), DIEA (2 equiv.) and the appropriately substituted amine (1 equiv.) in DCM or DCM/DMF and stir at ambient temperature for 4-16 h. Concentrate *in vacuo*, dissolve the residue in DCM and wash successively with saturated aqueous $NaHCO_3$, 1N aqueous HCl, water, brine, and dry over Na_2SO_4. Filter and concentrate the solution and use the material without further purification. Deprotect the residue using the General Procedure 1-5 and purify by SCX chromatography.

General Procedure 6-2

Dissolve 4-(*tert*-butoxycarbonylamino-methyl)-benzoic acid or 5-(*tert*-butoxycarbonylamino-methyl)-pyridine-2-carboxylic acid lithium salt (1 equiv.), HATU (1 equiv.), DIEA (2 equiv.) and the appropriately substituted amine (1 equiv.) in DCM or DCM/DMF and stir at ambient temperature for 4-16 h. Concentrate *in vacuo*, dissolve the residue in DCM and wash successively with saturated aqueous $NaHCO_3$, water, brine, and dry over Na_2SO_4. Filter and concentrate the solution and use the material without further purification. Deprotect the residue using the General Procedure 1-5 and purify by SCX chromatography.

General Procedure 6-3

Dissolve the appropriately substituted acetophenone (1.0-1.2 equiv.) in THF, add titanium(IV) ethoxide (33-35% TiO_2, 2.0 equiv.) and the corresponding (*R*)-2-methyl-2-propanesulfinamide or (*S*)-2-methyl-2-propanesulfinamide (1.0 equiv.). Heat the mixture to 40-60 °C for 2–16 h under a nitrogen atmosphere. Cool the reaction to –78°C, then add the cold mixture over 3-10 min to a slurry of THF/$NaBH_4$ (2-4 M) at –78 °C. Allow the

mixture to warm up to ambient temperature over 2-16 h. Pour the mixture into brine, filter the resulting slurry through Celite® and wash thoroughly with EtOAc. Concentrate *in vacuo*. Dilute the oil with EtOAc, wash with brine and extract the aqueous phase with EtOAc. Dry the combined organic extracts over Na_2SO_4 and concentrate *in vacuo*. Purify the crude sulfinamide on silica gel eluting with hexane/EtOAc mixtures to obtain the major diastereomer. Dissolve the major diastereomer in excess of 4M hydrogen chloride in dioxane, stir the mixture for 1 h and concentrate *in vacuo* to a solid. Slurry the solid in diethyl ether, then filter *in vacuo* to obtain the hydrochloride salt of the desired amine. The free base of the amine is prepared either via SCX chromatography or by basic extraction.

General Procedure 6-4

Add the appropriately substituted benzonitrile portion wise to a flask containing a slurry of lithium aluminum hydride (3.0–6.0 equiv.) in diethyl ether (0.1–0.3 M solution) under a nitrogen atmosphere. Stir the mixture for 1 h and quench slowly with water (0.5-2.0 mL), followed by 5N aqueous NaOH (0.5-2.0 mL). Filter the slurry through Celite® and wash the cake with diethyl ether. Concentrate *in vacuo* to obtain the desired amine. If additional purification is needed, dissolve the amine in ether and add an excess of 2M hydrogen chloride in ether. Filter to obtain the desired amine as the hydrochloride salt. Prepare the free base by using SCX chromatography or by dissolving the hydrochloride salt in an aqueous solution of cesium carbonate (1.0–5.0 equiv.) or saturated aqueous $NaHCO_3$ (1.0–5.0 equiv.). Extract the mixture with DCM or toluene, dry over Na_2SO_4 and concentrate *in vacuo* to obtain the amine.

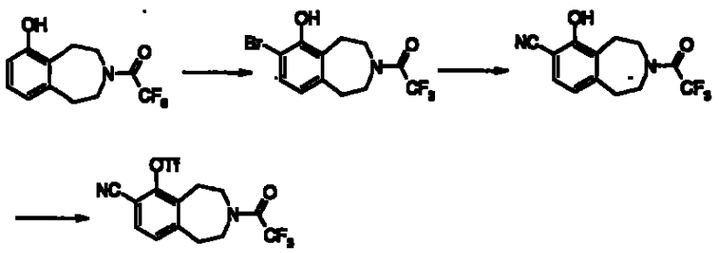
General Procedure 6-5

Add BH_3-THF complex (1-3 equiv., 1M solution in THF) dropwise to a solution of appropriately substituted benzonitrile in anhydrous THF at room temperature then stir overnight. Alternatively the reaction can be heated at reflux overnight. Add either methanol or aqueous HCl (3 equiv.) cautiously at room temperature and stir vigorously until gaseous evolution stops. Concentrate *in vacuo*, basify and then extract into EtOAc. Wash the organic phase with brine, dry over $MgSO_4$ and concentrate *in vacuo*. Purify by

SCX chromatography eluting with methanol followed by a solution of ammonia in methanol (3-7 M) to give the desired benzylamine.

Preparation 15

7-Cyano-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine



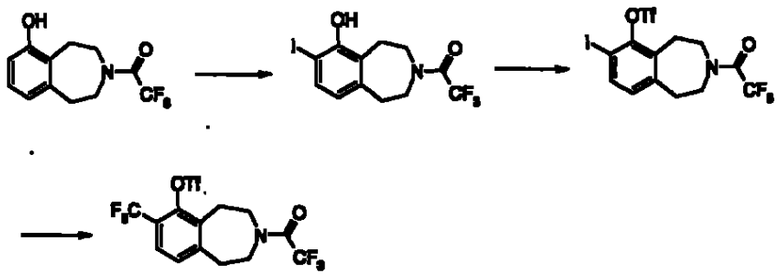
7-Bromo-6-hydroxy-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Dissolve 6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (18 g, 69.4 mmol) and DIEA (0.98 mL) in DCM (1.4 L). Add dropwise a solution of NBS (12.4 g, 69.4 mmol) in DCM (500 mL) over 75 min. Stir the reaction mixture at ambient temperature for 1 h, pour into water (500 mL) and extract the mixture with DCM. Wash the organic fraction with brine, dry over Na_2SO_4, filter and concentrate. Purify by chromatography on silica gel eluting with hexane/EtOAc (4:1) to give the desired intermediate as a white solid (20.9 g, 89%). MS (ES-) *m/z*: 337 $(M-H)^-$.

7-Cyano-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Add copper nitrile (2.6 g, 28 mmol) to a solution of 7-bromo-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (2.4 g, 7.0 mmol) in anhydrous NMP (45 mL), degas and purge with nitrogen and heat to 150°C for 18 h. Allow the reaction mixture to cool to ambient temperature and then dilute with EtOAc/heptane (2:1) and filter through a silica pad. Dilute the filtrate with water, and extract the aqueous phase twice with EtOAc. Dry the combined organic extracts over $MgSO_4$, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with EtOAc/heptane (1:4 to 1:1) to obtain the desired intermediate as an orange oil (1.7 g, 86%). MS (ES-) *m/z*: 283 $(M-H)^-$.

7-Cyano-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Add dry pyridine (3 mL) to 7-cyano-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.1 g, 3.9 mmol) in anhydrous DCM (45 mL) and cool to 0 °C. Add slowly trifluoromethanesulfonic anhydride (1.3 mL, 7.7 mmol), allow the reaction mixture to warm to ambient temperature and stir for 3 h. Dilute with DCM and wash with 2N aqueous HCl. Dry the organic layer over $MgSO_4$, filter and concentrate *in vacuo* to obtain the title compound as an orange/brown oil (1.6 g, 100%) that was used without purification. MS (ES-) *m/z*: 415 $(M-H)^-$.

Preparation 16

3-(2,2,2-Trifluoroacetyl)-6-trifluoromethanesulfonyloxy-7-trifluoromethyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine



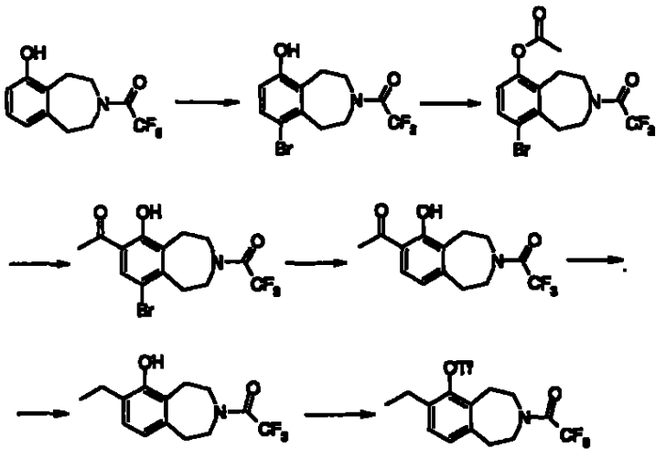
6-Hydroxy-7-iodo-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Add 6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.037 g, 4.0 mmol) and diisopropylamine (60.7 mg, 0.6 mmol) to anhydrous DCM (350 mL) and stir at 10-20 °C. Add slowly a solution of *N*-iodosuccinimide (1.035 g, 4.6 mmol) in DCM (100 mL) over a period of 3 h. Stir the reaction mixture overnight and gradually warm to ambient temperature. Quench the reaction with saturated aqueous $NaHCO_3$, separate the organic layer, wash the organic layer with 0.1N aqueous HCl, brine, dry over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with EtOAc/hexane (1:20 to 1:10) to give the desired intermediate as a white solid (1.0 g, 65%). MS (ES+) *m/z*: 386 $(M+H)^+$.

7-Iodo-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Add triethylamine (496 mg, 4.90 mmol) to a solution of 6-hydroxy-7-iodo-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (945 mg, 2.45 mmol) in DCM (30 mL) at 0 °C. Add dropwise trifluoromethanesulfonic anhydride (1.244 g, 4.41 mmol) and stir at 0°C for 1 h. Warm to ambient temperature overnight. Dilute the mixture with DCM, wash with water, saturated aqueous $NaHCO_3$ and brine. Dry over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with EtOAc/hexane (1:6) to give the desired intermediate as a white solid (1.246 g, 98%). MS (ES+) *m/z*: 518 $(M+H)^+$.

3-(2,2,2-Trifluoroacetyl)-6-trifluoromethanesulfonyloxy-7-trifluoromethyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Add CuI (367 mg, 1.93 mmol), methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (1.852 g, 9.64 mmol) and HMPA (1.728 g, 9.64 mmol) to a solution of 7-iodo-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.246 g, 2.41 mmol) in DMF (8 mL) and heat the mixture at 70 °C for 1.5 h. Add same amount of CuI, methyl 2,2-difluoro-2-(fluorosulfonyl)acetate, and HMPA and stir further for 4 h. Cool the mixture to ambient temperature, quench with saturated aqueous ammonium chloride, separate the organic layer, and extract the aqueous layer with EtOAc three times. Combine the organic layers, wash with saturated aqueous $NaHCO_3$, brine, dry over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with EtOAc/hexane (1:20 to 1:10) to give the title compound as a white solid (321 mg, 29%) and to recover the starting material (741 mg, 59%). MS (ES+) *m/z*: 460 $(M+H)^+$.

Preparation 17

7-Ethyl-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine



9-Bromo-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Add dropwise bromine (10.8 mL, 0.21 mol) in acetonitrile (260 mL) to a slurry of 6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (51.8 g, 0.2 mol) in acetonitrile (400 mL) at 0 °C cooling with ice-water to keep the temperature between 2-5°C. Warm the reaction to ambient temperature and stir for 30 min. Pour the mixture into ice-cold water (2 *L*) to obtain a white precipitate. Collect the solid by vacuum filtration, wash with water and dry under vacuum at 105 °C. Recrystallize the crude material in toluene/heptane and cool the mixture in an ice bath. Collect the solid by vacuum filtration, wash with heptane and dry under vacuum at 105 °C to obtain the desired intermediate as a white solid (54.63 g, 81%). MS (ES+) *m/z*: 338 $(M+H)^+$.

6-Acetoxy-9-bromo-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Under nitrogen atmosphere, mix 9-bromo-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (6 g, 17.8 mmol), anhydrous pyridine (0.06 mL, 0.72 mmol), DMAP (222 mg, 1.8 mmol) and acetic anhydride (30 mL). Heat the mixture at reflux for 8 h and then stir at ambient temperature for another 8 h. Concentrate *in vacuo*, dilute the residue in EtOAc, wash with 1N aqueous HCl, and then with saturated aqueous $NaHCO_3$. Dry the organic layer over Na_2SO_4, filter, and concentrate *in vacuo* to obtain the desired intermediate (5.64 g, 84%) that was used without further purification. MS (ES+) *m/z*: 380 $(M+H)^+$.

7-Acetyl-9-bromo-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Under nitrogen atmosphere, mix 6-acetoxy-9-bromo-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (2.8 g, 7.4 mmol) and nitrobenzene (5 mL). Add anhydrous aluminum chloride (980 mg, 7.4 mmol). Heat at ~180°C for 2 h. Cool the mixture to ambient temperature. Add concentrated HCl (10 mL) dropwise. Stir the mixture for 30 min. Add 1N aqueous HCl then extract with EtOAc. Dry the organic layer over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with EtOAc/hexane (0:1 to 1:4) to afford the desired intermediate (833 mg, 30%). MS (ES-) *m/z*: 378 $(M-H)^-$.

7-Acetyl-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Mix 7-acetyl-9-bromo-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (833 mg, 2.2 mmol), tetrakis(triphenylphosphine)palladium(0) (150 mg, 0.13 mmol) and sodium formate (224 mg, 3.3 mmol) in anhydrous DMF (15 mL). Degas twice then flush with argon. Keep the flask under argon and heat the reaction at 95°C for 16 h. Dilute with EtOAc then wash with 1N aqueous HCl. Separate the organic layer, dry over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with EtOAc/hexane (0:1, 1:9 and 1:4) to give the desired intermediate (448 mg, 68%). MS (ES+) *m/z*: 302 $(M+H)^+$.

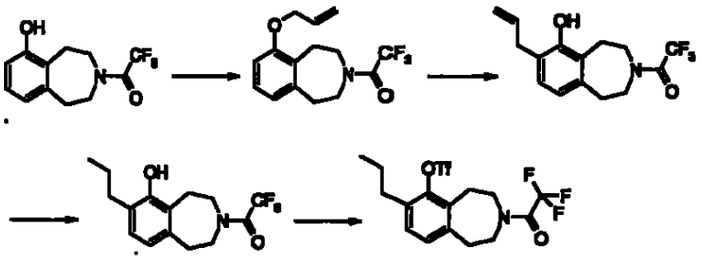
7-Ethyl-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Under nitrogen dissolve 7-acetyl-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.0 g, 3.32 mmol) in anhydrous THF (100 mL). Cool the solution to 0°C, add boron trifluoride diethyl etherate (3.4 mL, 26.6 mmol) and sodium cyanoborohydride (836 mg, 13.3 mmol). Remove the ice bath and stir for 5 h at ambient temperature. Dilute with EtOAc and wash with 0.1N aqueous HCl. Separate the organic layer, dry over Na_2SO_4, filter and concentrate *in vacuo*. MS (ES-) *m/z*: 302 $(M-H)^-$. Mix the residue with trifluoroacetic acid (40 mL) and anhydrous DCM (50 mL) under nitrogen. Cool to 0 °C in an ice bath and add triethyl silane (3.5 mL, 21.9 mmol). After 15 min, remove the ice bath and stir at ambient temperature for 16 h. Concentrate *in*

vacuo and purify by chromatography on silica gel eluting with EtOAc/hexane (1:9) to obtain the desired intermediate (698 mg, 73%). MS (ES-) *m/z*: 286 $(M-H)^-$.

7-Ethyl-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Under nitrogen mix 7-ethyl-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (698 mg, 2.4 mmol), triethylamine (0.67 mL, 4.8 mmol) and anhydrous DCM (25 mL). Cool the mixture in an ice bath, add dropwise trifluoromethanesulfonic anhydride (0.81 mL, 4.8 mmol) and stir at ambient temperature for 3 h. Quench with water and extract three times with DCM. Wash the organic extracts with 0.1N aqueous HCl and brine. Dry over Na_2SO_4, filter and concentrate to obtain the title compound (1.0 g, 100%). MS (ES+) *m/z*: 420 $(M+H)^+$.

Preparation 18

7-Propyl-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine



6-Allyloxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Dissolve 6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1 g, 3.9 mmol) in acetone (5 mL) and add powdered potassium carbonate (2.8 g, 20 mmol). Add dropwise a solution of allyl bromide (1.04 mL, 12 mmol) in acetone (3 mL) over 10 min and stir at ambient temperature overnight. Filter solids, wash with acetone and concentrate *in vacuo* to give the desired intermediate as an off-white solid (1.15 g, 98%). GC-MS *m/z*: 299 (M^+).

7-Allyl-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Dissolve 6-allyloxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.1 g, 3.7 mmol) in DCM (15 mL) and cool to –15 °C. Add 1M boron trichloride in DCM

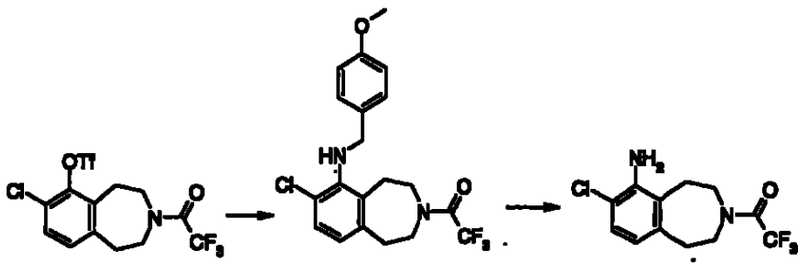
(15 mL, 15 mmol) and warm to ambient temperature. Stir for 30 min at ambient temperature. Add water (50 mL) and extract the aqueous layer three times with DCM. Wash the combined organic extracts with water (100 mL), brine (100 mL), dry over $MgSO_4$, filter, and concentrate *in vacuo* to give the desired intermediate (980 mg, 89%) as a light yellow oil which solidified to an off-white solid upon standing at ambient temperature. MS (ES+) *m/z*: 300 $(M+H)^+$.

6-Hydroxy-7-propyl-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Dissolve 7-allyl-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.5 g, 5 mmol) in EtOAc (50 mL) containing 10% Pd/C (1.3 g). Stir at ambient temperature at 1 atm with H_2 (balloon) for 30 min. Filter the catalyst and wash with water (100 mL). Extract the resulting filtrate three times with EtOAc, wash the combined organic extracts with brine, dry over $MgSO_4$, filter and concentrate *in vacuo* to give the desired intermediate as a white solid (1.45 g, 97%). MS (ES+) *m/z*: 302 $(M+H)^+$.

7-Propyl-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Cool a solution of 6-hydroxy-7-propyl-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (500 mg, 1.9 mmol), triethylamine (390 µL, 2.3 mmol) and DCM (20 mL) in a cryogenic bath set at –35°C and add dropwise over 20 min trifluoromethanesulfonic anhydride (325 µL, 2.3 mmol). Stir at this temperature overnight. Wash the reaction mixture sequentially with water, 1N aqueous HCl, water, and brine. Dry the organic layer over Na_2SO_4 and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to obtain the title compound as an off-white waxy solid (550 mg, 75%). MS (ES+) *m/z*: 434 $(M+H)^+$.

Preparation 19

6-Amino-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine

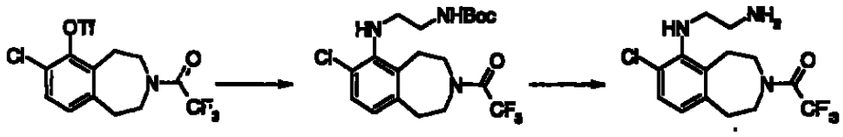


7-Chloro-6-(4-methoxybenzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (15 g, 35.3 mmol), with 4-methoxybenzylamine (13.7 mL, 106 mmol) using tris(dibenzylideneacetone)-dipalladium(0) (1.62 g, 1.76 mmol), BINAP (4.40 g, 3.5 mmol) and cesium carbonate (16.1 g, 49.4 mmol) at 80°C for 17 h. Filter the mixture through a pad of Celite® and evaporate the filtrate. Dissolve the residue in DCM and filter through a pad of silica gel. Evaporate the filtrate and purify by chromatography on silica gel eluting with hexane/EtOAc (1:0 to 2:3) to give the desired intermediate as a white solid (12.4 g, 86%). MS (ES+) *m/z*: 412 $(M+H)^+$.

6-Amino-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Treat 7-chloro-6-(4-methoxybenzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (5.41 g, 13.1 mmol) with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (3.59 g, 15.8 mmol) in toluene (66 mL) at ambient temperature for 2 h. Dilute the mixture with EtOAc and wash with saturated aqueous $NaHCO_3$ (5 x 100 mL). Extract the aqueous layer with ether, combine the organic extracts and evaporate to a volume of 300 mL. Extract the organic phase with 1N aqueous HCl (5 x 100 mL), and then wash the combined aqueous layers with ether (4 x 75 mL). Cool the aqueous phase to 0°C, neutralize with 5N aqueous NaOH (100 mL), and extract with DCM (5 x 200 mL). Wash the combined organic extracts with brine, dry over Na_2SO_4 and evaporate to obtain the title compound as a white solid (3.6 g, 94%). MS (ES+) *m/z*: 293 $(M+H)^+$.

Preparation 20

6-(2-Amino-ethylamino)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine

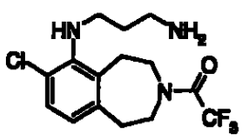


5 **6-(2-*tert*-Butoxycarbonylamino-ethylamino)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine:** Use a method similar to the General Procedure 5-1, using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (150 mg, 0.352 mmol), palladium(II) acetate (8 mg, 0.0352 mmol), BINAP (22 mg, 0.0352 mmol), cesium carbonate (163 mg, 0.5 mmol), *t*-
10 butyl *N*-(2-aminoethyl)-carbamate (254 mg, 1.59 mmol) and toluene (6 mL) to give, after chromatography on silica gel eluting with hexane/EtOAc (4:1), the desired intermediate (136 mg, 89%).

6-(2-Amino-ethylamino)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-
15 **benzo[*d*]azepine:** Dissolve 6-(2-*tert*-butoxycarbonylamino-ethylamino)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (136 mg, 0.31 mmol) in 4M hydrogen chloride in dioxane (20 mL) and stir at ambient temperature for 25 min. Concentrate to afford the hydrochloride salt. Dissolve the salt in DCM and wash with saturated aqueous $NaHCO_3$. Extract the basic aqueous layer with DCM, dry the organic
20 layer over $MgSO_4$, filter, and concentrate *in vacuo* to give the title compound (64 mg, 62%). MS (ES+) *m/z*: 336 $(M+H)^+$.

Preparation 21

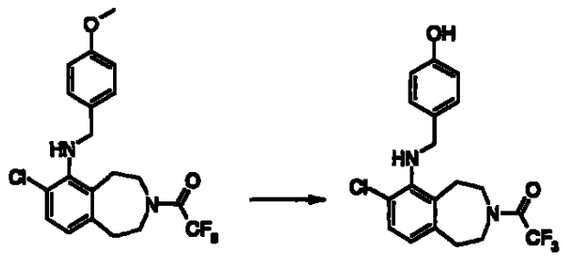
25 **6-(3-Amino-propylamino)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine**



Use a method similar to the Preparation 20, using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (600 mg, 1.41 mmol) and *tert*-butyl *N*-(3-aminopropyl)-carbamate (1.11 g, 6.34 mmol) to give the title compound (34% overall).

Preparation 22

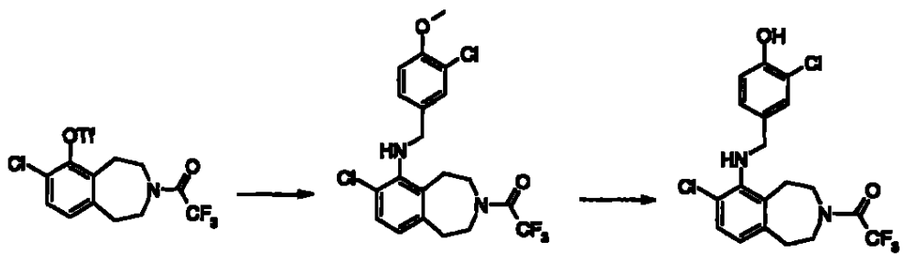
7-Chloro-6-(4-hydroxybenzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine



Dissolve 7-chloro-6-(4-methoxybenzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.667 g) in DCM (40 mL). Add a 1M solution of boron tribromide in DCM (10 mL) at 0°C. Stir the reaction for 12 h and gradually raise to room temperature. Quench the reaction with saturated aqueous $NaHCO_3$ and extract with DCM three times. Combine the organic extracts, wash with brine, dry over Na_2SO_4, filter and concentrate. Purify by chromatography on silica gel eluting with EtOAc/hexane (1:3) to give the title compound as an oil (888 mg). MS (ES+) *m/z*: 399 $(M+1)^+$.

Preparation 23

7-Chloro-6-(3-chloro-4-hydroxybenzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine

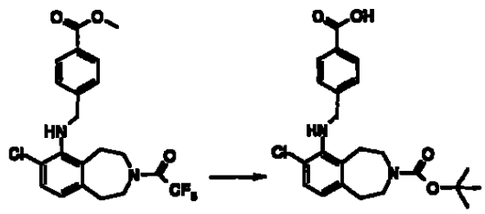


7-Chloro-6-(3-chloro-4-methoxybenzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Use a method similar to General Procedure 5-3, using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.277 g, 3.0 mmol) and 3-chloro-4-methoxy-benzylamine (669 mg, 3.9 mmol) to give the desired intermediate as a slightly yellow oil (1.554 g, 100%).

7-Chloro-6-(3-chloro-4-hydroxybenzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Use a method similar to Preparation 22, using 7-chloro-6-(3-chloro-4-methoxybenzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.36 g, 3.0 mmol) to give the title compound as an off-white solid (876 mg, 67% yield). MS (ES+) *m/z*: 433 $(M+H)^+$. MS (ES-) *m/z*: 431 $(M-H)^-$.

Preparation 24

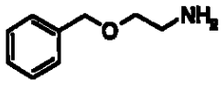
3-(*tert*-Butoxycarbonyl)-6-(4-carboxy-benzylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine



Combine 7-chloro-6-(4-methoxycarbonyl-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.4 g, 0.82 mmol), potassium carbonate (4 g, 28.9 mmol), methanol (3 mL), water (3 mL) and heat at 50°C for 2 h. Cool the reaction mixture to ambient temperature, add saturated aqueous Na_2CO_3 and dilute with DCM (10 mL). Add di-*tert*-butyl-dicarbonate (2.4 g, 10.9 mmol) by portions. Separate the organic layer and extract the aqueous layer with DCM (3 x 10 mL). Combine the organic extracts, dry over anhydrous Na_2SO_4, evaporate the solvent and purify by chromatography on silica gel eluting with DCM and DCM/methanol (9:1) to give the title compound as a white solid (0.3 g, 80%). MS (ES+) *m/z*: 331 $(M+H\text{-Boc})^+$.

Preparation 25

2-Benzyloxyethylamine

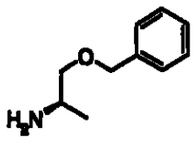


(2-Benzyloxyethyl)-carbamic acid *tert*-butyl ester: Dissolve *tert*-butyl-*N*-(2-hydroxyethyl)-carbamate (10 mL, 64.5 mmol) in anhydrous THF (500 mL) at 0 °C. Add sodium hydride (60% in mineral oil, 3.1 g, 77.4 mmol) and stir for 30 min at 0 °C. Add benzyl bromide (9.2 mL, 77 mmol) followed by tetrabutylammonium iodide (3.7 g, 10 mmol) and stir at ambient temperature overnight. Quench with water (500 mL), extract with diethyl ether (3 x 100 mL), wash the combined organic extracts with brine, dry over $MgSO_4$, filter, and evaporate to give the desired intermediate (15 g), that was used without further purification.

2-Benzyloxyethylamine: Dissolve (2-benzyloxyethyl)-carbamic acid *tert*-butyl ester (15 g) in DCM (50 mL), add trifluoroacetic acid (20 mL) and stir at 0°C for 3 h. Concentrate and dissolve the residue in a minimal amount of DCM. Purify by chromatography on silica gel eluting sequentially with hexane/EtOAc (4:1 and 1:1), EtOAc and 2M ammonia in methanol to give the title compound (8.3 g, 85%).

Preparation 26

(*R*)-2-Benzyloxy-1-methyl-ethylamine



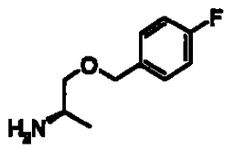
(*R*)-3-Benzyloxy-2-(*tert*-butoxycarbonylamino)-propane: Dissolve (*R*)-(+)-2-(*tert*-butoxycarbonylamino)-1-propanol (875 mg, 5 mmol) in anhydrous THF (50 mL). Add sodium hydride (60% in mineral oil, 210 mg, 5.2 mmol) and stir at 0°C for 30 min. Add benzyl bromide (620 µL, 5.2 mmol) followed by tetrabutylammonium iodide (20 mg, 0.05 mmol) and stir for 3 h at ambient temperature. Pour the mixture into water (200 mL), extract with DCM (3 x 50 mL), wash with brine, dry over $MgSO_4$, filter and concentrate.

Purify by chromatography on silica gel eluting with hexane/EtOAc (19:1) to give the desired intermediate as a colorless oil (800 mg, 60%).

(*R*)-2-Benzyloxy-1-methyl-ethylamine: Dissolve (*R*)-3-benzyloxy-2-(*tert*-butoxycarbonylamino)-propane (800 mg, 3 mmol) in DCM (10 mL), add trifluoroacetic acid (5 mL), and stir at 0 °C for 20 min. Evaporate and purify by SCX chromatography to give the title compound as a colorless oil (440 mg, 89%). MS (ES+) *m/z*: 166 $(M+H)^+$.

Preparation 27

(*R*)-2-(4-Fluorobenzyloxy)-1-methyl-ethylamine

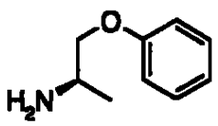


(*R*)-2-(*tert*-Butoxycarbonylamino)-3-(4-fluorobenzyloxy)-propane: Dissolve (*R*)-(+)-2-(*tert*-butoxycarbonylamino)-1-propanol (1.75 mg, 10.5 mmol) in anhydrous THF (50 mL). Add sodium hydride (60% in mineral oil, 480 mg, 12 mmol) and stir at 0°C for 30 min. Add 4-fluorobenzyl bromide (1.5 mL, 12 mmol) followed by tetrabutylammonium iodide (370 mg, 0.1 mmol) and stir for 72 h at ambient temperature. Pour the mixture into water (500 mL), extract with DCM (3 x 150 mL), wash with brine, dry over $MgSO_4$, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to give the desired intermediate as a yellow oil (2.18 g, 77%).

(*R*)-2-(4-Fluorobenzyloxy)-1-methyl-ethylamine: Dissolve (*R*)-2-(*tert*-butoxycarbonylamino)-3-(4-fluorobenzyloxy)-propane (2.18 g, 7.7 mmol) in DCM (50 mL), add trifluoroacetic acid (25 mL), and stir at 0°C for 20 min. Evaporate and purify by SCX chromatography to give the title compound as a colorless oil (1.2 g, 85%). MS (ES+) *m/z*: 184 $(M+H)^+$.

Preparation 28

(*R*)-1-Methyl-2-phenoxy-ethylamine

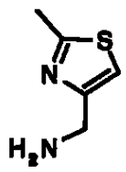


(*R*)-2-(*tert*-Butoxycarbonylamino)-3-phenoxy-propane: Dissolve (*R*)-(+)-2-(*tert*-butoxycarbonylamino)-1-propanol (1.75 g, 10 mmol) and phenol (0.95 g, 10 mmol) in anhydrous THF (75 mL). Cool to 0°C, add triphenylphosphine (4.0 g, 15 mmol) and diisopropylazodicarboxylate dropwise and stir at ambient temperature for 18 h. Pour the mixture into water (300 mL), basify to pH 10 with 5N aqueous NaOH, and extract with ethyl ether (3 x 100 mL). Wash the organic phase with brine, dry over $MgSO_4$, filter and concentrate. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to give the desired intermediate as an off-white solid (340 mg, 14%).

(*R*)-1-Methyl-2-phenoxy-ethylamine: Dissolve (*R*)-2-(*tert*-butoxycarbonylamino)-3-phenoxy-propane (340 mg, 1.35 mmol) in DCM (80 mL), add trifluoroacetic acid (35 mL), and stir at 0 °C for 2 h. Evaporate and purify by SCX chromatography to give the title compound as a colorless oil (186 mg, 91%). MS (ES+) *m/z*: 151 $(M+H)^+$.

Preparation 29

4-(Aminomethyl)-2-methyl-thiazole

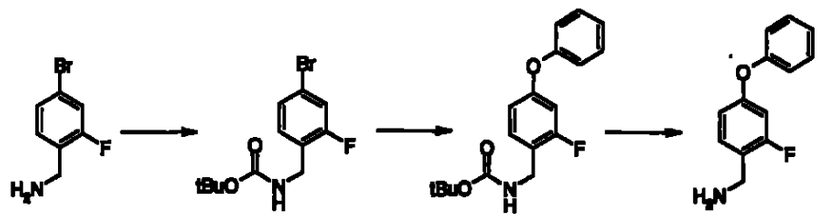


4-(Azidomethyl)-2-methyl-thiazole: Dissolve 4-(chloromethyl)-2-methyl-thiazole (350 mg, 2.37 mmol) and azidotrimethylsilane (315 µL, 2.37 mmol) in anhydrous THF (1 mL) under nitrogen. Add a 1M solution of tetrabutylammonium fluoride (3.6 mL, 3.56 mmol) in THF and stir at ambient temperature overnight. Pour the reaction mixture into water (10 mL), extract with ethyl ether (3 x 2 mL), wash the organic extracts with brine, dry over $MgSO_4$, filter, and evaporate. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to give the desired intermediate as a colorless oil (165 mg, 45%).

4-(Aminomethyl)-2-methyl-thiazole: Add 4-(azidomethyl)-2-methyl-thiazole (165 mg, 1.07 mmol) to a slurry of methanol containing 10% Pd/C (75 mg) and stir vigorously under 1 atm H_2 for 1 h. Filter, evaporate the solvent, and purify by SCX chromatography to give the title compound (55 mg, 40%).

Preparation 30

2-Fluoro-4-phenoxy-benzylamine



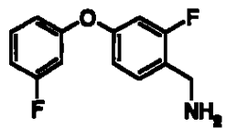
(4-Bromo-2-fluorobenzyl)-carbamic acid *tert*-butyl ester: Mix under nitrogen 4-bromo-2-fluorobenzylamine hydrochloride (7.2 g, 30 mmol), di-*tert*-butyl-dicarbonate (9.8 g, 45 mmol), and potassium carbonate (12.4 g, 90 mmol) in anhydrous THF (200 mL). Stir at ambient temperature for 16 h. Filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to obtain the desired intermediate (6.4 g, 70%). GC-MS *m/z*: 247 [$(M-C_4H_9)^+$].

(2-Fluoro-4-phenoxy-benzyl)-carbamic acid *tert*-butyl ester: Mix under argon atmosphere (4-bromo-2-fluorobenzyl)-carbamic acid *tert*-butyl ester (2.12 g, 7.0 mmol), phenol (1.32 g, 14 mmol), 2,2,6,6-tetramethylheptane-3,5-dione (129 mg, 0.7 mmol), and cesium carbonate (4.56 g, 14 mmol) in anhydrous NMP (15 mL). Degas the flask, fill with argon and add copper(I) chloride (346 mg, 3.5 mmol) quickly. Degas the flask then fill with argon and heat at 120°C for 5 h. Cool to ambient temperature, dilute with EtOAc and filter. Wash the mixture sequentially with 0.5N aqueous HCl, 0.5N aqueous NaOH and brine. Separate the organic layer, dry over Na_2SO_4 and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 9:1 and 3:1) to obtain the desired intermediate (1.28 g, 58%). GC-MS *m/z*: 260 [$(M-C_4H_9)^+$].

2-Fluoro-4-phenoxy-benzylamine: Dissolve (2-fluoro-4-phenoxy-benzyl)-carbamic acid *tert*-butyl ester (2.44 g, 7.72 mmol) in DCM (200 mL). Add trifluoroacetic acid (50 mL) then stir at ambient temperature for 16 h. Evaporate the solvent, dissolve the residue in DCM and wash with 1N aqueous NaOH. Dry over Na_2SO_4 and concentrate *in vacuo*. Purify by SCX chromatography to obtain the title compound (557 mg, 33%). MS (ES+) *m/z*: 201 $(M+H-NH_3)^+$.

Preparation 31

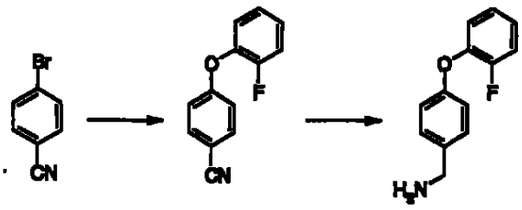
2-Fluoro-4-(3'-fluorophenoxy)-benzylamine



Use a method similar to Preparation 30, using (4-bromo-2-fluorobenzyl)-carbamic acid *tert*-butyl ester (2.12 g, 7.0 mmol) and *m*-fluorophenol (1.57 g, 14 mmol) to give the title compound (468 mg, 47% overall).

Preparation 32

4-(2'-Fluorophenoxy)-benzylamine



4-(2'-Fluorophenoxy)-benzonitrile: Mix under argon atmosphere 4-bromobenzonitrile (2.0 g, 11.3 mmol), 2-fluorophenol (2.5 g, 22.6 mmol), 2,2,6,6-tetramethylheptane-3,5-dione (203 mg, 1.1 mmol), and cesium carbonate (7.4 g, 22.6 mmol) in anhydrous NMP (19 mL). Degas the flask, fill with argon and add copper(I) chloride (554 mg, 5.6 mmol) quickly. Degas the flask then fill with argon and heat at 120°C for 3 h. Cool to ambient temperature, dilute with EtOAc, filter and wash the filtrate sequentially with 2M aqueous HCl, 0.3M aqueous HCl, 2M aqueous NaOH and brine. Separate the organic layer, dry over Na_2SO_4 and concentrate *in vacuo*. Purify by chromatography on silica gel eluting

with hexane/EtOAc (1:0 and 9:1) to obtain the desired intermediate (1.6 g, 66%). MS (ES+) *m/z*: 231 $(M+NH_4)^+$.

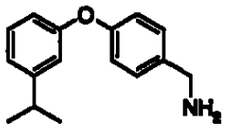
4-(2'-Fluorophenoxy)-benzylamine: Add 4-(2'-fluorophenoxy)-benzonitrile (1.5 g, 7.0 mmol) and ethanol wet Raney® activated nickel (0.4 g) to a Parr pressure vessel. Immediately add a 7N solution of ammonia in methanol (170 mL) and seal the vessel. Purge the reaction vessel with nitrogen, pressurize the reaction mixture with hydrogen (3400 KPa), seal the vessel, agitate the reaction and heat to 60°C. Continue the reaction for 18 h, turn off the heat and allow the reaction mixture to cool to ambient temperature. Vent the excess hydrogen from the vessel and purge the vessel with nitrogen. Filter the reaction mixture to remove the Raney® nickel. Concentrate *in vacuo* and purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (9:1) to obtain the title compound (1.2 g, 79%). MS (ES+) *m/z*: 201 $(M+H-NH_3)^+$.

The compound of Preparation 33 may be prepared essentially as described in Preparation 32 using 4-bromobenzonitrile and 3-fluorophenol. Overall yield and MS (ES+) data are shown in the Table below.

Prep.	Compound	Yield (%)	MS (ES+) *m/z*
33	4-(3'-Fluorophenoxy)-benzylamine	53	201 $(M+H-NH_3)^+$

Preparation 34

4-(3'-Isopropylphenoxy)-benzylamine



Use a method similar to Preparation 32 (Step 1), using 4-bromobenzonitrile (2.0 g, 11.3 mmol) and 3-isopropylphenol (3.08 g, 22.6 mmol) to give 4-(3'-isopropylphenoxy)-benzonitrile (885 mg, 33%). MS (ES+) m/z: 255 $(M+NH_4)^+$.

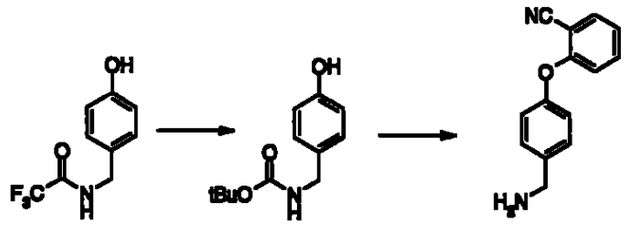
Use a method similar to the reduction procedure described in Preparation 45 (Step 2), using 4-(3'-isopropylphenoxy)-benzonitrile (875 mg, 3.7 mmol) to give the title compound (703 mg, 79%). MS (ES+) m/z: 225 $(M+H-NH_3)^+$.

The compounds of Preparations 35-39 may be prepared essentially as described in Preparation 34 by using 4-bromobenzonitrile and the appropriate phenol. Overall yields and MS (ES+) data are shown in the Table below.

Prep.	Compound	Yield (%)	MS (ES+) *m/z*
35	4-(2'-Isopropylphenoxy)-benzylamine	28	225 $(M+H-NH_3)^+$
36	4-(3'-Methylphenoxy)-benzylamine	60	197 $(M+H-NH_3)^+$
37	4-(2'-Methylphenoxy)-benzylamine	59	197 $(M+H-NH_3)^+$
38	4-(3',5'-Difluorophenoxy)-benzylamine	24	219 $(M+H-NH_3)^+$
39	4-(3'-Chlorophenoxy)-benzylamine	44	217 $(M+H-NH_3)^+$

Preparation 40

2-(4-Aminomethyl-phenoxy)-benzonitrile



(4-Hydroxybenzyl)-carbamic acid *tert*-butyl ester: Mix 2,2,2-trifluoro-*N*-(4-hydroxybenzyl)-acetamide (8.8 g, 40 mmol), and 5N aqueous NaOH (20 mL) in methanol (100 mL). Stir at ambient temperature for 4 h. Adjust pH to about 8 with aqueous HCl. Add solid sodium bicarbonate (4.4 g, 52 mmol), di-*tert*-butyl-dicarbonate (9.3 g, 40 mmol) and DCM. Stir at ambient temperature for 16 h. Dilute with DCM, wash with 1N aqueous HCl and purify by chromatography on silica gel eluting with hexane/EtOAc (9:1 to 5:5) to obtain the desired intermediate (7.8 g, 87%). MS (ES-) *m/z*: 222 $(M-H)^-$.

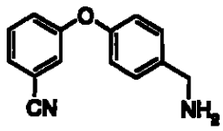
2-(4-Aminomethyl-phenoxy)-benzonitrile: Mix under argon (4-hydroxybenzyl)-carbamic acid *tert*-butyl ester (1.5 g, 6.7 mmol), 2-bromobenzonitrile (813 mg, 4.5 mmol), 2,2,6,6-tetramethylheptane-3,5-dione (83 mg, 0.45 mmol), and cesium carbonate (2.2 g, 6.7 mmol) in anhydrous NMP (8.5 mL). Degas the flask and fill with argon. Add copper(I) chloride (223 mg, 2.25 mmol) quickly. Degas the flask, fill with argon and heat at 120°C for 3 h. Cool to ambient temperature, dilute with EtOAc, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 9:1 and 3:1). Evaporate the solvent and dissolve the residue in DCM (100 mL). Add trifluoroacetic acid (20 mL) and stir at ambient temperature for 16 h. Concentrate *in vacuo*, dissolve the residue in EtOAc and wash with 1N aqueous NaOH. Dry over Na_2SO_4 and concentrate *in vacuo*. Purify by SCX chromatography to obtain the title compound (385 mg, 38%). MS (ES+) *m/z*: 225 $(M+H)^+$.

The compounds of Preparation 41-43 may be prepared essentially as described in Preparation 40 by using (4-hydroxybenzyl)-carbamic acid *tert*-butyl ester (1.5 g, 6.7 mmol) and the appropriate bromide. Overall yields and MS (ES+) data are shown in the Table below.

Prep.	Compound	Yield (%)	MS (ES+) *m/z*
41	4-(2'-Trifluoromethyl-phenoxy)-benzylamine	13	251 $(M+H-NH_3)^+$
42	4-(3'-Trifluoromethyl-phenoxy)-benzylamine	27	251 $(M+H-NH_3)^+$
43	4-(Pyridin-3-yloxy)-benzylamine	11	201 $(M+H)^+$

Preparation 44

3-(4-Aminomethyl-phenoxy)-benzonitrile

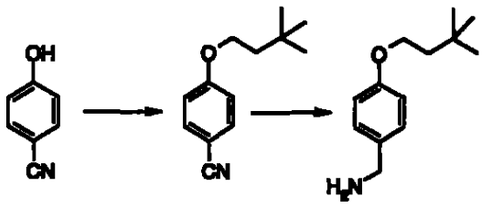


Use a method similar to Preparation 40 (Step 2), using 2,2,2-trifluoro-*N*-(4-hydroxybenzyl)-acetamide (1.0 g, 5.5 mmol) and 3-bromobenzonitrile (673 mg, 3.7

mmol). Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0 and 3:1). Concentrate *in vacuo*. Dissolve the residue (287 mg, 0.89 mmol) in methanol (25 mL) and add 5N NaOH (7 mL). Stir at room temperature for 4 h. Dilute with DCM and add solid sodium chloride to the mixture. Extract the aqueous layer three times with DCM. Combine organic extracts, dry over Na_2SO_4 and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (94:6) to obtain the title compound (124 mg, 62%). MS (ES+) *m/z*: 500 $(M+H)^+$.

Preparation 45

4-(3,3-Dimethylbutoxy)-benzylamine



4-(3,3-Dimethylbutoxy)-benzonitrile: Mix 4-cyanophenol (1.2 g, 10 mmol), 1-bromo-3,3-dimethylbutane (5.3 g, 32 mmol), powdered potassium carbonate (4.14 g, 30 mmol), and powdered potassium iodide (166 mg, 1 mmol) in acetone (60 mL). Stir under inert atmosphere and heat at reflux for 48 h. Cool the reaction mixture to ambient temperature. Dilute with acetone, filter and evaporate. Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0 and 9:1) to obtain the desired intermediate (1.8 g, 89%). MS (ES+) *m/z*: 221 $(M+NH_4)^+$.

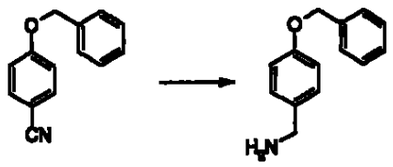
4-(3,3-Dimethylbutoxy)-benzylamine: Mix lithium aluminum hydride (1.0 g, 26.6 mmol) and anhydrous ethyl ether (70 mL) under nitrogen atmosphere. Stir and cool to 0 °C in an ice bath. Add dropwise a solution of 4-(3,3-dimethylbutoxy)-benzonitrile (1.8 g, 8.87 mmol) in anhydrous ethyl ether (20 mL). Stir for 2 h at 0 °C, remove the ice bath and stir at ambient temperature for 18 h. Cool the reaction flask in an ice bath and add carefully dropwise and sequentially water (1 mL), 2N aqueous NaOH (1 mL), and water (2 mL). Stir for 30 min, filter, separate the organic layer, dry over Na_2SO_4 and concentrate *in vacuo* to obtain the title compound (1.62 g, 88%). MS (ES+) *m/z*: 191 $(M+H-NH_3)^+$.

The compounds of Preparations 46-48 may be prepared essentially as described in Preparation 45 by using 4-cyanophenol and the appropriate bromide. Overall yields and MS (ES+) data are shown in the Table below.

Prep.	Compound	Yield (%)	MS (ES+) *m/z*
46	4-Cyclohexylmethoxy-benzylamine	90	203 $(M+H-NH_3)^+$
47	4-(2-Cyclohexylethoxy)-benzylamine	94	217 $(M+H-NH_3)^+$
48	4-(2,2-Dimethylpropoxy)-benzylamine	4	177 $(M+H-NH_3)^+$

Preparation 49

4-Benzyloxy-benzylamine

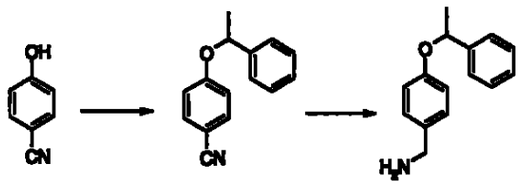


4-Benzyloxy-benzonitrile: Add 4-cyanophenol (1.191 g, 10 mmol), benzyl bromide (1.881 g, 11 mmol), potassium carbonate (3.455 g, 25 mmol) and potassium iodide (166 mg, 1 mmol) to acetonitrile (80 mL) and heat at reflux for 12 h. Cool, partition between EtOAc and water, separate the organic layer, and extract the aqueous layer with EtOAc. Combine the organic extracts, wash with brine, dry over Na_2SO_4, filter and concentrate. Purify by chromatography on silica gel eluting with EtOAc/hexane (1:6) to give the desired intermediate as a white solid (2.098 g, 100%). MS (ES+) *m/z*: 227 $(M+NH_4)^+$.

4-Benzyloxy-benzylamine: Use a method similar to Preparation 58, using 4-benzyloxy-benzonitrile (2.098 g, 10 mmol), to give the title compound as a white solid (2.021 g, 94%). MS (ES+) *m/z*: 197 $(M+H-NH_3)^+$.

Preparation 50

(±)-4-(1-Phenylethoxy)-benzylamine

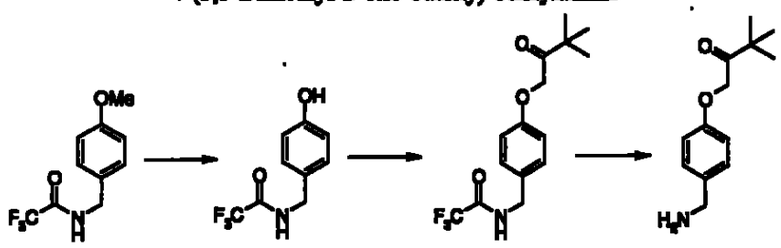


(±)-4-(1-Phenylethoxy)-benzonitrile: Add triphenylphosphine (7.869 g, 30 mmol) to a solution of *sec*-phenylethyl alcohol (1.467 g, 12 mmol), 4-cyanophenol (1.191 g, 10 mmol) and diethyl azodicarboxylate (4.528 g, 26 mmol) in anhydrous THF (50 mL) at 0 °C. Stir the reaction at ambient temperature for 12 h. Dilute with EtOAc, wash with brine, dry over Na_2SO_4, filter and concentrate. Purify by chromatography on silica gel eluting with EtOAc/hexane (1:8) to give (±)-4-(1-phenylethoxy)-benzonitrile with a small amount of triphenylphosphine (2.49 g total).

(±)-4-(1-Phenylethoxy)-benzylamine: Use a method similar to Preparation 58, using crude (±)-4-(1-phenylethoxy)-benzonitrile, to give the title compound as a colorless oil (1.6 g, 70% two steps). MS (ES+) *m/z*: 211 $(M+H-NH_3)^+$, 455.3 $(2M+H)^+$.

Preparation 51

4-(3,3-Dimethyl-2-oxo-butoxy)-benzylamine



2,2,2-Trifluoro-*N*-(4-methoxybenzyl)-acetamide: Mix under nitrogen atmosphere 4-methoxybenzylamine (13.7 g, 100 mmol) and *N*-methylmorpholine in anhydrous THF (300 mL). Cool to 0°C in an ice bath. Add dropwise a solution of trifluoroacetic anhydride (15.6 mL, 110 mmol) in anhydrous THF (25 mL). Warm up to ambient temperature slowly and stir for 16 h. Concentrate *in vacuo*. Dissolve in EtOAc and wash successively with 1N aqueous NaOH, 1N aqueous HCl, and brine. Separate the organic layer, dry over Na_2SO_4 and concentrate *in vacuo*. Purify by chromatography on silica gel

eluting with hexane/EtOAc (9:1 and 4:1) to obtain the desired intermediate (19 g, 81%). MS (ES-) *m/z*: 232 $(M-H)^-$.

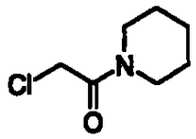
2,2,2-Trifluoro-*N*-(4-hydroxy-benzyl)-acetamide: Dissolve under nitrogen atmosphere 2,2,2-trifluoro-*N*-(4-methoxybenzyl)-acetamide (11.6 g, 50 mmol) in DCM (250 mL). Cool to 0°C in an ice bath. Add dropwise 1M boron tribromide in DCM (100 mL, 100 mmol) and stir for 20 min after addition. Warm to ambient temperature and stir for 16 h. Cool the reaction mixture in an ice bath and quench very carefully with saturated aqueous $NaHCO_3$. Separate the organic layer. Extract the aqueous layer twice with chloroform. Dry the combined organic extracts over Na_2SO_4 and concentrate *in vacuo* to obtain the desired intermediate (8.8 g, 40 mmol). MS (ES-) *m/z*: 218 $(M-H)^-$.

N-[4-(3,3-Dimethyl-2-oxo-butoxy)-benzyl]-2,2,2-trifluoroacetamide: Mix 2,2,2-trifluoro-*N*-(4-hydroxy-benzyl)-acetamide (438 mg, 2.0 mmol), 1-bromopinacolone (430 mg, 2.4 mmol), anhydrous potassium carbonate (829 mg, 6.0 mmol) and potassium iodide (33 mg, 0.1 mmol) with acetone. Heat under reflux for 12 h. Acidify with 1N aqueous HCl and extract with EtOAc three times. Combine the organic extracts, wash with brine, dry over Na_2SO_4, filter and concentrate. Purify by chromatography on silica gel eluting with EtOAc/hexane (1:3) to give the desired intermediate as a colorless oil. MS (ES+) *m/z*: 335 $(M+NH_4)^+$. MS (ES-) *m/z*: 316 $(M-H)^-$.

4-(3,3-Dimethyl-2-oxo-butoxy)-benzylamine: Add 5N aqueous NaOH (15 mL) to a solution of *N*-[4-(3,3-dimethyl-2-oxo-butoxy)-benzyl]-2,2,2-trifluoro-acetamide (552 mg, 1.74 mmol) in methanol (10 mL) and stir for 2 h at ambient temperature. Extract the mixture with DCM three times. Dry the combined organic extracts over Na_2SO_4, filter and concentrate. Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (92:8) to give the title compound as a colorless oil (337 mg, 87%). MS (ES+) *m/z*: 205 $(M+H-NH_3)^+$.

Preparation 52

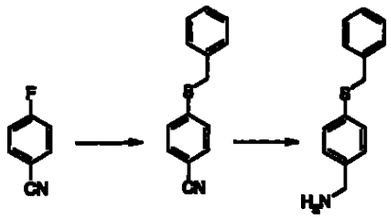
N-(2-Chloro-acetyl)-piperidine



Add chloroacetyl chloride (1.242 g, 11.0 mmol) to a mixture of potassium carbonate (2.073 g, 15 mmol) and piperidine (852 mg, 10 mmol) in THF (50 mL) at 0 °C. Stir the reaction for 12 h and gradually raise to room temperature. Dilute with water, extract with EtOAc three times. Combine the organic extracts and wash sequentially with saturated aqueous $NaHCO_3$, 0.1N aqueous HCl and brine. Dry over Na_2SO_4, filter and concentrate to give the title compound (1.65 g, 100%).

Preparation 53

4-Benzylthio-benzylamine

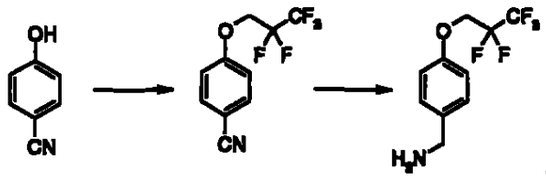


4-Benzylthio-benzonitrile: Mix under argon atmosphere 4-fluorobenzonitrile (1.21 g, 10 mmol), benzyl mercaptan (1.86 g, 15 mmol), and cesium carbonate (6.5 g, 20 mmol) in anhydrous NMP (20 mL). Degas the flask and fill with argon. Heat at 120°C for 3 h. Cool to ambient temperature, dilute with EtOAc, filter and wash with 1N aqueous HCl. Separate the organic layer, dry over Na_2SO_4 and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0 and 9:1) to obtain the desired intermediate (689 mg, 31%). GC-MS *m/z*: 225 (M^+).

4-Benzylthio-benzylamine: Use the reduction procedure described in Preparation 45 (Step 2), using 4-benzylthio-benzonitrile (689 mg, 3.1 mmol) to give, after SCX chromatography, the title compound (464 mg, 64%). MS (ES+) *m/z*: 213 $(M+H-NH_3)^+$.

Preparation 54

4-(2,2,3,3,3-Pentafluoropropoxy)-benzylamine

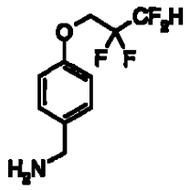


4-(2,2,3,3,3-Pentafluoropropoxy)-benzonitrile: Heat a mixture of 4-hydroxy-benzonitrile potassium fluoride complex (3.0 g, 16.9 mmol) and 1,1,1,2,2-pentafluoro-3-iodo-propane (10.8 g, 37.2 mmol) in DMSO (80 mL) to 130°C for 20 h. Cool the mixture to ambient temperature, dilute with hexane/EtOAc (1:1, 200 mL) and wash with aqueous 10% NaCl (3 x 50 mL). Dry the organic layer, concentrate *in vacuo* and purify by chromatography on silica gel eluting with hexane/EtOAc (10:1, 10:2 and 10:3) to obtain the desired intermediate (1.1 g, 26%). GC-MS *m/z*: 251 (M^+).

4-(2,2,3,3,3-Pentafluoropropoxy)-benzylamine: Use a method similar to the General Procedure 6-4, using 4-(2,2,3,3,3-pentafluoropropoxy)-benzonitrile (1.1 g, 4.1 mmol), to obtain the title compound (1.1 g, 99%). GC-MS *m/z*: 254 (M^+-H).

Preparation 55

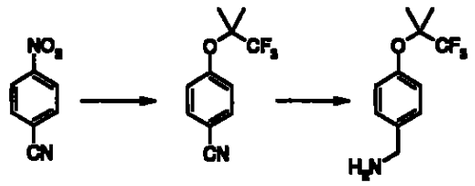
4-(2,2,3,3-Tetrafluoropropoxy)-benzylamine



Use a method similar to Preparation 54, using 4-hydroxy-benzonitrile potassium fluoride complex (4.2 g, 23.7 mmol) and 1,1,2,2-tetrafluoro-3-iodo-propane (10 g, 41.3 mmol), to give the title compound (38% overall). GC-MS *m/z*: 236 (M^+-H).

Preparation 56

4-(2,2,2-Trifluoro-1,1-dimethyl-ethoxy)-benzylamine

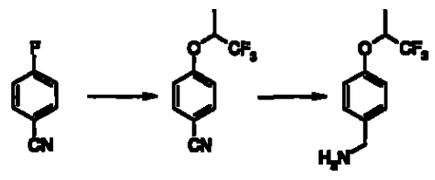


4-(2,2,2-Trifluoro-1,1-dimethyl-ethoxy)-benzonitrile: Add 2-trifluoromethyl-2-propanol (3.4 g, 27 mmol) slowly to a slurry of sodium hydride (0.6 g, 60% in mineral oil, washed with hexane) in HMPA (5 mL) under nitrogen. Stir the slurry for 15 min and add a solution of 4-nitrobenzonitrile (2.0 g, 13.5 mmol) in HMPA (10 mL). Stir the resulting purple slurry at ambient temperature for 16 h, dilute with diethyl ether (100 mL) and wash with 5% aqueous HCl (30 mL). Separate the layers and extract the aqueous layer with diethyl ether (2 x 50 mL). Combine the organic extracts and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1 to 1:1) to obtain the desired intermediate (780 mg, 25%). GC-MS *m/z*: 229 (M^+).

4-(2,2,2-Trifluoro-1,1-dimethyl-ethoxy)-benzylamine: Use a method similar to the General Procedure 6-4 to reduce 4-(2,2,2-trifluoro-1,1-dimethyl-ethoxy)-benzonitrile (780 mg, 3.4 mmol). Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (40:1, 20:1 and 10:1) to obtain the title compound (780 mg, 98%). GC-MS *m/z*: 232 (M^+-H).

Preparation 57

(±)-4-(2,2,2-Trifluoro-1-methyl-ethoxy)-benzylamine



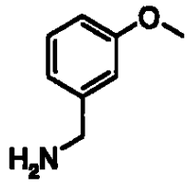
(±)-4-(2,2,2-Trifluoro-1-methyl-ethoxy)-benzonitrile: Add 1,1,1-trifluoro-2-propanol (3.8 g, 66 mmol) slowly to a slurry of sodium hydride (730 mg, 60% in mineral oil, washed with hexane) in HMPA (5 mL) under nitrogen. Stir the slurry for 15 min and add

4-fluorobenzonitrile (2 g, 16.5 mmol). Heat the slurry in a sealed flask to 90°C for 16 h. Cool the mixture to ambient temperature and pour the mixture into a flask containing 5% aqueous HCl (20 mL). Extract the mixture with diethyl ether (3 x 50 mL), and wash with 5% aqueous HCl (25 mL). Dry the organic layer over Na_2SO_4 and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to obtain the desired intermediate (2.5 g, 70%). GC-MS *m/z*: 215 (M^+).

(±)-4-(2,2,2-Trifluoro-1-methyl-ethoxy)-benzylamine: Use a method similar to the General Procedure 6-4, using (±)-4-(2,2,2-trifluoro-1-methyl-ethoxy)-benzonitrile (1.0 g, 4.6 mmol), to obtain the title compound (1.1 g, 95%). GC-MS *m/z*: 218 (M^+-H).

Preparation 58

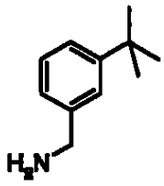
3-Methoxybenzylamine



Add lithium aluminum hydride (3.795 g, 100 mmol) portion wise to a solution of 3-methoxybenzonitrile (5.326 g, 40 mmol) in anhydrous ethyl ether (200 mL) at 0°C. Stir for 1 h, warm to ambient temperature and continue to stir for 12 h. Quench the reaction with 0.1N aqueous NaOH, filter the solid, dry the filtrate over Na_2SO_4 and concentrate to give the title compound as a colorless oil (5.107 g, 93%). MS (ES+) *m/z*: 138 $(M+H)^+$.

Preparation 59

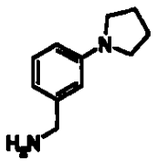
3-(*tert*-Butyl)benzylamine



Dissolve 3-*tert*-butyltoluene (0.5 mL, 2.9 mmol) in carbon tetrachloride (20 mL). Add NBS (530 mg, 3 mmol) and irradiate the reaction mixture with a 250 watt sun-lamp with simultaneous heating to reflux for 1 h. Cool to ambient temperature, filter, and concentrate filtrate to dryness to give crude 1-bromomethyl-3-*tert*-butylbenzene. Dissolve crude 1-bromomethyl-3-*tert*-butylbenzene (600 mg) in anhydrous DMF. Add portion wise sodium azide (260 mg, 4 mmol) and stir at room temperature for 2 h. Pour the mixture into water (250 mL), extract with EtOAc (3x50 mL), wash combined organic extracts with brine, dry over $MgSO_4$, filter and evaporate solvent to give crude 1-azidomethyl-3-*tert*-butylbenzene, that was used without further purification. Dissolve crude 1-azidomethyl-3-*tert*-butylbenzene in methanol containing 10% Pd/C (75 mg) at 5°C, and stir the resulting slurry under 1 atm H_2 for 1 h. Filtrate, concentrate *in vacuo* and purify by chromatography on silica gel eluting sequentially with hexane/EtOAc (4:1 and 1:1), EtOAc, methanol and 2M ammonia in methanol to give the title compound (255 mg, 53% overall). MS (ES+) *m/z*: 164 $(M+H)^+$.

Preparation 60

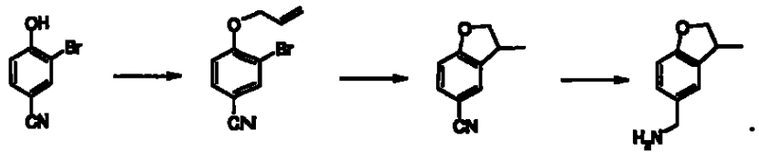
(3-Pyrrolidin-1-yl)benzylamine



Slurry a mixture of (3-bromobenzyl)-carbamic acid *tert*-butyl ester (600 mg, 2.1 mmol, U.S. Pat. Appl. Publ. US 2003134885), pyrrolidine (450 mL, 5.2 mmol), tris(dibenzylideneacetone)dipalladium(0) (200 mg, 0.21 mmol), BINAP (400 mg, 0.63 mmol) and cesium carbonate (960 mg, 2.94 mmol) in anhydrous toluene (10 mL). Degas under vacuum, fill the system with nitrogen and heat in a sealed flask at 90 °C for 18 h. Cool to room temperature, dilute with diethyl ether, filter, and concentrate *in vacuo*. Dissolve the resulting residue in DCM (10 mL) and add trifluoroacetic acid (5 mL). Stir at ambient temperature for 1 h and concentrate *in vacuo*. Purify by chromatography on silica gel eluting sequentially with hexane/EtOAc (1:1), EtOAc and 2M ammonia in methanol. Purify again by SCX chromatography to give the title compound as a brown oil (300 mg, 85% overall). MS (ES+) *m/z*: 178 $(M+H)^+$.

Preparation 61

(±)-*C*-(3-Methyl-2,3-dihydro-benzofuran-5-yl)-methylamine

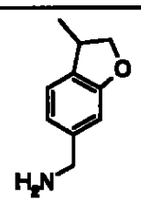
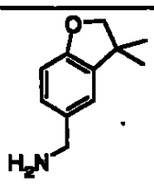
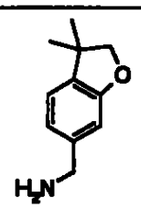


4-Allyloxy-3-bromo-benzonitrile: Mix 3-bromo-4-hydroxy-benzonitrile (1.520 g, 8.0 mmol), allyl bromide (1.161 g, 9.6 mmol), potassium carbonate (3.317 g, 24 mmol) and potassium iodide (133 mg, 0.1 mmol) in acetone (80 mL). Heat the mixture to reflux for 12 h. Cool to ambient temperature, add EtOAc, wash the organic layer with water, and extract the aqueous layer twice with EtOAc. Dry the combined organic extracts over Na_2SO_4, filter and concentrate. Purify by chromatography on silica gel eluting with EtOAc/hexane (1:8) to obtain the desired intermediate.

(±)-3-Methyl-2,3-dihydro-benzofuran-5-carbonitrile: Add tri-*n*-butyltin hydride (5.821 g, 20 mmol) and AIBN (411 mg, 2.5 mmol) to a solution of 4-allyloxy-3-bromo-benzonitrile (595 mg, 2.5 mmol). Heat the reaction at reflux for 20 h. Dilute with EtOAc and wash with water. Extract the aqueous layer with EtOAc three times. Combine the organic extracts, wash with brine, dry over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with EtOAc/hexane (1:8) to give the desired intermediate as a white solid (474 mg, 100% with a trace amount of tributyltin derivative).

(±)-*C*-(3-Methyl-2,3-dihydro-benzofuran-5-yl)-methylamine: Use a method similar to Preparation 58, using (±)-3-methyl-2,3-dihydro-benzofuran-5-carbonitrile (474 mg, 2.98 mmol) to give the title compound as a colorless oil (410 mg, 84%).

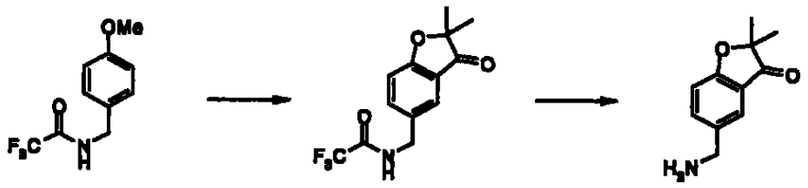
The compounds of Preparations 62-64 may be prepared essentially as described in Preparation 61 by using 3-bromo-4-hydroxy-benzonitrile or 4-bromo-3-hydroxy-benzonitrile and the appropriately substituted allyl bromide. MS (ES+) data are shown in the Table below.

Prep.	Structure	Compound	MS (ES+) *m/z*
62		(±)-*C*-(3-Methyl-2,3-dihydro-benzofuran-6-yl)-methylamine	164 $(M+H)^+$
63		C-(3,3-Dimethyl-2,3-dihydro-benzofuran-5-yl)-methylamine	ND
64		*C*-(3,3-Dimethyl-2,3-dihydro-benzofuran-6-yl)-methylamine	178 $(M+H)^+$

ND= Not determined

Preparation 65

C-(2,2-Dimethyl-3-oxo-2,3-dihydro-benzofuran-5-yl)-methylamine



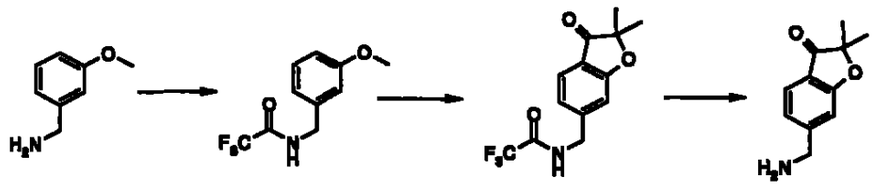
N-(2,2-Dimethyl-3-oxo-2,3-dihydro-benzofuran-5-ylmethyl)-2,2,2-trifluoro-acetamide: Add 2-bromoisobutyryl bromide (1.724 g, 7.5 mmol) to a solution of 2,2,2-trifluoro-*N*-(4-methoxy-benzyl)-acetamide (1.166 g, 5.0 mmol) in 1,2-dichloroethane (8 mL) at 15°C, then add powdered anhydrous iron(III) chloride (973 mg, 6.0 mmol). Stir the reaction at 15°C for 3 h and at ambient temperature for 8 days. Add dropwise saturated aqueous potassium sodium tartrate, then water and EtOAc, and stir for 1 h. Filter off the solid, separate the organic layer, and extract the aqueous layer three times

with EtOAc. Combine the organic extracts, wash with brine, dry over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with EtOAc/hexane (1:3) to give the desired intermediate (253 mg, 17%).

C-(2,2-dimethyl-3-oxo-2,3-dihydro-benzofuran-5-yl)-methylamine: Dissolve *N*-(2,2-dimethyl-3-oxo-2,3-dihydro-benzofuran-5-ylmethyl)-2,2,2-trifluoro-acetamide (253 mg, 0.88 mmol) in 7*M* ammonia in methanol and stir at ambient temperature for 5 days. Remove volatiles *in vacuo*, purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (92:8) to give the title compound (44 mg, 26%). MS (ES+) *m/z*: 175 $(M+H-NH_3)^+$.

Preparation 66

C-(2,2-Dimethyl-3-oxo-2,3-dihydro-benzofuran-6-yl)-methylamine

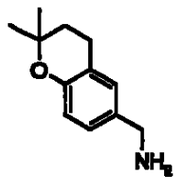


2,2,2-Trifluoro-*N*-(3-methoxy-benzyl)-acetamide: Add trifluoroacetic anhydride (6.3 g, 30 mmol) to a solution of 3-methoxybenzylamine (3.43 g, 25 mmol) and *N*-methyl-morpholine (3.793 g, 37.5 mmol) in THF (80 mL) at 0°C and stir at this temperature for 4 h. Warm to ambient temperature and stir for 12 h. Dilute with EtOAc, wash sequentially with water, 1N aqueous HCl, saturated aqueous $NaHCO_3$ and brine. Dry the organic layer over Na_2SO_4, filter and concentrate. Purify by chromatography on silica gel eluting with EtOAc/hexane (1:3) to give the desired intermediate (5.344 g, 91%).

C-(2,2-Dimethyl-3-oxo-2,3-dihydro-benzofuran-6-yl)-methylamine: Use a method similar to Preparation 65, using 2,2,2-trifluoro-*N*-(3-methoxy-benzyl)-acetamide (1.166 g, 5 mmol), to give the title compound (220 mg, 23% two steps). MS (ES+) *m/z*: 192 $(M+H)^+$.

Preparation 67

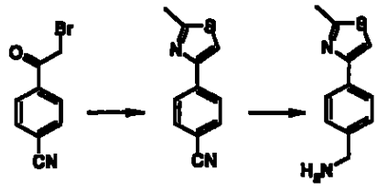
6-Aminomethyl-2,2-dimethyl-2*H*-chromene



Add 2,2-dimethyl-2*H*-chromene-6-carbonitrile (1.5 g, 8.1 mmol) and ethanol wet Raney® activated nickel (0.4 g) to a Parr pressure vessel. Immediately add 7N ammonia in methanol (170 mL) and seal the vessel. Purge the reaction vessel with nitrogen, pressurize the reaction mixture with hydrogen (3400 KPa), seal the vessel, agitate the reaction and heat to 60°C for 20 h. Turn off the heat and allow the reaction mixture to cool to ambient temperature. Vent the excess hydrogen from the vessel and purge the vessel with nitrogen. Filter the reaction mixture to remove the Raney® nickel. Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (9:1) to obtain the title compound (1.5 g, 97%). MS (ES+) *m/z*: 175 $(M+H-NH_3)^+$.

Preparation 68

4-(2-Methylthiazol-4-yl)-benzylamine

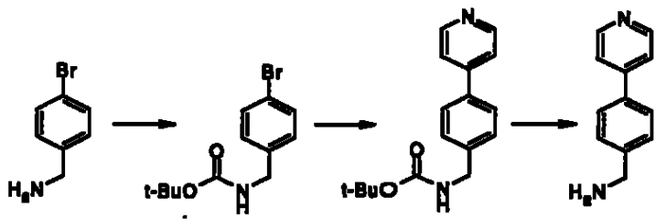


4-(2-Methylthiazol-4-yl)-benzonitrile: Suspend 4-cyanophenacyl bromide (515 mg, 2.23 mmol) in ethanol (15 mL). Add thioacetamide (171 mg, 2.23 mmol) and sodium bicarbonate (187 mg, 2.23 mmol) and heat the mixture under reflux for 2 h. Concentrate *in vacuo* and dissolve the residue in DCM. Wash the organic fraction with water, dry over Na_2SO_4, filter and concentrate to give a solid. Suspend the solid in ether/hexane and filter under vacuum washing with hexane to obtain the desired intermediate as a white solid (415 mg, 93%). GC-MS *m/z*: 200 (M^+).

4-(2-Methylthiazol-4-yl)-benzylamine: Dissolve 4-(2-methylthiazol-4-yl)-benzonitrile (305 mg, 1.52 mmol) in anhydrous THF (50 mL). Add a 1M solution of lithium aluminum hydride in THF (3.05 mL, 3.05 mmol). Heat the mixture overnight under reflux. Cool the reaction mixture with ice/water and work-up sequentially with EtOAc and water. Filter the mixture over Celite®. Separate the organic phase, and extract the aqueous phase with chloroform. Dry the combined organic extracts over Na_2SO_4, filter and concentrate to obtain the title compound as an oil (120 mg) that was used without further purification. GC-MS *m/z*: 204 (M^+).

Preparation 69

4-(Pyridin-4-yl)-benzylamine



N-(*tert*-Butoxycarbonyl)-4-bromo-benzylamine: Add di-*tert*-butyl-dicarbonate (1.173 g, 5.375 mmol) and triethylamine (1.087 g, 1.0 mL, 10.75 mmol) to a stirred solution of 4-bromobenzylamine (1.0 g, 5.375 mmol) in anhydrous DCM (15 mL). Stir overnight at ambient temperature, dilute with DCM and wash with water. Separate the organic phase, dry over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 19:1 and 9:1) to obtain the desired intermediate as a solid (1.24 g, 81%).

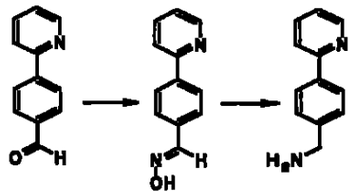
N-(*tert*-Butoxycarbonyl)-4-(pyridin-4-yl)-benzylamine: Dissolve *N*-(*tert*-butoxycarbonyl)-4-bromo-benzylamine (0.8 g, 2.807 mmol) in anhydrous DME (12 mL) under nitrogen. Add tetrakis(triphenylphosphine)palladium(0) (0.162 g, 0.14 mmol), pyridine-4-boronic acid (0.513 g, 4.211 mmol), and a 2M aqueous Na_2CO_3 solution (2.8 mL, 5.614 mmol). Heat the reaction overnight at 70°C. Cool the mixture to ambient temperature, dilute with EtOAc, and filter over Celite®. Wash the organic fraction with water, dry over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on

silica gel eluting with hexane/EtOAc (1:0, 4:1 and 1:1) to give the title compound as an oil (0.295 g, 37%). GC-MS *m/z*: 284 (M^+).

4-(Pyridin-4-yl)-benzylamine: Dissolve *N*-(*tert*-butoxycarbonyl)-4-(4-pyridyl)-benzylamine (363 mg, 1.276 mmol) in anhydrous DCM (10 mL). Add 4N hydrogen chloride in dioxane (10 mL) and stir overnight at ambient temperature. Concentrate *in vacuo* to obtain the hydrochloride salt in pure form as a solid. Dissolve the solid in saturated aqueous $NaHCO_3$ and extract three times with DCM and three more times with EtOAc. Combine the organic extracts, dry over Na_2SO_4, filter and concentrate to obtain the title compound as a solid (166 mg, 71 %). GC-MS *m/z*: 184 (M^+).

Preparation 70

4-(Pyridin-2-yl)-benzylamine



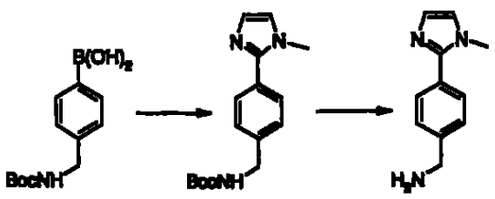
4-(2-Pyridyl)-benzaldehyde oxime: Add hydroxylamine hydrochloride (0.379 g, 5.458 mmol) and a solution of NaOH (0.327 g, 8.187 mmol) in water (2 mL) to a solution of 4-(2-pyridyl)-benzaldehyde (0.5 g, 2.729 mmol) in ethanol (10 mL). Heat the mixture at 80 °C for 2 h. Cool to ambient temperature and remove the solvent *in vacuo*. Partition the residue between EtOAc and water. Separate and dry the organic phase over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0 and 4:1) to obtain the desired intermediate (311 mg, 58%). GC-MS *m/z*: 198 (M^+).

4-(Pyridin-2-yl)-benzylamine: Add Pd/C (10%, 50 mg) and concentrated HCl (2 mL) to a solution of 4-(2-pyridyl)-benzaldehyde oxime (0.29 g, 1.46 mmol) in absolute ethanol (20 mL). Hydrogenate the mixture at 50 psi for 2 h. Filter over Celite®, wash with ethanol and concentrate *in vacuo* to obtain the hydrochloride salt in pure form as a solid. Dissolve the solid in saturated aqueous $NaHCO_3$, extract the aqueous solution three times

with DCM and three more times with EtOAc. Combine the organic extracts, dry over Na_2SO_4, filter and concentrate *in vacuo* to obtain the title compound as a solid (130 mg, 48 %). GC-MS *m/z*: 184 (M^+).

Preparation 71

4-(1-Methyl-1*H*-imidazol-2-yl)-benzylamine

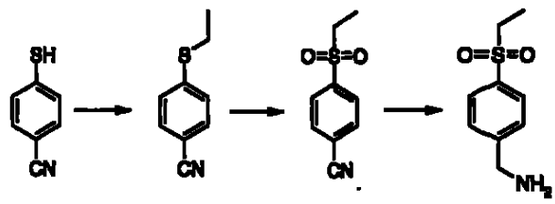


[4-(1-Methyl-1*H*-imidazol-2-yl)-benzyl]-carbamic acid *tert*-butyl ester: Add 4-(*N*-*tert*-Butoxycarbonyl-aminomethyl)phenylboronic acid (1.9 g, 7.4 mmol), 2-bromo-1-methyl-1*H*-imidazole (800 mg, 5.0 mmol), tetrakis(triphenylphosphine)-palladium(0) (287 mg, 0.25 mmol) and potassium carbonate (860 mg, 6.2 mmol) to a flask containing toluene (10 mL). Heat the mixture in a sealed flask at 90°C for 16 h. Cool the mixture, dilute with EtOAc (50 mL), filter through Celite®, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc/methanol (49:50:1) to obtain the desired intermediate (1.2 g, 83%). GC-MS *m/z*: 287(M^+).

4-(1-Methyl-1*H*-imidazol-2-yl)-benzylamine: Dissolve [4-(1-methyl-1*H*-imidazol-2-yl)-benzyl]-carbamic acid *tert*-butyl ester (500 mg, 1.7 mmol) in DCM (20 mL) and trifluoroacetic acid (5 mL). Stir the mixture for 1 h at ambient temperature. Concentrate *in vacuo* and purify by SCX chromatography to obtain the title compound (240 mg, 74%). MS (ES+) *m/z*: 188 $(M+H)^+$.

Preparation 72

4-Ethanesulfonyl-benzylamine



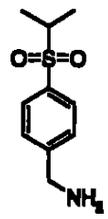
4-Ethylthio-benzonitrile: Combine 4-mercapto-benzonitrile (0.4 g, 2.96 mmol), bromoethane (1.4 mL, 8.88 mmol) and potassium carbonate (3.3 g, 23.7 mmol) in anhydrous DMF (7 mL) and heat at 60°C for 17 h. Cool the reaction mixture to ambient temperature and partition between brine (20 mL) and EtOAc (20 mL). Separate the organic layer, dry over anhydrous Na_2SO_4 and concentrate. Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 9:1 and 4:1) to obtain the desired intermediate as a colorless oil (0.4 g, 83%).

4-Ethanesulfonyl-benzonitrile: Dissolve 4-ethylthio-benzonitrile (0.4 g, 2.4 mmol) in TFA (10 mL) and add slowly hydrogen peroxide (30 w%, 10 mL) at 5 °C. Stir the reaction mixture at ambient temperature for 2 h and partition between brine (20 mL) and DCM (20 mL). Separate the organic layer, dry over anhydrous Na_2SO_4 and concentrate to obtain the desired intermediate as a white solid (0.5 g, 100%). GC-MS *m/z*: 195 (M^+).

4-Ethanesulfonyl-benzylamine: Combine 4-ethanesulfonyl-benzonitrile (0.7 g, 3.5 mmol), Raney® 3201 nickel (slurry in water, 0.1 g), 2N ammonia in methanol (20 mL) and hydrogenate at 50 psi for 17 h. Filter the reaction mixture through a pad of Celite® and concentrate *in vacuo*. Purify by SCX chromatography to obtain the title compound as a yellow oil (0.3 g, 43%).

Preparation 73

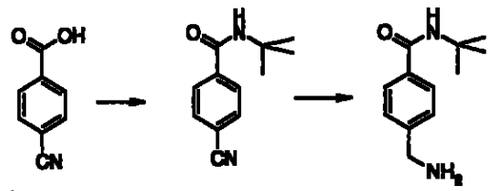
4-(2-Propanesulfonyl)-benzylamine



Use a method similar to Preparation 72, using 4-mercapto-benzonitrile (0.5 g, 3.7 mmol) and 2- bromopropane (1.4 g, 11.38 mmol), to obtain the title compound as a yellow oil (0.3 g, 39% overall).

Preparation 74

4-Aminometyl-*N-tert*-butyl-benzamide

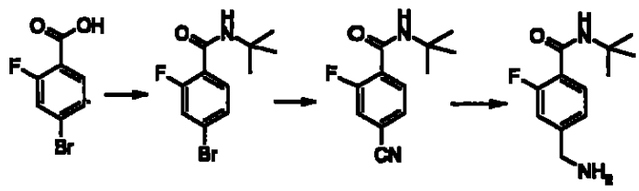


N-tert-butyl-4-cyano-benzamide: Combine 4-cyanobenzoic acid (30 mg, 2.07 mmol), *tert*-butylamine (0.5 mL, 4.13 mmol), triethylamine (0.4 mL, 2.89 mmol), and HATU (1.1 g, 2.89 mmol) in anhydrous DMF (7 mL). Stir at ambient temperature for 17 h. Partition the reaction mixture between brine (15 mL) and diethyl ether (15 mL), separate the organic layer, dry over anhydrous Na_2SO_4 and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with DCM to obtain the desired intermediate as a white solid (0.4 g, 89%). MS (ES+) *m/z*: 203 $(M+H)^+$.

4-Aminometyl-*N-tert*-butyl-benzamide: Combine *N-tert*-butyl-4-cyano-benzamide (0.4 g, 1.78 mmol), Raney® 3201 nickel (slurry in water, 0.03 g), 2N ammonia in methanol (20 mL) and hydrogenate at 50 psi for 1 h. Filter the reaction mixture through a pad of Celite®, remove the solvent and purify by SCX chromatography to obtain the title compound as a colorless oil (0.4 g, 95%). MS (ES+) *m/z*: 207 $(M+H)^+$.

Preparation 75

4-Aminometyl-2-fluoro-*N-tert*-butyl-benzamide



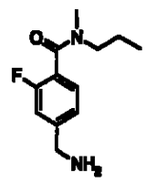
4-Bromo-*N*-*tert*-butyl-2-fluoro-benzamide: Combine 4-bromo-2-fluoro-benzoic acid (5.0 g, 22.83 mmol), thionyl chloride (10 mL, 0.137 mol) in toluene (10 mL) and reflux for 2 h. Evaporate the reaction mixture to obtain 4-bromo-2-fluoro-benzoyl chloride (5.0 g, 93%) and use for the next step without further purification. Dissolve *tert*-butylamine (0.8 mL, 5.12 mmol) and triethylamine (0.8 mL, 6.32 mmol) in anhydrous DCM (20 mL), cool to 0°C and add a solution of 4-bromo-2-fluoro-benzoyl chloride (1.0 g, 4.22 mmol) in anhydrous DCM (10 mL). Stir the reaction mixture at 0°C for 10 min, warm to ambient temperature and continue to stir for 30 min. Wash the reaction mixture with brine (2 x 10 mL), dry the organic extracts over anhydrous Na_2SO_4, evaporate the solvent and purify by chromatography on silica gel eluting with DCM to obtain the desired intermediate as a white solid (1.0 g, 87%). MS (ES+) *m/z*: 275 $(M+H)^+$.

N-*tert*-Butyl-4-cyano-2-fluoro-benzamide: Combine 4-bromo-*N*-*tert*-butyl-2-fluoro-benzamide (1.0 g, 3.65 mmol) and copper(I) cyanide (0.7 g, 7.29 mmol) in anhydrous DMF (10 mL) and reflux for 17 h. Cool the reaction mixture to ambient temperature and treat with 50% (v/v) aqueous ethylenediamine (20 mL). Extract the reaction mixture with diethyl ether (3 x 10 mL), combine the organic extracts, wash with brine (2 x 10 mL) and dry the organic layer over Na_2SO_4. Evaporate the solvent and purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 9:1, 4:1, 7:3 and 3:2) to obtain the desired intermediate as a white solid (0.6 g, 77%). MS (ES+) *m/z*: 221 $(M+H)^+$.

4-Aminomethyl-2-fluoro-*N*-*tert*-butyl-benzamide: Combine *N*-*tert*-butyl-4-cyano-2-fluoro-benzamide (0.6 g, 1.78 mmol), Raney® 3201 nickel (slurry in water, 30 mg), 2N ammonia in methanol (30 mL) and hydrogenate at 50 psi for 1 h. Filter the reaction mixture through a pad of Celite®, concentrate *in vacuo* and purify by SCX chromatography to obtain the title compound as a colorless oil (0.6 g, 96%).

Preparation 76

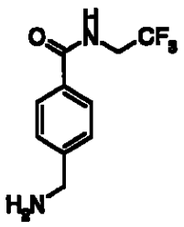
4-Aminomethyl-2-fluoro-*N*-methyl-*N*-propyl-benzamide



Use a method similar to Preparation 75, using 4-bromo-2-fluoro-benzoic acid (1.0 g, 4.56 mmol) and *N*-methyl-propylamine (0.5 mL, 5.05 mmol), to give the title compound as a colorless oil (0.5 g, 49%). GC-MS *m/z*: 224 (M^+).

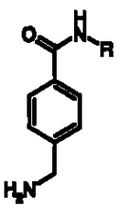
Preparation 77

4-Aminomethyl-*N*-(2,2,2-trifluoro-ethyl)-benzamide

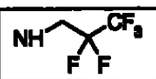
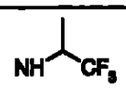
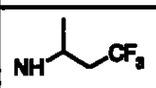
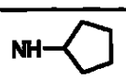
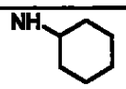
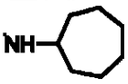
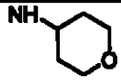
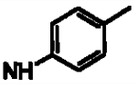
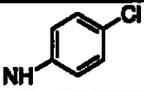
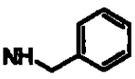
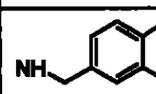
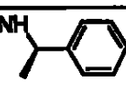
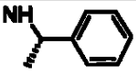
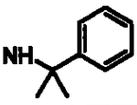


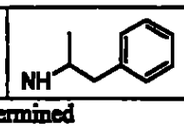
Use the General Procedure 6-1, using 2,2,2-trifluoroethylamine (197 mg, 2 mmol) and 4-(*tert*-butoxycabonylamino-methyl)-benzoic acid, to give the title compound as a clear oil (440 mg, 94%). MS (ES+) *m/z*: 233 $(M+H)^+$.

The compounds of Preparations 78-93 may be prepared essentially as described in Preparation 77 by using 4-(*tert*-butoxycabonylamino-methyl)-benzoic acid and the appropriate amine. Overall yields and MS (ES) data are shown in the Table below.



Preparation	NH-R	Compound	Yield (%)	MS (ES) *m/z*

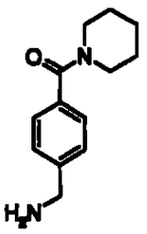
78		4-Aminomethyl-*N*-(2,2,3,3,3-pentafluoro-propyl)-benzamide	100	283 $(M+H)^+$
79		(±)-4-Aminomethyl-*N*-(2,2,2-trifluoro-1-methyl-ethyl)-benzamide	78	247 $(M+H)^+$
80		4-Aminomethyl-*N*-(3,3,3-trifluoro-propyl)-benzamide	100	247 $(M+H)^+$
81		(±)-4-Aminomethyl-*N*-(3,3,3-trifluoro-1-methyl-propyl)-benzamide	100	261 $(M+H)^+$
82		4-Aminomethyl-*N*-(cyclopentyl)-benzamide	100	219 $(M+H)^+$
Preparation	**NH-R**	**Compound**	**Yield (%)**	**MS (ES) *m/z***
83		4-Aminomethyl-*N*-(cycloheryl)-benzamide	100	233 $(M+H)^+$
84		4-Aminomethyl-*N*-(cycloheptyl)-benzamide	80	247 $(M+H)^+$
85		4-Aminomethyl-*N*-(tetrahydro-pyran-4-yl)-benzamide	56	ND
86		4-Aminomethyl-*N*-(4-methyl-phenyl)-benzamide	100	239 $(M-H)^-$
87		4-Aminomethyl-*N*-(4-chloro-phenyl)-benzamide	84	259 $(M-H)^-$
88		4-Aminomethyl-*N*-benzyl-benzamide	59	241 $(M+H)^+$
89		4-Aminomethyl-*N*-(3,4-difluoro-phenyl)-benzamide	100	ND
90		(*R*)-4-Aminomethyl-*N*-(1-phenyl-ethyl)-benzamide	94	255 $(M+H)^+$
91		(*S*)-4-Aminomethyl-*N*-(1-phenyl-ethyl)-benzamide	94	255 $(M+H)^+$
92		4-Aminomethyl-*N*-(1-methyl-1-phenyl-ethyl)-benzamide	22	269 $(M+H)^+$

93		(±)-4-Aminomethyl-*N*-(1-methyl-2-phenyl-ethyl)-benzamide	85	269 $(M+H)^+$

ND = Not determined

Preparation 94

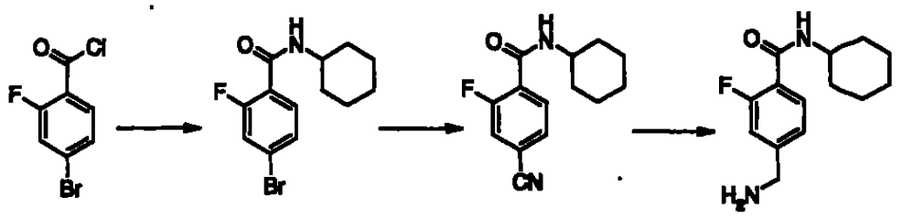
4-(Piperidin-1-ylcarbonyl)-benzylamine



Use the General Procedure 6-1, using piperidine (373 mg, 4.4 mmol) and 4-(*tert*-butoxycabonylamino-methyl)-benzoic acid to give the title compound as a white solid (1.03 g, 100%). MS (ES+) *m/z*: 219 $(M+H)^+$.

Preparation 95

4-Aminomethyl-*N*-cyclohexyl-2-fluoro-benzamide



4-Bromo-*N*-cyclohexyl-2-fluoro-benzamide: Dissolve 4-bromo-2-fluoro-benzoyl chloride (1 g, 4.21 mmol) in DCM and cool the solution in an ice bath. Add triethylamine (0.87 mL, 6.32 mmol) and cyclohexylamine (502 mg, 5.1 mmol) and stir the mixture at ambient temperature for 2 h. Partition the reaction mixture between brine and DCM. Dry the organic layer over Na_2SO_4, filter and concentrate *in vacuo* to give the desired intermediate as a white solid (1.24 g, 98%).

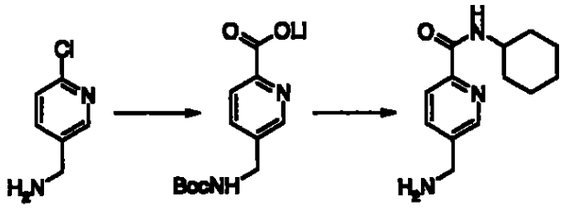
4-Cyano-*N*-cyclohexyl-2-fluoro-benzamide: Heat a mixture of 4-bromo-*N*-cyclohexyl-2-fluoro-benzamide (1.24 g, 4.13 mmol) and copper cyanide (740 mg, 8.26 mmol) in

DMF (20 mL) to reflux for 16 h. Cool the mixture to ambient temperature, add aqueous ethylenediamine and stir for 30 min. Extract the mixture with hexane/EtOAc (1:1), dry the organic layer over Na_2SO_4, filter and concentrate *in vacuo*. Purify the residue by chromatography on silica gel eluting with hexane/EtOAc (5:1) to give the desired intermediate as a white solid (620 mg, 61%). MS (ES-) *m/z*: 245 $(M-H)^-$.

4-Aminomethyl-*N*-cyclohexyl-2-fluoro-benzamide: Dissolve 4-cyano-*N*-cyclohexyl-2-fluoro-benzamide (620 mg, 2.5 mmol) in 7*N* ammonia in methanol (150 mL) and hydrogenate at 500 psi pressure in the presence of Raney® nickel (500 mg) for 16 h at 60°C. Filter the mixture and concentrate *in vacuo*. Purify by SCX chromatography to give the title compound as a white solid (600 mg, 94%). MS (ES-) *m/z*: 251 $(M-H)^-$.

Preparation 96

5-(Aminomethyl)-pyridine-2-carboxylic acid cyclohexylamide



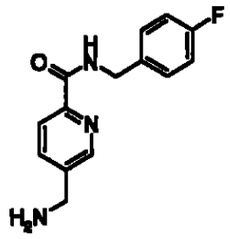
Lithium 5-(*tert*-butoxycarbonylamino-methyl)-pyridine-2-carboxylate: Dissolve 5-aminomethyl-2-chloro-pyridine (2 g, 14 mmol) and di-*tert*-butyl-dicarbonate (3.37 g, 15.4 mmol) in DCM (30 mL) and stir at room temperature for 2 h. Concentrate the reaction mixture and purify by chromatography on silica gel eluting with hexane/EtOAc (10:1 and 5:1) to give 5-(*tert*-butoxycarbonylamino-methyl)-2-chloro-pyridine as a yellow solid (3.6 g, 100%). MS (ES+) *m/z*: 243 $(M+H)^+$. Dissolve 5-(*tert*-butoxycarbonylamino-methyl)-2-chloro-pyridine (1 g, 4.12 mmol) in a mixture of ethanol (15 mL) and DMF (5 mL), and add potassium carbonate (427 mg, 3.09 mmol), palladium(II) acetate (92 mg, 0.4 mmol) and diphenylphosphinoferrocene (240 mg, 0.44 mmol). Pressurize the mixture to 15 psi with carbon monoxide gas and heat the reaction mixture to 90°C for 16 h. Filter the reaction mixture, concentrate the filtrate, and partition the residue between water and hexane/EtOAc (1:1). Dry the organic layer over Na_2SO_4, filter, and concentrate *in vacuo*. Purify the residue by chromatography on silica gel eluting with hexane/EtOAc (3:2) to

give 5-(*tert*-butoxycarbonylamino-methyl)-pyridine-2-carboxylic acid ethyl ester as a brown oil (920 mg, 80%). MS (ES+) *m/z*: 281 $(M+H)^+$. Dissolve 5-(*tert*-butoxycarbonylamino-methyl)-pyridine-2-carboxylic acid ethyl ester (920 mg, 3.28 mmol) in a mixture of water/THF (1:2, 15 mL) and add lithium hydroxide (87 mg, 3.61 mmol). Stir the mixture at ambient temperature for 4 h and concentrate to a solid. Dry the material by azeotrope distillation with toluene to give the desired intermediate as a brown solid (1 g, 100%). MS (ES+) *m/z*: 253 $(M+H)^+$.

5-(Aminomethyl)-pyridine-2-carboxylic acid cyclohexylamide: Use the General Procedure 6-2, using cyclohexylamine (1 mL), lithium 5-(*tert*-butoxycarbonylamino-methyl)-pyridine-2-carboxylate (1 g, 3.96 mmol) and DIEA (5 mL) as cosolvent, to give the title compound as a white solid (200 mg, 22%). MS (ES+) *m/z*: 234 $(M+H)^+$.

Preparation 97

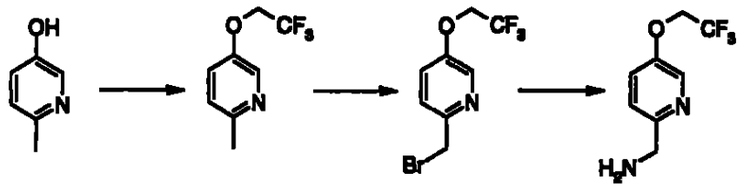
5-(Aminomethyl)-pyridine-2-carboxylic acid 4-fluoro-benzylamide



Use the General Procedure 6-2, using 4-fluoro-benzylamine (551 mg, 4.4 mmol), lithium 5-(*tert*-butoxycarbonylamino-methyl)-pyridine-2-carboxylate (740 mg, 2.93 mmol) and DIEA (2.6 mL) as cosolvent, to give the title compound as a white solid (200 mg, 26%). MS (ES+) *m/z*: 260 $(M+H)^+$.

Preparation 98

2-Aminomethyl-5-(2,2,2-trifluoroethoxy)-pyridine



2-Methyl-5-(2,2,2-trifluoroethoxy)-pyridine: Add 5-hydroxy-2-methyl-pyridine (3.3 g, 30.6 mmol), potassium carbonate (17 g, 122.4 mmol) and 2-bromo-1,1,1-trifluoroethane (10 g, 61.2 mmol) to a flask containing DMF (60 mL) and heat to 95°C for 20 h. Cool the mixture, dilute with aqueous 10% NaCl (20 mL) and extract with hexane/EtOAc (1:1, 100 mL). Filter the bi-phasic mixture through Celite®, separate and wash the organic layer with aqueous 10% NaCl (3 x 50 mL) and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1 to 1:1) to obtain the desired intermediate (4.1 g, 70%).

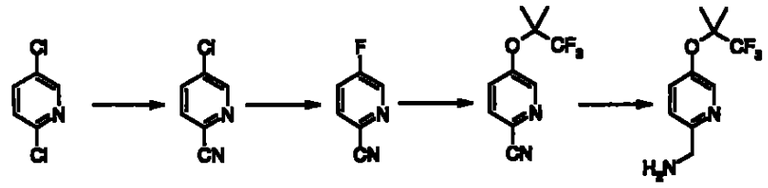
2-Bromomethyl-5-(2,2,2-trifluoroethoxy)-pyridine: Add 2-methyl-5-(2,2,2-trifluoroethoxy)-pyridine (2.5 g, 13.1 mmol), NBS (2.3 g, 13.1 mmol) and benzoyl peroxide (50 mg) to a flask containing carbon tetrachloride (30 mL). Heat the mixture at 80°C in a sealed flask for 16 h. Cool the flask, add NBS (1.1 g, 6.5 mmol) and benzoyl peroxide (100 mg), then continue heating at 80°C for an additional 5 h. Cool the mixture, dilute with DCM, then wash with saturated sodium bisulfite (10 mL). Collect the organic layer and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to obtain the desired intermediate (460 mg, 13%).

2-Aminomethyl-5-(2,2,2-trifluoroethoxy)-pyridine: Dissolve sodium azide (270 mg, 4.0 mmol) in DMF (30 mL). Cool the solution to 0°C, then add 2-bromomethyl-5-(2,2,2-trifluoroethoxy)-pyridine (440 mg, 1.6 mmol) at 0°C. Slowly heat the mixture from 0°C to 80°C over 30 min. Cool the reaction, dilute with EtOAc (100 mL) and wash with 10% aqueous NaCl (3 x 25 mL). Collect the organic layer and concentrate *in vacuo* to a volume of 50 mL. Transfer the solution to a pressure vessel. Add 10 % Pd/C (Degussa

type E101, 50% water by wt, 500 mg) and pressurize the vessel under hydrogen (10 psi) for 1 h with stirring. Filter the mixture through Celite® and wash filter cake with warm methanol followed by DCM. Concentrate *in vacuo*, then purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (20:1) to obtain the title compound (180 mg, 54%). MS (ES+) *m/z*: 207 $(M+H)^+$.

Preparation 99

2-Aminomethyl-5-(2,2,2-trifluoro-1,1-dimethyl-ethoxy)-pyridine



5-Chloro-pyridine-2-carbonitrile: Add 2,5-dichloropyridine (6.0 g, 40.5 mmol), zinc cyanide (2.9 g, 24.7 mmol), zinc dust (116 mg, 1.8 mmol) and 1,1'-[bis(diphenylphosphino)ferrocene]dichloropalladium(II) (20 mg, 0.98 mmol) to a flask containing DMF (40 mL). Heat the mixture to reflux for 5 h, then cool to ambient temperature. Dilute the mixture with EtOAc (300 mL) and wash with 10% aqueous NaCl (3x75 mL). Collect the organic layer, concentrate *in vacuo* and purify by chromatography on silica gel eluting with hexane/EtOAc (9:1 to 1:1) to obtain the desired intermediate (2.6 g, 46%).

5-Fluoro-pyridine-2-carbonitrile: Add 5-chloro-pyridine-2-carbonitrile (3.0 g, 21.7 mmol) and potassium fluoride (3.9 g, 67.1 mmol) to a flask containing NMP (75 mL). Heat the mixture to reflux for 16 h. Add additional potassium fluoride (1.0 g, 17.2 mmol) and NMP (10 mL), then continue heating at reflux for 3 h. Cool the mixture, dilute with EtOAc, then wash with saturated NaCl (3 x 50 mL). Collect the organic layer, concentrate *in vacuo* and purify by chromatography on silica gel eluting with hexane/EtOAc (20:1) to obtain the desired intermediate (1.5 g, 53%).

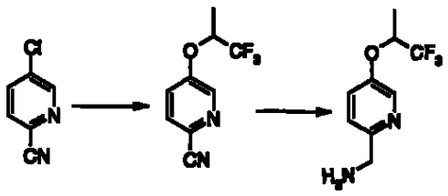
5-(2,2,2-Trifluoro-1,1-dimethyl-ethoxy)-pyridine-2-carbonitrile: Add 2-trifluoromethyl-2-propanol (1.1 g, 8.3 mmol) slowly to a slurry of sodium hydride (202

mg, 60% mineral oil, washed with hexane) in HMPA (3 mL) under nitrogen. Stir the slurry for 15 min, then add 5-fluoro-pyridine-2-carbonitrile (510 mg, 4.2 mmol). Stir the slurry for 16 h at ambient temperature. Adjust the mixture to pH 9 with sodium carbonate then extract with diethyl ether (3 x 50 mL). Collect the organic layer, dry over Na_2SO_4 and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (95/5 to 80/20) to obtain the desired intermediate (768 mg, 79%). GC-MS *m/z*: 230 (M^+).

2-Aminomethyl-5-(2,2,2-trifluoro-1,1-dimethyl-ethoxy)-pyridine: Add 5-(2,2,2-trifluoro-1,1-dimethyl-ethoxy)-pyridine-2-carbonitrile (580 mg, 2.5 mmol), 10 % Pd/C (Degussa type E101, 50% water by wt, 400 mg) and trifluoroacetic acid (2 mL) in ethanol (20 mL) to a pressure vessel. Pressurize the vessel to 50 psi with hydrogen for 1 h. Filter the mixture through Celite® and wash the cake with warm ethanol followed by DCM under a nitrogen atmosphere. Concentrate *in vacuo* to obtain the crude product as the trifluoroacetic acid salt. Prepare the free base with SCX chromatography, then purify using silica gel chromatography eluting with DCM/2M ammonia in methanol (20:1) to obtain the title compound (261 mg, 45%). MS (ES+) *m/z*: 235 $(M+H)^+$.

Preparation 100

(±)-2-Aminomethyl-5-(2,2,2-trifluoro-1-methyl-ethoxy)-pyridine



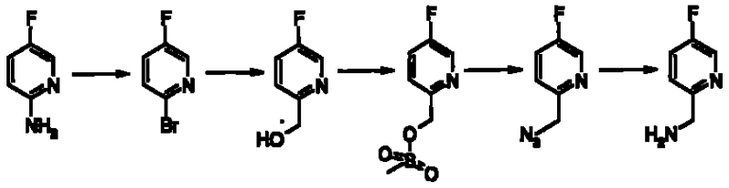
(±)-5-(2,2,2-Trifluoro-1-methyl-ethoxy)-pyridine-2-carbonitrile: Add 1,1,1-trifluoro-2-propanol (971 mg, 8.5 mmol) slowly to a slurry of sodium hydride (205 mg, 60% mineral oil, washed with hexane) in HMPA (8 mL) under nitrogen at 0°C. Allow the slurry to warm to ambient temperature and stir for 5 min. Add 5-chloro-pyridine-2-carbonitrile (590 mg, 4.2 mmol), then heat the mixture at 90°C for 4 h. Adjust the mixture to pH 9 with sodium carbonate then extract with diethyl ether (2 x 50 mL). Dry the combined organic extracts over Na_2SO_4 and concentrate *in vacuo*. Purify by

chromatography on silica gel eluting with hexane/EtOAc (95/5 to 80/20) to obtain the desired intermediate (818 mg, 89%). GC-MS *m/z*: 216(M^+).

(±)-2-Aminomethyl-5-(2,2,2-trifluoro-1-methyl-ethoxy)-pyridine: Add (±)-5-(2,2,2-trifluoro-1-methyl-ethoxy)-pyridine-2-carbonitrile (810 mg, 3.7 mmol), 10 % Pd/C (Degussa type E101, 50% water by wt, 300 mg), and trifluoroacetic acid (4 mL) in methanol (50 mL) to a pressure vessel. Pressurize the vessel to 40 psi with hydrogen for 0.25 h. Filter the mixture through Celite® and wash the cake with warm ethanol followed by DCM under a nitrogen atmosphere. Concentrate *in vacuo* to obtain the crude product as a trifluoroacetic acid salt. Prepare the free base with SCX ion chromatography, then purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (20:1) to obtain the title compound (676 mg, 82%). GC-MS *m/z*: 220 (M^+).

Preparation 101

2-Aminomethyl-5-fluoro-pyridine



2-Bromo-5-fluoro-pyridine: Cool 48% hydrobromic acid (44 mL, 4.4 equiv.) in an ice/acetone bath to –5°C, then add 2-amino-5-fluoropyridine (10.0 g, 89.2 mmol, 1.0 equiv.) portion wise over 10 min and maintain the temperature below 5°C throughout addition. Add bromine (14 mL, 3 equiv.) at 0°C over 2 h and maintain the temperature at 0°C throughout the addition. Stir the mixture for 30 min, then add a solution of sodium nitrite (15.4 g) in water (30 mL) via addition funnel over 2 h and maintain the temperature below 0°C throughout the addition. Stir the mixture for 30 min., then add a solution of NaOH (34 g) in water (34 mL) over 1 h and maintain the temperature below 10°C. Stir the mixture for 3 min. Extract with diethyl ether (5 x 250 mL), dry the combined organic extracts over Na_2SO_4 and concentrate *in vacuo* to give the desired intermediate (12.1 g, 77%).

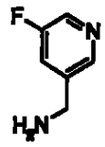
(5-Fluoro-pyridin-2-yl)-methanol: At –78°C under nitrogen, add *n*-butyllithium (2.5 M in hexane, 16.4 mL, 40.9 mmol) via syringe to a solution of 2-bromo-5-fluoro-pyridine (6.0 g, 34.1 mmol) in toluene (220 mL), while keeping the reaction temperature below –60°C. Stir the mixture at –78°C and then add DMF (3.4 mL, 44.3 mmol) and stir for 1 h at this temperature. Warm to –10°C and quench with methanol (10 mL). Concentrate the mixture to half of the volume *in vacuo*. Dilute with methanol (150 mL), cool the mixture to –78°C and add sodium borohydride (3.2 g, 85.2 mmol) portion wise over 5 min. Warm the mixture to ambient temperature and stir for 2 h. Quench with water (10 mL) and remove the organic solvent *in vacuo* to obtain an oil/water mixture. Extract with diethyl ether (3 x 100 mL), dry the combined organic extracts, wash with brine, dry and concentrate *in vacuo* to obtain the desired intermediate as an oil (3.9 g, 91%).

Methanesulfonic acid (5-fluoro-pyridin-2-yl)methyl ester: Add methanesulfonyl chloride (1.8 mL, 23.5 mmol) to a solution of (5-fluoro-pyridin-2-yl)-methanol (2.5 g, 19.7 mmol) and triethylamine (8.2 mL, 59.0 mmol) in DCM (150 mL) at 0°C under nitrogen. Stir the mixture for 30 min and concentrate *in vacuo*. Dilute with water (20 mL) and extract the mixture with EtOAc (3 x 50 mL). Combine the organic extracts and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc to obtain the desired intermediate (2.2 g, 54%).

2-Aminomethyl-5-fluoro-pyridine: Dissolve methanesulfonic acid (5-fluoro-pyridin-2-yl)-methyl ester (1.5 g, 7.3 mmol) in DMF (5mL) and add sodium azide (950 mg, 14.6 mmol). Stir the mixture for 30 min, then dilute with hexane/EtOAc (1:1, 50 mL). Wash the mixture with 10% aqueous NaCl (3 x 10 mL). Dry the combined organic extracts over Na_2SO_4 and remove half of the solvent *in vacuo*. Add EtOAc (20 mL) and a suspension of 10% Pd/C (200 mg) in EtOAc (2 mL). Stir the mixture for 1 h at ambient temperature in a pressurized vessel under 50 psi of hydrogen. Filter the slurry through Celite® and concentrate *in vacuo* to obtain 2-aminomethyl-5-fluoro-pyridine (613 mg, 60% yield, 80% purity by GC/MS). GC-MS *m/z*: 126 (M^+).

Preparation 102

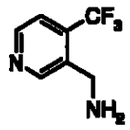
3-Aminomethyl-5-fluoro-pyridine



In a Parr Bottle add 2,6-dichloro-3-cyano-5-fluoropyridine (20 g, 0.105 mol), ethanol (336 mL), triethylamine (24 mL), and 5% Pd/C (4 g). Place on a Parr Shaker Apparatus under 60 psi hydrogen for 1 h at ambient temperature. Filter the reaction mixture and bubble ammonia gas into filtrate for 10 min. Add Raney® nickel (5.2 g) and place on a Parr Shaker Apparatus under 500 psi hydrogen for 18 h at 60-70°C. Filter the reaction mixture and concentrate *in vacuo*. Dissolve in methanol and add 1N hydrogen chloride in ether until form a precipitate. Cool in an ice bath, filter off the precipitate, wash the solid several times with ether, and dry to give the title compound as the hydrochloride salt (12 g, 70%). MS (ES+) *m/z*: 127 $(M+H)^+$. Dissolve the hydrochloride salt in water, add 0.1 N aqueous NaOH to adjust to pH 10, extract with DCM, dry the organic layer over Na_2SO_4, filter and concentrate to give the title compound.

Preparation 103

3-Aminomethyl-4-trifluoromethyl-pyridine

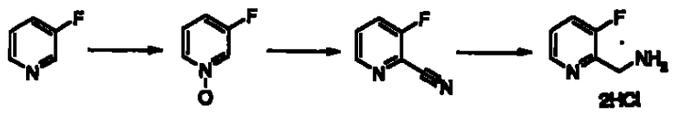


Add 4-trifluoromethyl-nicotinonitrile (1.0 g, 5.8 mmol) and ethanol wet Raney® activated nickel (0.2 g) to a Parr pressure vessel. Immediately add, at ambient temperature, 2B-ethanol (25 mL) previously saturated with ammonia gas and seal the vessel. Purge the reaction vessel with nitrogen, pressurize the reaction mixture with hydrogen (400 KPa), seal the vessel, agitate the reaction and heat to 40°C. Continue the reaction for 20 h then turn off the heat and allow the reaction mixture to cool to ambient temperature. Vent the excess hydrogen from the vessel and purge the vessel with nitrogen. Filter the reaction mixture to remove the Raney® nickel, wash with ethanol and

concentrate *in vacuo*. Purify by SCX chromatography to give the title compound (560 mg, 55%). MS (ES+) *m/z*: 177 $(M+H)^+$.

Preparation 104

2-Aminomethyl-6-fluoropyridine Dihydrochloride



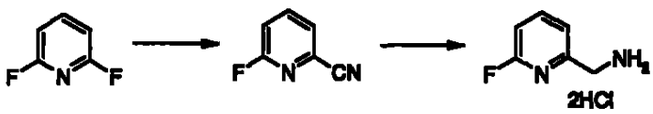
3-Fluoropyridine-*N*-Oxide: Dissolve 3-fluoropyridine (2.5 g, 25.749 mmol) in anhydrous DCM (75 mL). Add *m*-CPBA (70% suspension, 12.696 g, 51.499 mmol) and stir at ambient temperature overnight. Wash the reaction mixture with saturated aqueous $NaHCO_3$, dry the organic phase over Na_2SO_4, filter, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with DCM and DCM/methanol (97:3) to obtain the desired intermediate as a solid (1.413 g, 49%). MS (ES+) *m/z*: 115 $(M+H)^+$.

2-Cyano-3-fluoropyridine: Dissolve 3-fluoropyridine-*N*-oxide (1.0 g, 8.687 mmol) in anhydrous acetonitrile (100 mL). Add triethylamine (1.319 g, 1.82 mL, 13.031 mmol), trimethylsilylcyanide (3.447 g, 4.63 mL, 34.749 mmol) and heat the mixture to reflux overnight. Cool to ambient temperature and concentrate *in vacuo*. Dissolve the residue in EtOAc and wash with saturated aqueous $NaHCO_3$. Dry the organic layer over Na_2SO_4, filter, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0 and 17:3) to give the desired intermediate as a solid (746 mg, 70%). GC-MS *m/z*: 122 (M^+).

2-Aminomethyl-3-fluoropyridine dihydrochloride: Dissolve 2-cyano-3-fluoropyridine (300 mg, 2.457 mmol) in absolute ethanol (12 mL). Add 10% Pd/C (93 mg) and concentrated HCl (0.614 mL, 7.37 mmol). Hydrogenate at 40 psi overnight. Filter through Celite® and concentrate *in vacuo* to give the title compound as a solid (440 mg, 90%). MS (ES+) *m/z*: 127 $(M+H)^+$.

Preparation 105

2-Aminomethyl-6-fluoropyridine Dihydrochloride

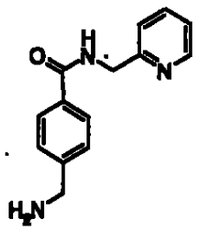


2-Cyano-6-fluoropyridine: Dissolve 2,6-difluoropyridine (12 g, 104.2 mmol) in anhydrous DMSO (5 mL). Add a solution of sodium cyanide (1.3 g, 26.53 mmol) in DMSO (60 mL) over 12 h using a syringe pump. Heat the mixture to 100°C overnight. Cool to ambient temperature, dilute with EtOAc (500 mL), and wash with brine. Dry the organic phase over Na_2SO_4, filter, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0 and 4:1) to give the desired intermediate as a solid (723 mg, 22%). GC-MS *m/z*: 122 (M^+).

2-Aminomethyl-6-fluoropyridine Dihydrochloride: Dissolve 2-cyano-6-fluoropyridine (300 mg, 2.46 mmol) in absolute ethanol (12 mL). Add 10% Pd/C (93 mg) and concentrated HCl (0.614 mL, 7.37 mmol). Hydrogenate at 40 psi overnight. Filter through Celite® and concentrate to give the title compound as a solid (356 mg, 73%). MS (ES+) *m/z*: 127 $(M+H)^+$.

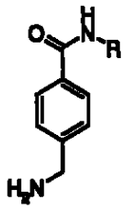
Preparation 106

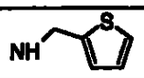
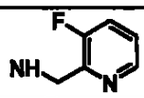
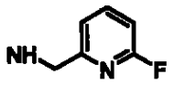
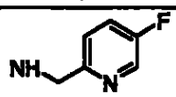
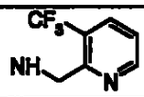
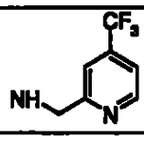
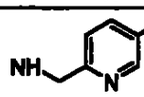
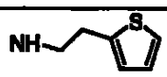
4-Aminomethyl-*N*-(pyridin-2-yl-methyl)-benzamide

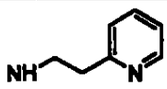
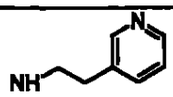
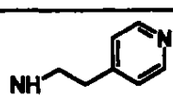


Use the General Procedure 6-2, using 2-(aminomethyl)pyridine (181 mg, 0.172 mL, 1.67 mmol) and 4-(*tert*-butoxycarbonylamino-methyl)-benzoic acid (420 mg, 1.67 mmol) to give the title compound as a solid (427 mg, 100 %). MS (ES+) *m/z*: 242 $(M+H)^+$.

The compounds of Preparations 107-117 may be prepared essentially as described in Preparation 106 by using 4-(*tert*-butoxycarbonylamino-methyl)-benzoic acid and the appropriate amine. Overall yields and MS (ES+) data are shown in the Table below.

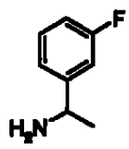


Prep.	NHR	Compound	Yield (%)	MS (ES+) or GC-MS
107		4-Aminomethyl-*N*-(thiophen-2-yl-methyl)-benzamide	100	247 $(M+H)^+$
108		4-Aminomethyl-*N*-(3-fluoro-pyridin-2-ylmethyl)-benzamide	58	259 $(M)^+$
109		4-Aminomethyl-*N*-(6-fluoro-pyridin-2-ylmethyl)-benzamide	98	259 $(M)^+$
110		4-Aminomethyl-*N*-(5-fluoro-pyridin-2-ylmethyl)-benzamide	67	259 $(M)^+$
111		4-Aminomethyl-*N*-(3-trifluoromethyl-pyridin-2-ylmethyl)-benzamide	62	310 $(M+H)^+$
112		4-Aminomethyl-*N*-(4-trifluoromethyl-pyridin-2-ylmethyl)-benzamide	76	309 $(M)^+$
113		4-Aminomethyl-*N*-(5-trifluoromethyl-pyridin-2-ylmethyl)-benzamide	65	310 $(M+H)^+$
114		4-Aminomethyl-*N*-(2-thiophen-2-yl-ethyl)-benzamide	100	261 $(M+H)^+$

Prep.	NHR	Compound	Yield (%)	MS (ES+) or GC-MS
115		4-Aminomethyl-*N*-(2-pyridin-2-yl-ethyl)-benzamide	81	256 $(M+H)^+$
116		4-Aminomethyl-*N*-(2-pyridin-3-yl-ethyl)-benzamide	97	256 $(M+H)^+$
117		4-Aminomethyl-*N*-(2-pyridin-4-yl-ethyl)-benzamide	96	256 $(M+H)^+$

Preparation 118

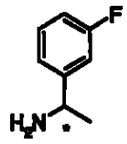
(±)-1-(3-Fluorophenyl)ethylamine



Add sodium cyanoborohydride (452 mg, 7.2 mmol) to a solution of 3-fluoroacetophenone (500 mg, 3.6 mmol) and ammonium acetate (2.8 g, 36 mmol) in methanol (11 mL). Stir the mixture for 96 h at ambient temperature under a nitrogen atmosphere. Adjust to pH 2 with 2M hydrogen chloride in diethyl ether. Concentrate the slurry *in vacuo*, dilute the residue with DCM and wash with 5N aqueous NaOH followed by saturated aqueous $NaHCO_3$. Dry the organic layer, concentrate *in vacuo* to half of the volume, and load the solution onto a SCX column (pre-wash column with methanol followed by DCM, then elute with 2M ammonia in methanol). Concentrate the fractions to half of the volume to remove ammonia, add excess of 2M hydrogen chloride in diethyl ether and concentrate to obtain the hydrochloride salt (70:30 mixture of title compound and dimer). Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (20:1) to obtain the title compound (323 mg, 51%). MS (ES+) *m/z*: 140 $(M+H)^+$

Preparation 119

1-(3-Fluorophenyl)ethylamine, Isomer 2



Set-up flask equipped with condenser, mechanical stirrer and addition funnel. Add 3-fluoroacetophenone (25 g, 0.18 mol) and formic acid (4.2 g, 0.09 mol) via addition funnel to a flask containing formamide (32.6 g, 0.72 mol) at 140°C over 15 min, and then heat the mixture to 160°C. Add formic acid successively (4.2 g, 0.5 equiv.) via addition funnel to the flask every hour for 4 h while maintaining the reaction temperature at 160°C. Cool the reaction mixture, extract with toluene (3 x 100 mL), and concentrate the organic layer *in vacuo*. Add aqueous HCl (37%, 40 mL) to the residue and heat to reflux for 2 h. Cool to ambient temperature and wash the aqueous mixture with toluene (2 x 100 mL), then basify the aqueous mixture with 5N aqueous NaOH (120 mL). Extract the basic mixture with EtOAc (3 x 100 mL), dry the combined organic extracts over Na_2SO_4 and filter. Acidify the filtrate with 2M hydrogen chloride in diethyl ether to pH 2 and concentrate *in vacuo* to a solid. Suspend the solid in diethyl ether, filter and wash with diethyl ether. Dry the solid in a vacuo-oven at 50°C to obtain (±)-1-(3-fluorophenyl)ethylamine hydrochloride (21.5 g, 68%). MS (ES+) *m/z*: 140 $(M+H)^+$.

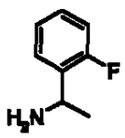
Dissolve (±)-1-(3-fluorophenyl)ethylamine hydrochloride (42.5 g, 0.24 mol) in THF (520 mL) and saturated aqueous $NaHCO_3$ (430 mL). Add di-*tert*-butyl-dicarbonate (69 g, 0.31 mol) and stir for 16 h at ambient temperature. Separate the organic layer, dilute with EtOAc (300 mL) and wash with 2N aqueous NaOH (1 x 400 mL) and water (2 x 200 mL). Concentrate the organic layer *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to obtain (±)-*N*-[1-(3-fluorophenyl)ethyl]-carbamic acid *tert*-butyl ester (56 g, 97%). GC-MS *m/z*: 183 $[(M-C_4H_9)^+]$.

Separate the racemic mixture of (±)-*N*-[1-(3-fluorophenyl)ethyl]-carbamic acid *tert*-butyl ester by normal phase chiral chromatography (Chiralcel OD 8 x 34 cm, elute with 95:5, heptane/isopropanol). Using the General Procedure 1-4, deprotect the desired

isomer [20.7 g, >95% ee (Chiralcel OD, 4.6 x 250 mm, eluent: 95:5 heptane/isopropanol with 0.2% DMEA, 1.0 mL/min)] to obtain the title compound (9.4 g, 78%). MS (ES+) *m/z*: 140 $(M+H)^+$.

Preparation 120

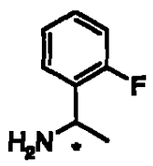
(±)-1-(2-Fluorophenyl)ethylamine



Add sodium cyanoborohydride (1.8 g, 29 mmol) to a solution of 2-fluoro-acetophenone (2.0 g, 14.5 mmol) and ammonium acetate (11.2 g, 145 mmol) in methanol (45 mL). Stir the mixture for 20 h at ambient temperature under a nitrogen atmosphere. Adjust the mixture to pH 1 with 2M hydrogen chloride in diethyl ether. Concentrate the slurry *in vacuo*, dilute the residue with DCM and wash with 5N aqueous NaOH. Dry the organic layer, concentrate carefully, as the amine is volatile, under reduced pressure to one third of the volume, and load the material onto an SCX column (pre-wash column with methanol, followed by DCM, elute with 2M ammonia in methanol). Concentrate the fraction to one half of the volume to remove the ammonia, then add excess 2M hydrogen chloride in diethyl ether and concentrate to obtain the hydrochloride salt. Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (20:1) to obtain the title compound (280 mg, 13%). MS (ES+) *m/z*: 140 $(M+H)^+$.

Preparation 121

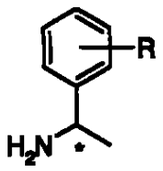
1-(2-Fluorophenyl)ethylamine, Isomer 1



Use a method similar to the General Procedure 6-3, using 2-fluoroacetophenone (1.4 g, 9.9 mmol) and (*R*)-(+)-2-methyl-2-propanesulfinamide (1.0 g, 8.2 mmol). Purify by chromatography on silica gel eluting with hexane/EtOAc/2M ammonia in methanol

(90:9:1 to 50:45:5). Add 4M hydrogen chloride in dioxane to obtain the title compound as the hydrochloride (600 mg, 35%). MS (ES+) *m/z*: 140 $(M+H)^+$. Dissolve the hydrochloride in an aqueous solution of cesium carbonate (1.5 equiv.) and extract with toluene to obtain the free base.

The compounds of Preparations 122-141 may be prepared essentially as described in Preparation 121 by using (*R*)-(+)-2-methyl-2-propanesulfinamide or (*S*)-(-)-2-methyl-2-propanesulfinamide and the appropriate acetophenone. Overall yields and mass spectrum data are shown in the Table below.



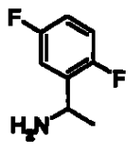
Prep.	R	Compound	Yield (%)	MS (ES+) or GC-MS
122	3-CN	1-(3-Cyanophenyl)ethylamine, Isomer 1	37	130 $(M+H-NH_3)^+$
123	3-CN	1-(3-Cyanophenyl)ethylamine, Isomer 2	49	130 $(M+H-NH_3)^+$
124	4-CN	1-(4-Cyanophenyl)ethylamine, Isomer 1	49	130 $(M+H-NH_3)^+$
125	4-CN	1-(4-Cyanophenyl)ethylamine, Isomer 2	49	130 $(M+H-NH_3)^+$
126	2-Cl	1-(2-Chlorophenyl)ethylamine, Isomer 1	25	156 $(M+H)^+$
127	3-Cl	1-(3-Chlorophenyl)ethylamine, Isomer 1	68	156 $(M+H)^+$
128	3-CF_3	1-(3-Trifluoromethylphenyl)-ethylamine, Isomer 1	40	190 $(M+H)^+$
129	4-CF_3	1-(4-Trifluoromethylphenyl)-ethylamine, Isomer 2	70	190 $(M+H)^+$

Prep.	R	Compound	Yield (%)	MS (ES+) or GC-MS
130	3-Cl,4-F	1-(3-Chloro-4-fluorophenyl)-ethylamine, Isomer 1	66	174 $(M+H)^+$
131	3-Cl-4-F	1-(3-Chloro-4-fluorophenyl)-ethylamine, Isomer 2	68	174 $(M+H)^+$
132	2,3-diF	1-(2,3-Difluorophenyl)-ethylamine, Isomer 1	20	141 $(M+H-NH_3)^+$
133	2,3-diF	1-(2,3-Difluorophenyl)-ethylamine, Isomer 2	45	141 $(M+H-NH_3)^+$
134	2,4-diF	1-(2,4-Difluorophenyl)-ethylamine, Isomer 1	58	158 $(M+H)^+$
135	2,4-diF	1-(2,4-Difluorophenyl)-ethylamine, Isomer 2	49	158 $(M+H)^+$
136	3,5-diF	1-(3,5-Difluorophenyl)-ethylamine, Isomer 1	26	158 $(M+H)^+$
137	3,5-diF	1-(3,5-Difluorophenyl)-ethylamine, Isomer 2	83	158 $(M+H)^+$
138	3,4-diF	1-(3,4-Difluorophenyl)-ethylamine, Isomer 1	67	158 $(M+H)^+$
139	3,4-diF	1-(3,4-Difluorophenyl)-ethylamine, Isomer 2	77	158 $(M+H)^+$
140	3,4,5-triF	1-(3,4,5-Trifluorophenyl)-ethylamine, Isomer 2	20	176 $(M+H)^+$
141	3,5-diCF_3	1-(3,5-bis-trifluoromethylphenyl)-ethylamine, Isomer 2	49	258 $(M+H)^+$
142	2-OCF_3	1-(2-Trifluoromethoxyphenyl)-ethylamine, Isomer 2	47	ND
143	2-Me	1-(2-Methyl)-ethylamine, Isomer 1	13	136 (M^+)

ND = Not determined

Preparation 144

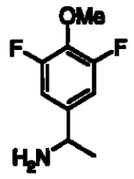
(±)-1-(2,5-Difluorophenyl)ethylamine



Slurry 2',5'-difluoroacetophenone (0.9 g, 5.76 mmol), ammonium acetate (4.44 g, 57.5 mmol) and sodium cyanoborohydride (755 mg, 12 mmol) in anhydrous methanol (25 mL) and stir for 18 h at ambient temperature. Acidify with 5N aqueous HCl (5 mL), dilute, extract with ethyl ether (3 x 150 mL), basify aqueous layer with 5N aqueous NaOH, extract with DCM (3 x 75 mL), wash the organic layer with brine, dry over $MgSO_4$, filter and concentrate *in vacuo*. Purify by SCX chromatography to give a mixture of (±)-1-(2,5-difluorophenyl)ethylamine and bis-[1-(±)-2,5-difluorophenyl)ethyl]-amine (total 400 mg, crude weight). MS (ES+) *m/z*: 158 $(M+H)^+$ and *m/z*: 298 $(M+H)^+$.

Preparation 145

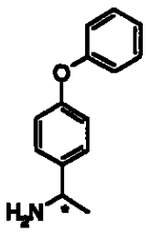
(±)-1-(3,5-Difluoro-4-methoxyphenyl)ethylamine



Slurry 3',5'-difluoro-4'-methoxyacetophenone (1.0 g, 5.0 mmol), ammonium acetate (4.14 g, 50 mmol) and sodium cyanoborohydride (630 mg, 20 mmol) in anhydrous methanol (35 mL) and stir for 18 h at ambient temperature. Acidify with 1N aqueous HCl (5 mL), dilute, extract with ethyl ether (3 x 150 mL), basify aqueous with 1N aqueous NaOH, extract with DCM (3 x 50 mL), wash the organic extracts with brine, dry over $MgSO_4$, filter and concentrate *in vacuo*. Purify by SCX chromatography to give crude the title compound as a yellow oil (380 mg).

Preparations 146 and 147

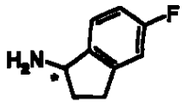
1-(4-Phenoxyphenyl)-ethylamine, Isomer 1 and Isomer 2



Mix 4-phenoxyacetophenone (5.3 g, 25 mmol), ammonium acetate (14.5 g, 187.5 mmol) and sodium cyanoborohydride (3.2 g, 50 mmol) in anhydrous methanol (200 mL). Stir for 18 h at ambient temperature. Acidify with 1N aqueous HCl (10 mL), dilute, extract with ethyl ether (3 x 150 mL), dry over $MgSO_4$, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting sequentially with hexane/EtOAc (4:1, 1:1 and 0:1) and EtOAc/methanol (1:1) to give (±)-1-(4-phenoxyphenyl)-ethylamine (1.6 g, 30%). Dissolve the racemate (1.1 g, 5.2 mmol) in DCM (100 mL), add triethylamine (1.6mL, 11.4 mmol) followed by di-*tert*-butyl-dicarbonate (1.7 g, 7.8 mmol). Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to give (±)-α-methyl-(4'-phenoxy)-benzylamino]carbamic acid *tert*-butyl ester as an off-white solid (1.3 mg, 81%). Separate via chiral chromatography (heptane/isopropanol/DMEA 95:5:0.2, 4.6 x 250 mm Chiralpak AD, 1 mL/min, UV detector at 260 nm) to give [α-methyl-(4'-phenoxy)benzylamino]carbamic acid *tert*-butyl ester, isomer 1 (315 mg, chiral HPLC: t_R = 7.35 min; 99.1% ee) and [α-methyl-(4'-phenoxy)benzyl-aminocarbamic acid *tert*-butyl ester, isomer 2 (400 mg, chiral HPLC: t_R = 8.7 min; 97.2% ee). Dissolve [α-methyl-(4'-phenoxy)benzylamino]carbamic acid *tert*-butyl ester isomer 1 or isomer 2 in DCM/trifluoroacetic acid (1:1, 20 mL) to give, after solvent evaporation and chromatography over SCX column, 1-(4-phenoxyphenyl)-ethylamine, isomer 1 (Preparation 146) and 1-(4-phenoxyphenyl)-ethylamine, isomer 2 (Preparation 147). MS (ES+) *m/z*: 214 $(M+H)^+$.

Preparation 148

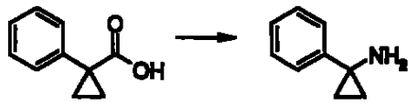
(5-Fluoro-indan-1-yl)amine, Isomer 1



Use a method similar to the General Procedure 6-3 to react 5-fluoro-indan-1-one (1.5 g, 9.9 mmol) and (*R*)-(+)-2-methyl-2-propanesulfinamide (1.0 g, 8.3 mmol). Purify by chromatography on silica gel eluting with hexane/EtOAc (5:2). Add 4M hydrogen chloride in dioxane to obtain the title compound as the hydrochloride (254 mg, 16%). MS (ES+) *m/z*: 152 $(M+H)^+$. Dissolve the hydrochloride in an aqueous solution of cesium carbonate (1.5 equiv.) and extract with toluene to obtain the free base.

Preparation 149

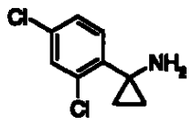
1-Phenyl-cyclopropylamine



Dissolve 1-phenyl-cyclopropanecarboxylic acid (2.5 g, 15.4 mmol) in a mixture of sulfuric acid (12.5 mL) and DCM (25 mL). Add sodium azide (2.3 g, 35.4 mmol) by small portions at ambient temperature. Heat the reaction mixture at 50°C for 8 h, cool to 0°C and slowly add 2M aqueous NaOH until pH 11. Extract the reaction mixture with DCM (3 x 100 mL), combine the organic extracts and dry over anhydrous Na_2SO_4. Evaporate the solvent and purify by chromatography on silica gel eluting with DCM and DCM/2M ammonia in methanol (9:1) to obtain the title compound as a brown oil (1.1 g, 54%). MS (ES+) *m/z*: 134 $(M+H)^+$.

Preparation 150

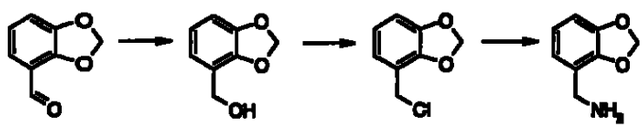
1-(2,4-Dichlorophenyl)-cyclopropylamine



Use a method similar to Preparation 149, using 1-(2,4-dichlorophenyl)-cyclopropanecarboxylic acid (3.5 g, 15.4 mmol), to obtain the title compound as a yellow oil (1.0 g, 32%). MS (ES+) *m/z*: 203 $(M+H)^+$.

Preparation 151

4-Methylamino-benzo[1,3]dioxole



Benzo[1,3]dioxol-4-yl-methanol: Dissolve benzo[1,3]dioxole-4-carbaldehyde (2.0 g, 13.3 mmol) in anhydrous THF (30 mL) and treat with sodium borohydride (0.5 g, 13.3

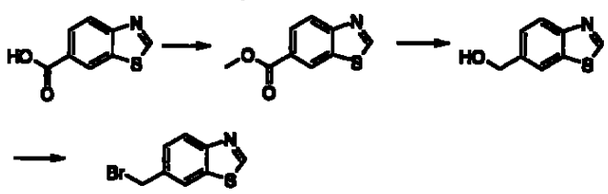
mmol) at 0°C. Stir the reaction mixture for 30 min at ambient temperature and quench with water (30 mL). Extract the reaction mixture with DCM (3 x 10 mL), combine the organic extracts and dry over anhydrous Na_2SO_4. Remove the solvent to obtain the desired intermediate as a colorless oil (1.9 g, 94%).

4-Chloromethyl-benzo[1,3]dioxole: Dissolve benzo[1,3]dioxol-4-yl-methanol (1.9 g, 12.5 mmol) in thionyl chloride (3 mL, 41.1 mmol) and reflux the reaction mixture for 1 h. Concentrate *in vacuo* to obtain the desired intermediate as a yellow oil (1.9 g, 91%) that was used without further purification. GC-MS *m/z*: 170 (M^+).

4-Methylamino-benzo[1,3]dioxole: Dissolve 4-chloromethyl-benzo[1,3]dioxole (1.9 g, 11.1 mmol) in methanol (5 mL), cool the solution to 0°C and saturate with anhydrous ammonia for 15 min. Keep the reaction mixture at 0°C for 18 h. Evaporate the solvent and purify by SCX chromatography to obtain the title compound as a yellow oil (0.6 g, 36%). GC-MS *m/z*: 151 (M^+).

Preparation 152

6-Bromomethyl-benzothiazole



Benzothiazole-6-carboxylic acid methyl ester: Add 1-methyl-3-nitro-1-nitrosoguanidine (5.0 g, 33.9 mmol) to a mixture of diethyl ether (20 mL) and 1N aqueous NaOH (20 mL) at ambient temperature. Separate the organic layer and add it slowly to a solution of benzothiazole-6-carboxylic acid (1.0 g, 5.58 mmol) in THF (50 mL) at 0°C. Evaporate the solvent to obtain the desired intermediate as a yellow solid (1.1 g, 100%). MS (ES+) *m/z*: 194 $(M+H)^+$.

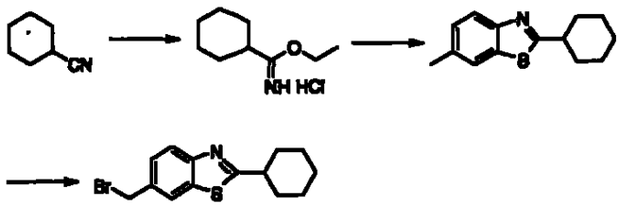
Benzothiazol-6-yl-methanol: Add slowly a solution of benzothiazole-6-carboxylic acid methyl ester (0.5 g, 2.59 mmol) in anhydrous THF (10 mL) to a suspension of lithium

aluminum hydride (0.1 g, 2.85 mmol) in anhydrous THF (20 mL) at –10°C and stir for 20 min at –10°C. Treat the reaction mixture with 2N aqueous NaOH until a granular precipitate starts to form and filter through a pad of Celite®. Evaporate the solvent and purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 9:1, 4:1, 7:3, 3:2 and 1:1) to obtain the desired intermediate as a yellow oil (0.4 g, 99%). MS (ES+) *m/z*: 166 $(M+H)^+$.

6-Bromomethyl-benzothiazole: Dissolve benzothiazol-6-yl-methanol (0.4 g, 2.55 mmol) in diethyl ether (10 mL) and add slowly a solution of phosphorus tribromide (0.7 g, 2.55 mmol) in diethyl ether (5 mL). Stir the reaction mixture for 2 h at ambient temperature, wash with brine, dry the organic phase over anhydrous Na_2SO_4, evaporate the solvent and purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 9:1 and 4:1) to obtain the title compound as a white solid (0.5 g, 86%). MS (ES+) *m/z*: 229 $(M+H)^+$.

Preparation 153

6-Bromomethyl-2-cyclohexyl-benzothiazole



Cyclohexanecarboximidic acid ethyl ester, hydrochloride: Combine cyclohexanecarbonitrile (1.0 g, 9.20 mmol), ethanol (0.4 g, 9.20 mmol) and 4N hydrogen chloride in dioxane (8 mL) and stir the reaction mixture for 17 h at ambient temperature. Evaporate the solvent and triturate the residue with diethyl ether to obtain the desired intermediate as a white solid (1.4 g, 80%).

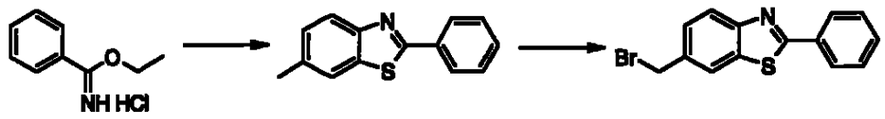
2-Cyclohexyl-6-methyl-benzothiazole: Combine 2-amino-5-methyl-benzenethiol zinc salt (1.0 g, 2.91 mmol, prepared as described in *Synth. Commun.* 1980, *10*, 167-173), cyclohexanecarboximidic acid ethyl ester hydrochloride (1.1 g, 5.82 mmol), methanol (20

mL) and reflux the reaction mixture for 17 h. Evaporate the solvent and purify by chromatography on silica gel eluting with hexane/EtOAc (1:0 and 9:1) to obtain the desired intermediate as a white solid (1.15 g, 85%).

6-Bromomethyl-2-cyclohexyl-benzothiazole: Combine 2-benzyl-6-methyl-benzothiazole (0.6 g, 2.42 mmol), NBS (0.5 g, 2.54 mmol), AIBN (40 mg, 0.24 mmol), carbon tetrachloride (10 mL) and reflux for 3 h. Cool the reaction mixture to ambient temperature, dilute with chloroform and wash with water. Dry the organic extracts over anhydrous Na_2SO_4, concentrate *in vacuo* and purify by chromatography on silica gel eluting with hexane/EtOAc (1:0 and 9:1) to obtain the title compound as a white solid (0.4 g, 53%). MS (ES+) *m/z*: 311 $(M+H)^+$.

Preparation 154

6-Bromomethyl-2-phenyl-benzothiazole

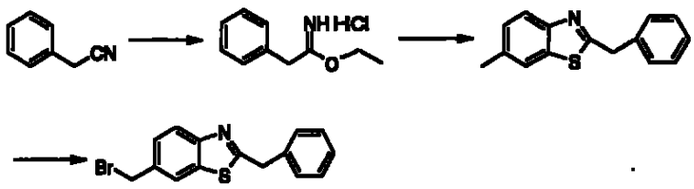


6-Methyl-2-phenyl-benzothiazole: Combine 2-amino-5-methyl-benzenethiol zinc salt (1.0 g, 2.91 mmol, prepared as described in *Synth. Commun.* 1980, *10*, 167-173), ethyl benzimidate hydrochloride (1.1 g, 5.82 mmol), methanol (20 mL), and reflux the reaction mixture for 17 h. Evaporate the solvent and purify by chromatography on silica gel eluting with hexane/EtOAc (1:0 and 9:1) to obtain the desired intermediate as a white solid (1.1 g, 85%). MS (ES+) *m/z*: 226 $(M+H)^+$.

6-Bromomethyl-2-phenyl-benzothiazole: Combine 6-methyl-2-phenyl-benzothiazole (0.2 g, 0.98 mmol), NBS (0.2 g, 1.02 mmol), AIBN (20 mg, 0.10 mmol), carbon tetrachloride (5 mL) and reflux for 3 h. Cool the reaction mixture to ambient temperature, dilute with chloroform and wash with water. Dry the organic extracts over anhydrous Na_2SO_4, concentrate and purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 9:1, 8:2 and 7:3) to obtain the title compound as a white solid (0.2 g, 69%).

Preparation 155

2-Benzyl-6-bromomethyl-benzothiazole



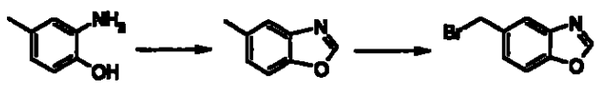
2-Phenyl-acetimidic acid ethyl ester, hydrochloride: Combine benzyl cyanide (1.0 g, 8.50 mmol), ethanol (0.4 g, 8.50 mmol) and 4N hydrogen chloride in dioxane (8 mL) and stir the reaction mixture at ambient temperature for 17 h. Evaporate the solvent and triturate the residue with diethyl ether to obtain the desired intermediate as a white solid (1.7 g, 100%).

2-Benzyl-6-methyl-benzothiazole: Combine 2-amino-5-methyl-benzenethiol zinc salt (1.0 g, 2.91 mmol, prepared as described in *Synth. Commun.* 1980, *10*, 167-173), 2-phenyl-acetimidic acid ethyl ester hydrochloride (1.16 g, 5.82 mmol), methanol (20 mL) and reflux the reaction mixture for 17 h. Evaporate the solvent and purify by chromatography on silica gel eluting with hexane/EtOAc (1:0 and 9:1) to obtain the desired intermediate as a white solid (1.0 g, 72%). MS (ES+) *m/z*: 240 $(M+H)^+$.

2-Benzyl-6-bromomethyl-benzothiazole: Combine 2-benzyl-6-methyl-benzothiazole (0.6 g, 2.51 mmol), NBS (0.5 g, 2.63 mmol), AIBN (40 mg, 0.25 mmol), carbon tetrachloride (10 mL) and reflux for 3 h. Cool the reaction mixture to ambient temperature, dilute with chloroform and wash with water. Dry the combined organic extracts over anhydrous Na_2SO_4, evaporate the solvent and purify by chromatography on silica gel eluting with hexane/EtOAc (1:0 and 9:1) to obtain the title compound as a white solid (0.2 g, 69%). MS (ES+) *m/z*: 319 $(M+H)^+$.

Preparation 156

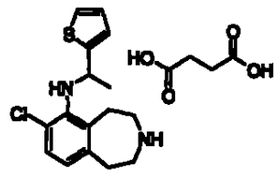
5-Bromomethyl-benzoxazole



(Example 292, 75 mg, 38%), 95% ee [Chiralpak AD, 4.6x150 mm, eluent: 85/15 heptane/3A ethanol with 0.2% DMEA, 0.6 mL/min)]; MS (ES+) *m/z*: 400 $(M+H)^+$. $[\alpha]^{20}_D$ -12.1° (c 0.5, MeOH). (+)-7-Chloro-6-{[5-(2,2,2-trifluoro-1-methyl-ethoxy)-pyridin-2-ylmethyl]-amino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine succinate (Example 293, 72 mg, 37%), 93% ee [Chiralpak AD, 4.6x150 mm, eluent: 85/15 heptane/3A ethanol with 0.2% DMEA, 0.6 mL/min)]. MS (ES+) *m/z*: 400 $(M+H)^+$. $[\alpha]^{20}_D$ +7.4° (c 0.5, MeOH).

Example 294

(±)-7-Chloro-6-[(1-thiophen-2-yl-ethyl)-amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Use a method similar to the General Procedure 5-3 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (200 mg, 0.47 mmol) with (±)-1-thiophen-2-yl-ethylamine (prepared as described in *J. Amer. Chem. Soc.* 1942, *64*, 477-479) (200 mg, 1.57 mmol). Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 9:1 and 4:1) to give (±)-7-chloro-6-[(1-thiophen-2-yl-ethyl)-amino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (126 mg, 67%).

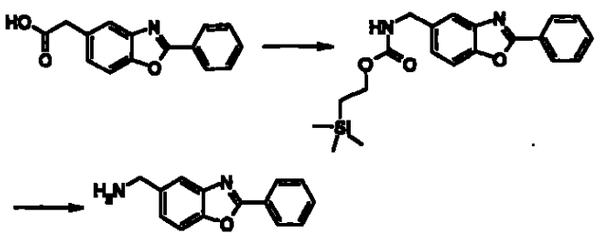
Use a method similar to the General Procedure 1-1, using (±)-7-chloro-6-[(1-thiophen-2-yl-ethyl)-amino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (126 mg, 0.313 mmol), to give the free base of the title compound (73 mg, 77%). Use a method similar to the General Procedure 2-1, using (±)-7-chloro-6-[(1-thiophen-2-yl-ethyl)-amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (73 mg, 0.241 mmol) to give the title compound (100 mg, 50% overall). MS (ES+) *m/z*: 307 $(M+H)^+$.

5-Methyl-benzoxazole: Combine 2-amino-4-methyl-phenol (1.0 g, 8.12 mmol), [(dimethylaminomethylene-aminomethylene)dimethylammonium chloride (Gold's reagent) (1.6 g, 9.91 mmol), anhydrous 1,4-dioxane (25 mL) and reflux for 17 h. Cool the reaction mixture to ambient temperature, evaporate the solvent and purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to obtain the desired intermediate as a yellow oil (0.7 g, 65%).

5-Bromomethyl-benzoxazol: Combine 5-methyl-benzoxazole (0.5 g, 3.75 mmol), NBS (0.7 g, 3.93 mmol), AIBN (60 mg, 0.37 mmol), chloroform (10 mL) and reflux for 1 h. Cool the reaction mixture to ambient temperature, dilute with chloroform and wash with water. Dry the organic extracts over anhydrous Na_2SO_4, evaporate the solvent and purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 9:1, 4:1 and 7:3) to obtain the title compound as a white solid (0.1 g, 13%).

Preparation 157

5- Methylamino-2-phenyl-benzoxazole

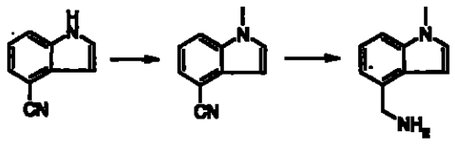


2-(Phenyl-benzoxazol-5-ylmethyl)-carbamic acid 2-trimethylsilanyl-ethyl ester: Combine (2-phenyl-benzoxazol-5-yl)-acetic acid (1.0 g, 3.95 mmol), triethylamine (0.5 g, 4.34 mmol), and anhydrous toluene (20 mL), heat to reflux and slowly add diphenylphosphoryl azide (1.2 g, 4.15 mmol) in anhydrous toluene (8 mL). Continue to reflux for 3 h, cool to ambient temperature, add 2-trimethylsilylethanol (0.9 g, 7.89 mmol) to the reaction mixture and continue to reflux for 3 h. Evaporate the solvent and purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 9:1, 4:1 and 7:3) to obtain the desired intermediate as a yellow solid (0.4 g, 26%).

5- Methylamino-2-phenyl-benzoxazole: Dissolve (2-phenyl-benzoxazol-5-yl-methyl)-carbamic acid 2-trimethylsilanyl-ethyl ester (0.4, 0.99 mmol) in anhydrous THF (5 mL) and treat with 1M tetrabutylammonium fluoride in THF (1.5 mL, 1.54 mmol). Heat the mixture at reflux for 30 min, evaporate the solvent and purify by SCX chromatography to obtain the title compound as a yellow oil (0.1 g, 27%).

Preparation 158

4-Aminomethyl-1-methylindole

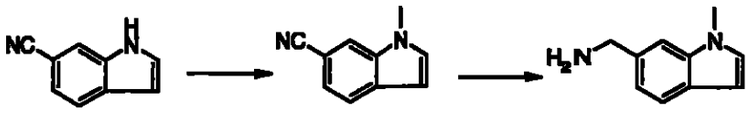


1-Methylindole-4-carbonitrile: Add slowly a solution of indole-4-carbonitrile (1.0 g, 7.04 mmol) in anhydrous DMF (5 mL) to a suspension of sodium hydride (60% dispersion in mineral oil, 0.6 g, 8.64 mmol) in anhydrous DMF (2 mL) at 0°C and warm the reaction mixture to ambient temperature. Add iodomethane (0.7 mL, 10.6 mmol) and stir the reaction for 1 h at ambient temperature. Dilute the reaction mixture with 1M aqueous NH_4OH (30 mL) and extract with diethyl ether (3 x 10 mL). Combine the organic extracts, dry over anhydrous Na_2SO_4, concentrate *in vacuo* and purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 9:1, 4:1 and 7:3) to obtain the desired intermediate as a yellow oil (1.0 g, 87%). GC-MS *m/z*: 156 (M^+).

4-Aminomethyl-1-methylindole: Dissolve 1-methylindole-4-carbonitrile (1.0 g, 6.18 mmol) in anhydrous THF (10 mL) and add slowly to 1M lithium aluminum hydride in THF (12.4 mL, 12.37 mmol) at ambient temperature. Heat the reaction mixture at 50°C for 17 h and cool to ambient temperature. Quench the reaction mixture with water until a granular precipitate starts to form and filter through a pad of Celite®. Evaporate the solvent and purify by SCX chromatography to obtain the title compound as a yellow oil (0.9 g, 91%). GC-MS *m/z*: 160 (M^+).

Preparation 159

6-Aminomethyl-1-methylindole

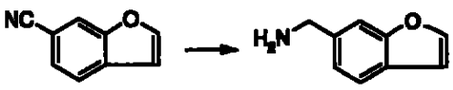


1-Methylindole-6-carbonitrile: Add slowly a solution of indole-6-carbonitrile (1.0 g, 7.04 mmol) in anhydrous DMF (5 mL) to a suspension of sodium hydride (60% dispersion in mineral oil, 0.6 g, 14.1 mmol) in anhydrous DMF (2 mL) at 0°C and warm the reaction mixture to ambient temperature. Add iodomethane (0.7 mL, 1.06 mmol) and stir the reaction mixture for 1 h at ambient temperature. Dilute the reaction mixture with 1M aqueous NH_4OH (30 mL) and extract with diethyl ether (3 x 10 mL). Combine the organic layers, dry over anhydrous Na_2SO_4, remove the solvent and purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 9:1, 4:1 and 7:3) to obtain the desired intermediate as a yellow oil (1.0 g, 87%). MS (ES+) *m/z*: 156 $(M+H)^+$.

6-Aminomethyl-1-methylindole: Dissolve 1-methylindole-6-carbonitrile (0.97 g, 6.18 mmol) in anhydrous THF (10 mL) and add slowly to 1M lithium aluminum hydride in THF (1.24 mL, 1.24 mmol) at ambient temperature. Heat the reaction mixture at 50°C for 17 h and cool to ambient temperature. Quench the reaction mixture with water until a granular precipitate starts to form and filter through a pad of Celite®. Evaporate the solvent and purify by SCX chromatography to obtain the title compound as a yellow oil (0.9 g, 91%). GC-MS *m/z*: 160 (M^+).

Preparation 160

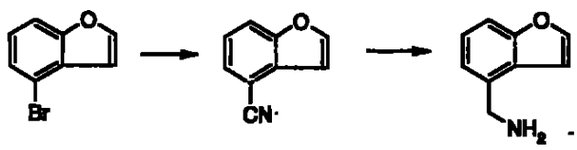
6-Aminomethyl-benzofuran



Dissolve benzofuran-6-carbonitrile (0.5 g, 3.28 mmol) in anhydrous THF (10 mL) and add slowly to 1M lithium aluminum hydride in THF (6.56 mL, 6.56 mmol) at ambient temperature. Heat the reaction mixture at 50°C for 17 h and cool to ambient temperature. Quench the reaction mixture with water until a granular precipitate starts to form and filter through a pad of Celite®. Evaporate the solvent and purify by SCX chromatography to obtain the title compound as a yellow oil (0.4 g, 79%).

Preparation 161

4-Aminomethyl-benzofuran

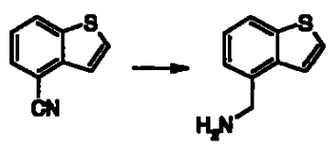


Benzofuran-4-carbonitrile: Combine 4-bromo-benzofuran (1.0 g, 5.07 mmol), copper(I) cyanide (0.9 g, 10.2 mmol), anhydrous DMF (16 mL) and reflux for 17 h. Cool the reaction mixture to ambient temperature, treat with 50% (v/v) aqueous ethylenediamine (25 mL). Extract the reaction mixture with diethyl ether (3 x 15 mL), combine the organic extracts, wash with brine (15 mL) and dry over anhydrous Na_2SO_4. Evaporate the solvent and purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 9:1 and 4:1) to obtain the desired intermediate as a colorless oil (0.3 g, 39%).

4-Aminomethyl-benzofuran: Dissolve benzofuran-4-carbonitrile (0.3 g, 1.96 mmol) in anhydrous THF (5 mL) and add slowly to 1M lithium aluminum hydride in THF (3.91 mL, 3.91 mmol) at ambient temperature. Heat the reaction mixture at 50°C for 5 h and cool to ambient temperature. Quench the reaction mixture with water until a granular precipitate starts to form and filter through a pad of Celite®. Evaporate the solvent and purify by SCX chromatography to obtain the title compound as a brown oil (0.4 g, 79%). GC-MS *m/z*: 147 (M^+).

Preparation 162

4-Aminomethyl-benzo[*b*]thiophene

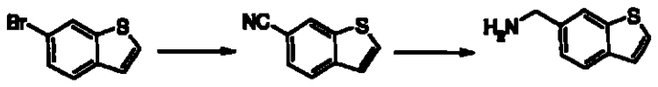


Add lithium aluminum hydride (1M solution in THF, 7.5 mL) to benzo[*b*]thiophene-4-carbonitrile (prepared as described in WO 0168653) (0.6 g, 3.8

mmol) at 0°C in THF (38 mL). After 17 h at ambient temperature, cool to 0°C and add sequentially water (1.89 mL), 2N aqueous NaOH (1.89 mL) and water (2.69 mL). Filter the solids and evaporate the filtrate to obtain the crude amine. Purify by SCX chromatography. Rinse the column with methanol, add a solution of the crude amine in methanol, wash the column with methanol and then elute with 1N ammonia in methanol. Concentrate to give the title compound (0.57 g, 93%). GC-MS *m/z*: 163 (M^+).

Preparation 163

6-Aminomethyl-benzo[*b*]thiophene

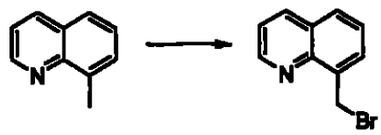


Benzo[*b*]thiophen-6-carbonitrile: Heat copper(I) cyanide (0.84 g, 9.4 mmol) and 6-bromobenzo[*b*]thiophene (prepared as described in WO 01/23381) (1.0 g, 4.7 mmol) at 160°C for 13 h. Cool the mixture to 0°C, add 33% aqueous ethylenediamine (20 mL) and dilute with ether. Wash the organic mixture with brine, dry over Na_2SO_4 and evaporate. Purify by chromatography on silica gel eluting with EtOAc/hexane (0:1 to 1:3) to give the desired intermediate (0.58 g, 78%). GC-MS *m/z*: 159 (M^+).

6-Aminomethyl-benzo[*b*]thiophene: Add 1M lithium aluminum hydride in THF (7.3 mL) to benzo[*b*]thiophene-6-carbonitrile (0.6 g, 3.6 mmol) at 0°C in THF (36 mL). After 15 h at ambient temperature, cool to 0°C and add sequentially water (1.82 mL), 2N aqueous NaOH (1.82 mL) and water (2.60 mL). Filter the solid and evaporate the filtrate to obtain the crude amine. Purify by SCX chromatography. Rinse the column with methanol, add a solution of the crude amine in methanol, wash the column with methanol and then elute with 1N ammonia in methanol. Concentrate *in vacuo* to give the title compound (0.55 g, 92%).

Preparation 164

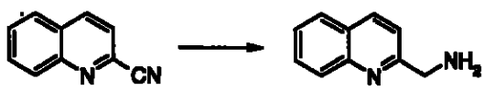
8-Bromomethyl-quinoline



Combine 8-methyl-quinoline (1.0 g, 6.99 mmol), NBS (1.3 g, 7.13 mmol), benzoyl peroxide (6.0 mg, 0.03 mmol), carbon tetrachloride (30 mL) and reflux for 17 h. Cool the reaction mixture to ambient temperature and evaporate the solvent. Dissolve the residue in chloroform (30 mL), wash the organic solution with saturated aqueous $NaHCO_3$ (2 x 10 mL), brine (10 mL) and dry over anhydrous Na_2SO_4. Evaporate the solvent and purify by chromatography on silica gel eluting with DCM to obtain the title compound as a white solid (1.3 g, 83%). MS (ES+) *m/z*: 223 $(M+H)^+$.

Preparation 165

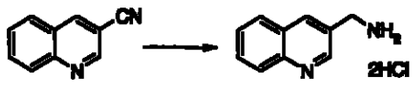
2-Aminomethyl-quinoline



Combine quinoline-2-carbonitrile (0.2 g, 1.29 mmol), Raney® 3201 nickel (slurry in water, 0.05 g), 2N ammonia in methanol (10 mL) and hydrogenate at 50 psi for 15 min. Filter the reaction mixture through a pad of Celite®, remove the solvent and purify by SCX chromatography to obtain the title compound as a yellow oil (0.2 g, 98%). MS (ES+) *m/z*: 159 $(M+H)^+$.

Preparation 166

3-Aminomethyl-quinoline Dihydrochloride

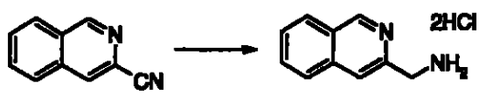


Combine quinoline-3-carbonitrile (1.0 g, 6.49 mmol), 10% Pd/C (0.2 g), 5% TFA in methanol (100 mL) and hydrogenate at 30 psi for 2 h. Filter the reaction mixture through a pad of Celite® and evaporate the solvent. Dissolve the residue in ethanol (10 mL), treat with 1N hydrogen chloride in diethyl ether (5 mL) and allow the mixture to

stand at 5°C for 18 h. Filter the precipitate, wash with ethanol and dry under *vacuo* to obtain the title compound as a white solid (0.6 g, 53%).

Preparation 167

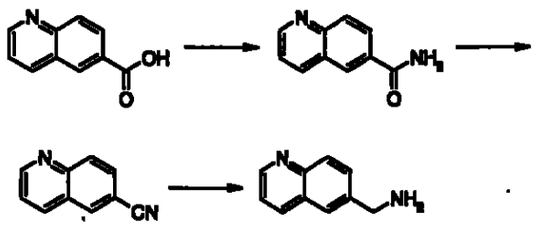
2-Aminomethyl-isoquinoline Dihydrochloride



Combine isoquinoline-3-carbonitrile (1.0 g, 6.49 mmol), 10% Pd/C (0.2 g), 5% TFA in methanol (95 mL) and hydrogenate at 30 psi for 17 h. Filter the reaction mixture through a pad of Celite® and evaporate the solvent. Dissolve the residue in ethanol (10 mL), treat with 1N hydrogen chloride in diethyl ether (5 mL) and allow to stand at 5 °C for 18 h. Filter the precipitate, wash with ethanol and dry under *vacuo* to obtain the title compound as a white solid (0.6 g, 55%).

Preparation 168

6-Aminomethyl-quinoline



<u>6-Quinolinecarboxamide:</u> Combine 6-quinolinecarboxylic acid (2.0 g, 11.6 mmol), 1,1-carbonyldiimidazol (3.8 g, 23.45 mmol) in DCM (50 mL) and stir at ambient temperature for 1 h. Saturate the reaction mixture with anhydrous ammonia and continue to stir for 1 h. Quench the reaction mixture with water (100 mL) and extract with chloroform (3 x 50 mL). Combine the organic extracts, dry over anhydrous Na_2SO_4 and evaporate the solvent to obtain the desired intermediate as a white solid (1.6 g, 78%).

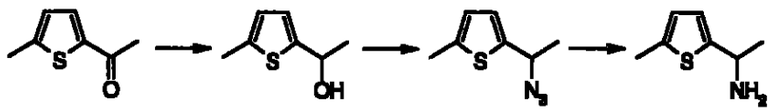
<u>6-Quinolinecarbonitrile:</u> Dissolve 6-quinolinecarboxamide (1.5 g, 8.95 mmol) in DCM (50 mL), add triethylamine (2.7 g, 26.8 mmol) and cool the reaction mixture to 0°C. Add trifluoroacetic acid anhydride (2.4 g, 11.16 mmol) to the reaction mixture and stir for 10

min at 0 °C. Quench the reaction mixture with water (20 mL) and separate the organic layer. Extract aqueous layer with DCM (2 x 15 mL). Combine the organic extracts and dry over anhydrous Na_2SO_4. Evaporate the solvent to obtain the desired intermediate as a white solid (1.0 g, 73%). GC-MS *m/z*: 154 (M^+).

6-Aminomethyl-quinoline: Combine 6-quinolinecarbonitrile (1.0 g, 6.49 mmol), Raney® 3201 nickel (slurry in water, 0.2 g), 2N ammonia in methanol (20 mL) and hydrogenate at 50 psi for 1 h. Filter the reaction mixture through a pad of Celite®, remove the solvent and purify by SCX chromatography to obtain the title compound as a yellow oil (0.8 g, 78%).

Preparation 169

(±)-2-(1-Aminoethyl)-5-methylthiophene



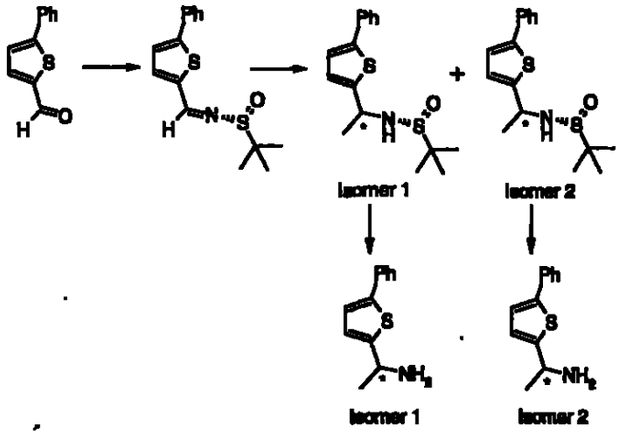
(±)-2-(1-Hydroxyethyl)-5-methylthiophene: Add sodium borohydride (270 mg, 7.13 mmol) to a solution of 2-acetyl-5-methylthiophene (1.0 g, 7.13 mmol) in methanol (40 mL). Stir the mixture for 1 h at room temperature. Remove the solvent *in vacuo* and partition the residue between water and DCM. Separate the organic phase, dry over Na_2SO_4, filter and concentrate to obtain the desired intermediate as an oil (0.995 g, 98%) that was used without further purification. GC-MS *m/z* 142 (M^+).

(±)-2-(1-Azidoethyl)-5-methylthiophene: Add DBU (1.228 g, 1.2 mL, 8.07 mmol) to a solution of (±)-2-(1-hydroxyethyl)-5-methylthiophene (0.955 g, 6.72 mmol) and diphenylphosphoryl azide (2.22 g, 1.74 mL, 8.07 mmol) in anhydrous toluene. Stir at room temperature for 18 h. Dilute the mixture with EtOAc and wash with water and 0.5N aqueous HCl. Dry the organic phase over Na_2SO_4, filter and concentrate. Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0 and 19:1) to obtain the desired intermediate as an oil (0.875 g, 78%). GC-MS *m/z* 167 (M^+).

(±)-2-(1-Aminoethyl)-5-methylthiophene: Add lithium aluminum hydride (29 mg, 0.72 mmol) to a solution of (±)-2-(1-azidoethyl)-5-methylthiophene (100 mg, 0.59 mmol) in anhydrous THF (5 mL). Stir at room temperature overnight. Work-up the mixture with EtOAc and water. Filter the mixture over Celite®. Separate and wash the organic phase with brine. Dry over Na_2SO_4, filter and concentrate *in vacuo*. Purify by SCX chromatography. Rinse with DCM/methanol (1:1), load the crude mixture in methanol and elute sequentially with methanol and 1N ammonia in methanol to obtain the title compound as an oil (80 mg, 95%). GC-MS *m/z* 141 (M^+).

Preparations 170 and 171

1-(5-Phenyl-thiophen-2-yl)ethylamine, Isomers 1 and 2



N-[(5-Phenylthiophen-2-yl)-methylene]-2-methylpropanesulfinamide: To a solution of 5-phenyl-2-thiophenecarboxaldehyde (1.25 g, 6.64 mmol) in anhydrous THF (50 mL), add titanium(IV) ethoxide (3.03 g, 2.78 mL, 13.28 mmol) and (*R*)-(+)-2-methyl-2-propanesulfinamide (0.965 g, 7.968 mmol) under nitrogen. Heat the reaction at 80°C overnight. Cool the mixture to room temperature and dilute with EtOAc. Add water and filter the resulting precipitate over Celite®. Separate and dry the organic phase over Na_2SO_4, filter and concentrate *in vacuo* to obtain the desired intermediate as a yellow solid (1.93 g, 100% yield) that was used without purification.

N-[1-(5-Phenylthiophen-2-yl)ethyl]-2-methylpropanesulfinamide (Isomer 1) and *N*-[1-(5-phenylthiophen-2-yl)ethyl]-2-methylpropanesulfinamide (Isomer 2): Add slowly methyllithium (8.1 mL, 12.92 mmol, 1.6 M solution in ether) to a solution of *N*-[(5-phenylthiophen-2-yl)-methylene]-2-methylpropanesulfinamide (1.883 g, 6.46 mmol) in anhydrous THF (50 mL) at –40°C. Warm the reaction to –20°C and stir for 2 h. Warm to 0°C and stir for an additional 2 h. Add saturated aqueous NH_4Cl and extract with EtOAc. Dry the organic phase over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (7:3 and 1:1) to obtain *N*-[1-(5-phenylthiophen-2-yl)ethyl]-2-methylpropanesulfinamide (Isomer 1) (575 mg, 30% yield) and *N*-[1-(5-phenylthiophen-2-yl)ethyl]-2-methylpropanesulfinamide (Isomer 2) (847 mg, 44% yield).

1-(5-Phenyl-thiophen-2-yl)ethylamine (Isomer 1, Preparation 170) Add 4N hydrogen chloride in dioxane (0.837 mL, 3.349 mmol) to a stirred solution of *N*-[1-(5-phenylthiophen-2-yl)ethyl]-2-methylpropanesulfinamide (Isomer 1) (515 mg, 1.675 mmol) in methanol (8 mL) at room temperature. Stir for 2 h and remove the solvent *in vacuo* to obtain a solid that was washed with ethyl ether. Dissolve the solid in DCM and wash with saturated aqueous $NaHCO_3$. Dry the organic phase over Na_2SO_4, filter and concentrate *in vacuo* to obtain the desired intermediate (236 mg, 69% yield).

1-(5-Phenyl-thiophen-2-yl)ethylamine (Isomer 2, Preparation 171) Add 4N hydrogen chloride in dioxane (1.112 mL, 4.449 mmol) to a stirred solution of *N*-[1-(5-phenylthiophen-2-yl)ethyl]-2-methylpropanesulfinamide (Isomer 2) (684 mg, 2.225 mmol) in methanol (10 mL) at room temperature. Stir for 2 h and remove the solvent *in vacuo* to obtain a solid that was washed with ethyl ether. Dissolve the solid in DCM and wash with saturated aqueous $NaHCO_3$. Dry the organic phase over Na_2SO_4, filter and concentrate *in vacuo* to obtain the desired intermediate (347 mg, 77% yield).

Example 49

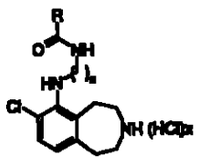
6-(2-Benzoylamino-ethylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



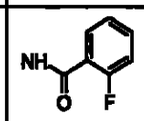
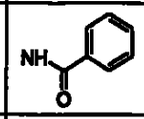
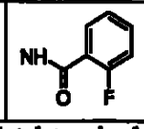
Dissolve 6-(2-amino-ethylamino)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (70 mg, 0.208 mmol) in DCM (4 mL). Add benzoyl chloride (24 μL, 0.208 mmol), and triethylamine (44 μL, 0.312 mmol) and stir at ambient temperature for 24 h under nitrogen atmosphere. Dilute with DCM and add 1M aqueous HCl. Extract the aqueous layer with DCM. Dry the organic layer over $MgSO_4$ and concentrate in *vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 7:3 and 1:1) to obtain 6-(2-benzoylamino-ethylamino)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine.

Use a method similar to the General Procedure 1-1, using 6-(2-benzoylamino-ethylamino)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine, to give the free base of the title compound. Use a method similar to the General Procedure 2-2 to give the title compound (77 mg, 90% overall). HPLC: t_R = 2.64 min (20–80% of Solvent B in 7.5 min. Solvent A: water, 0.1% TFA. Solvent B: acetonitrile, 0.1% TFA. Column: C18 Metachem, 5 micron, 4.6x50).

Examples 50-52 may be prepared essentially as described in Example 49 by using 6-(2-amino-ethylamino)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine or 6-(3-amino-propylamino)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate benzoyl chloride. Overall yields and MS (ES+) data are shown in the Table below.



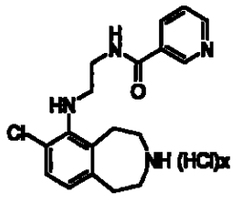
Ex.	NH-CO-R	n	Compound	Yield (%)	MS (ES+)

					m/z
50		2	7-Chloro-6-[2-(2-fluorobenzoylamino)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	40	362 $(M+H)^+$
51		3	6-(3-Benzoylamino-propylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	90	ND
52		3	7-Chloro-6-[3-(2-fluorobenzoylamino)-propylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	40	376 $(M+H)^+$

ND = Not determined

Example 53

7-Chloro-6-{2-[(pyridine-3-carbonyl)-amino]-ethylamino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



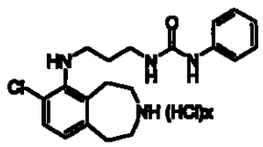
Dissolve nicotinic acid (28.2 mg, 0.23 mmol) in DCM (3 mL). Add EDC (40 mg, 0.208 mmol), HOBT (28.1 mg, 0.2081mmol) and stir at ambient temperature for 10 min. Add 6-(2-amino-ethylamino)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (70 mg, 0.208 mmol) and stir at ambient temperature for 10 hr. Dilute with DCM, add water and extract the aqueous layer three times with DCM. Wash combined organic extracts with 1N aqueous NaOH, and brine. Dry the organic layer over $MgSO_4$, concentrate *in vacuo* and purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 1:1, 3:7 and 1:9) to obtain 7-chloro-6-{2-[(pyridine-3-carbonyl)-amino]-ethylamino}-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine.

Use a method similar to the General Procedure 1-1, using 7-chloro-6-{2-[(pyridine-3-carbonyl)-amino]-ethylamino}-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine, to give the free base of the title compound. Use a method similar to

the General Procedure 2-2 to give the title compound as a solid (92 mg, 98%). HPLC: t_R= 1.38 min (20–80% of Solvent B in 7.5 min. Solvent A: water, 0.1% TFA. Solvent B: acetonitrile, 0.1% TFA. Column: C18 Metachem, 5 micron, 4.6x50).

Example 54

7-Chloro-6-[3-(3-phenyl-ureido)-propylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

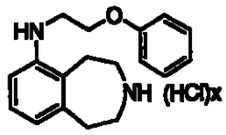


Combine phenyl isocyanate (15 µL, 0.137 mmol) and 6-(3-amino-propylamino)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (48 mg, 0.137 mmol) in DCM and stir for 16 h. Concentrate, add DCM, filter and collect the solid to obtain 7-chloro-6-[3-(3-phenyl-ureido)-propylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (18 mg, 28%).

Use a method similar to the General Procedure 1-1, using 7-chloro-6-[3-(3-phenyl-ureido)-propylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine, to give the free base of the title compound. Use a method similar to the General Procedure 2-2 to give the title compound (14 mg, 23%). MS (ES+) *m/z*: 373 $(M+H)^+$.

Example 55

6-(2-Phenoxy-ethylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

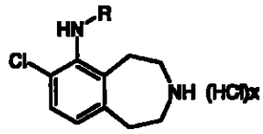


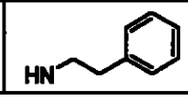
Use a method similar to the General Procedure 5-1, using 3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (100 mg, 0.23 mmol) and phenoxyethylamine (63 mg, 0.4 mmol) to give, after chromatography on silica gel eluting with hexane/EtOAc (85:15) followed by SCX chromatography, 6-(2-phenoxy-

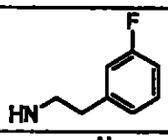
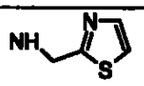
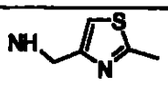
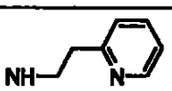
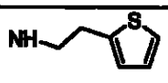
ethylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow oil. MS (ES+) *m/z*: 379 $(M+H)^+$.

Use a method similar to the General Procedure 1-1 to deprotect 6-(2-phenoxy-ethylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (75 mg, 0.19 mmol). Purify by SCX chromatography to give the free base of the title compound. Use a method similar to the General Procedure 2-2 to give the title compound as a white solid. MS (ES+) *m/z*: 283 $(M+H)^+$.

Examples 56-61 may be prepared essentially as described in Example 55 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. The yields for the Step1 (General Procedure 5-1) and MS (ES+) data are shown in the Table below.



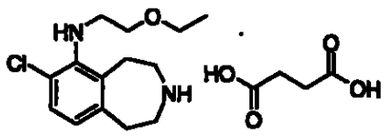
Ex.	NH-R	Compound	Yield (%)	MS (ES+) *m/z*
56		7-Chloro-6-phenethylamino-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	47	301 $(M+H)^+$

Ex.	NH-R	Compound	Yield (%)	MS (ES+) *m/z*
57		7-Chloro-6-(3-fluoro-phenethylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	55	319 $(M+H)^+$
58		7-Chloro-6-[(thiazol-2-yl)methylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	21	294 $(M+H)^+$
59		7-Chloro-6-[(2-methyl-thiazol-4-yl)methylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	16	308 $(M+H)^+$
60		7-Chloro-6-(2-pyridin-2-yl-ethylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	86	302 $(M+H)^+$
61		7-Chloro-6-(2-thiophen-2-yl-ethylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	78	ND

ND = Not determined

Example 62

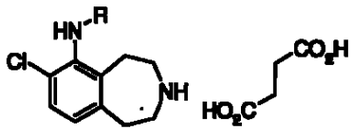
7-Chloro-6-[(2-ethoxyethyl)amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

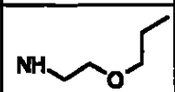
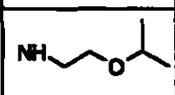
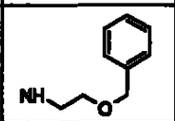
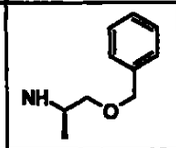
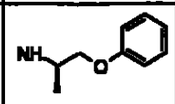


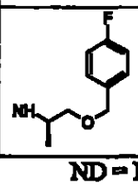
Use a method similar to the General Procedure 5-1, using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (200 mg, 0.47 mmol) and 2-ethoxyethyl amine (105 μL, 1.0 mmol) to give, after chromatography on silica gel eluting with hexane/EtOAc (95:5) and additional SCX chromatography, 7-chloro-6-[(2-ethoxyethyl)amino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (32 mg, 19%). MS (ES+) *m/z*: 365 $(M+H)^+$.

Use a method similar to the General Procedure 1-1 to deprotect 7-chloro-6-[(2-ethoxyethyl)amino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (30 mg, 0.08 mmol). Purify by SCX chromatography to give the free base of the title compound. Use a method similar to the General Procedure 2-1 to give the title compound as an oil (23.8 mg, 75% over 2 steps). MS (ES+) *m/z*: 269 $(M+H)^+$.

Examples 63-68 may be prepared essentially as described in Example 62 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. The yields for the Step 1 (General Procedure 5-1), optical rotations and MS (ES+) data are shown in the Table below.



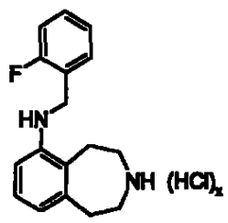
Ex.	NH-R	Compound	Yield (%)	MS (ES+) *m/z*	$[\alpha]^{20}_D$ (c, solvent)
63		7-Chloro-6-[2-(1-propoxy)ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	57	283 $(M+H)^+$	-
64		7-Chloro-6-[2-(2-propoxy)ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	75	283 $(M+H)^+$	-
65		6-(2-Benzyloxy-ethylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	37	331 $(M+H)^+$	-
66		(*R*)-6-(2-Benzyloxy-1-methyl-ethylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	15	345 $(M+H)^+$	ND
67		(*R*)-6-(2-Phenoxy-1-methyl-ethylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	15	331 $(M+H)^+$	+54.7° (c 0.5, CH_3OH)

Ex.	NH-R	Compound	Yield (%)	MS (ES+) m/z	$[\alpha]^{20}_D$ (c, solvent)
68		(*R*)-6-[2-(4-Fluorobenzyloxy)-1-methyl-ethylamino]-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	69	363 $(M+H)^+$	+22.6° (c 0.5, CH_3OH)

ND = Not determined

Example 69

6-(2-Fluorobenzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

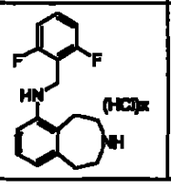


Use a method similar to the General Procedure 5-1, using 3-(2,2,2-trifluoroacetyl)-6-trifluoromethylsulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (100 mg, 0.26 mmol) and 2-fluorobenzylamine (88 μL, 0.77 mmol) to give, after chromatography on silica gel eluting with hexane/EtOAc (9:1), 6-(2-fluorobenzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow oil (45 mg, 48%). MS (ES+) *m/z*: 367 $(M+H)^+$.

Use a method similar to the General Procedure 1-1 to deprotect 6-(2-fluorobenzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (40 mg, 0.11 mmol). Purify by SCX chromatography to give the free base of the title compound as a yellow oil (28 mg, 94 %). Use a method similar to the General Procedure 2-2 to give the title compound as an off-white solid (29 mg, 95%). MS (ES+) *m/z*: 271 $(M+H)^+$.

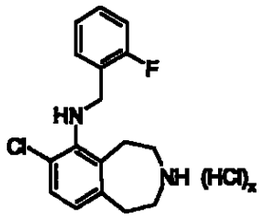
Example 70 may be prepared essentially as described in Example 69 by using 3-(2,2,2-trifluoroacetyl)-6-trifluoromethylsulfonyloxy-2,3,4,5-tetrahydro-1*H*-

benzo[*d*]azepine and 2,6-difluorobenzylamine. The yield for the Step 1 (General Procedure 5-1) and MS (ES+) data are shown in the Table below.

Ex.	Structure	Compound	Yield (%)	MS (ES+) *m/z*
70		6-(2,6-Difluorobenzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	69	289 $(M+H)^+$

Example 71

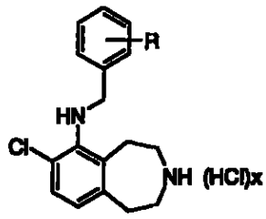
7-Chloro-6-(2-fluorobenzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the General Procedure 5-1 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 2-fluorobenzyl amine. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1 and 4:1) to give 7-chloro-6-(2-fluorobenzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow solid. MS (ES+) *m/z*: 401 $(M+H)^+$.

Use a method similar to the General Procedure 1-1 to deprotect 7-chloro-6-(2-fluorobenzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Purify by SCX chromatography to give the free base of the title compound as a yellow oil. Use a method similar to the General Procedure 2-2 to give the title compound as a light yellow solid. MS (ES+) *m/z*: 305 $(M+H)^+$.

Examples 72-80 may be prepared essentially as described in Example 71 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. MS (ES+) data are shown in the Table below.

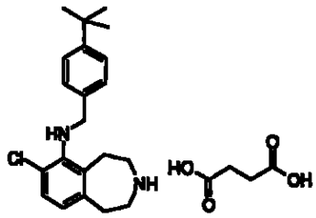


Ex.	R	Compound	MS (ES+) *m/z*
72	3-F	7-Chloro-6-(3-fluorobenzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	305 $(M+H)^+$
73	4-F	7-Chloro-6-(4-fluorobenzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	305 $(M+H)^+$
74	2,3-diF	7-Chloro-6-(2,3-difluorobenzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	323 $(M+H)^+$
75	3,4-diF	7-Chloro-6-(3,4-difluorobenzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	323 $(M+H)^+$
76	3,5-diF	7-Chloro-6-(3,5-difluorobenzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	323 $(M+H)^+$
77	3,4,5-triF	7-Chloro-6-(3,4,5-trifluorobenzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	341 $(M+H)^+$
78	3-CF_3	7-Chloro-6-(3-trifluoromethyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	355 $(M+H)^+$
79	3,5-diCF_3	7-Chloro-6-[3,5-bis(trifluoromethyl)benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	423 $(M+H)^+$
80	4-$O(CH_2)_2N(CH_3)_2$	7-Chloro-6-{4-[2-(*N*,*N*-dimethylamino)ethoxy]benzylamino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	374 $(M+H)^+$

5

Example 81

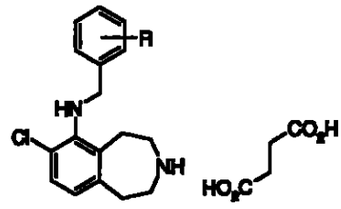
6-(4-*tert*-Butylbenzylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Use a method similar to the General Procedure 5-1 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (300 mg, 0.7 mmol) with 4-(*tert*-butyl)benzyl amine (375 μL, 2.1 mmol). Purify by chromatography on silica gel eluting with hexane/EtOAc (95:5) followed by SCX chromatography to give 6-(4-*tert*-butylbenzylamino)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a colorless oil (240 mg, 78%). MS (ES+) *m/z*: 439 $(M+H)^+$.

Use a method similar to the General Procedure 1-1 to deprotect 6-(4-*tert*-butylbenzylamino)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (235 mg, 0.54 mmol). Purify by SCX chromatography to give the free base of the title compound (161 mg, 87%). Use a method similar to the General Procedure 2-1 to give the title compound as an off-white gum (190 mg, 88%). MS (ES+) *m/z*: 343 $(M+H)^+$.

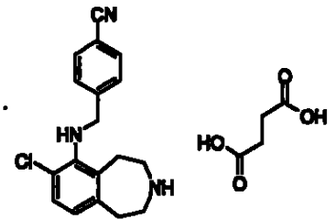
Examples 82-88 may be prepared essentially as described in Example 81 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. MS (ES+) data are shown in the Table below.



Ex.	R	Compound	MS (ES+) *m/z*
82	3-*t*-Bu	6-(3-*tert*-Butylbenzylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	343 $(M+H)^+$
83	4-OCF_3	7-Chloro-6-(4-trifluoromethoxy-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	371 $(M+H)^+$
84	4-F,3-CF_3	7-Chloro-6-[(4-fluoro-3-trifluoromethyl)benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	373 $(M+H)^+$
85	4-F,3-OCH_3	7-Chloro-6-[(4-fluoro-3-methoxy)benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	321 $(M+H)^+$
86	4-Ph	7-Chloro-6-(4-phenylbenzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	363 $(M+H)^+$
87	4-OPh	7-Chloro-6-(4-phenoxy-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	379 $(M+H)^+$
88	4-SO_2CH_3	7-Chloro-6-(4-methanesulfonyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	365 $(M+H)^+$

Example 89

7-Chloro-6-(4-cyanobenzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



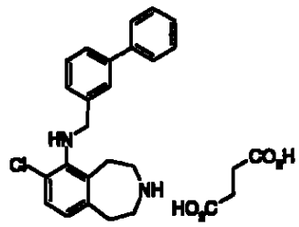
Use a method similar to the General Procedure 5-1 to react 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (504 mg, 1.2 mmol), 4-cyanobenzylamine (476 mg, 3.6 mmol), palladium(II) acetate (29 mg, 0.1 mmol), BINAP (148 mg, 0.2 mmol) and cesium carbonate (540 mg, 1.7 mmol) in

toluene (5 mL). Purify by chromatography on silica gel eluting with isohexane/EtOAc (1:0 to 1:1) to give 7-chloro-6-(4-cyanobenzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a white gum (108 mg, 22%). MS (ES+) *m/z*: 408 $(M+H)^+$.

Use a method similar to the General Procedure 1-2 to deprotect 7-chloro-6-(4-cyanobenzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (98 mg, 0.2 mmol). Purify by preparative liquid chromatography eluting with a gradient of water/acetonitrile (19:1 to 1:19) to give the free base of the title compound (31 mg, 42%). MS (ES+) *m/z*: 312 $(M+H)^+$. Use a method similar to the General Procedure 2-1, using 7-chloro-6-(4-cyanobenzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (31 mg, 0.1 mmol) to give the title compound as a beige solid (41 mg, 95%). MS (ES+) *m/z*: 312 $(M+H)^+$.

Example 90

7-Chloro-6-(3-phenyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



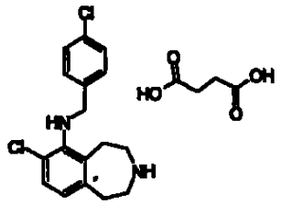
Use a method similar to the General Procedure 5-3 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.3 g, 0.706 mmol) with 3-phenyl-benzylamine (0.388 g, 2.117 mmol) using palladium(II) acetate (32 mg, 0.141 mmol), tris(dibenzylideneacetone)dipalladium(0) (65 mg, 0.070 mmol), BINAP (264 mg, 0.424 mmol) and cesium carbonate (460 mg, 1.412 mmol) in toluene (12 mL). Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 19:1) to give 7-chloro-6-(3-phenyl-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (0.257 g, 79%). MS (ES+) *m/z*: 459 $(M+H)^+$.

Use a method similar to the General Procedure 1-2, using 7-chloro-6-(3-phenyl-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (237 mg, 0.516 mmol), to give the free base of the title compound as an oil (188 mg, 100%) that was used without further purification.

Use a method similar to the General Procedure 2-1, using 7-chloro-6-(3-phenyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (188 mg, 0.518 mmol) to give the title compound as a white solid (191 mg, 77%). MS (ES+) *m/z*: 363 $(M+H)^+$.

Example 91

7-Chloro-6-(4-chlorobenzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

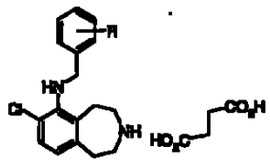


Use a method similar to the General Procedure 5-3 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (700 mg, 1.6 mmol) with 4-chlorobenzylamine (354 mg, 2.5 mmol). Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0 and 9:1) and then SCX chromatography to give 7-chloro-6-(4-chlorobenzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (459 mg, 69%). MS (ES+) *m/z*: 417 $(M+H)^+$.

Use a method similar to the General Procedure 1-1 to deprotect 7-chloro-6-[1-(4-chlorobenzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (95:5) to give the free base of the title compound. MS (ES+) *m/z*: 321 $(M+H)^+$. Use a method similar to the General Procedure 2-1 to obtain the title compound.

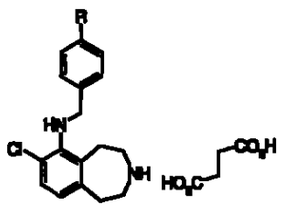
Examples 92-98 may be prepared essentially as described in Example 91 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-

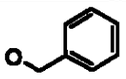
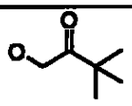
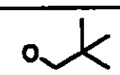
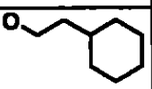
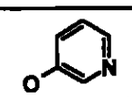
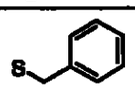
benzo[*d*]azepine and the appropriate amine. The yields for the Step 1 (General Procedure 5-3) and MS (ES+) data are shown in the Table below.



Ex.	R	Compound	Yield (%)	MS (ES+) *m/z*
92	3-Cl	7-Chloro-6-(3-chlorobenzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	45	321 $(M+H)^+$
93	3-Cl,4-F	7-Chloro-6-(3-chloro-4-fluoro-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	90	339 $(M+H)^+$
94	2-Cl,4-F	7-Chloro-6-(2-chloro-4-fluoro-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	75	339 $(M+H)^+$
95	3-OCH_3	7-Chloro-6-(3-methoxy-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	84	316 $(M+H)^+$
96	2-F,4-CH_3	7-Chloro-6-(2-fluoro-4-methyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	53	319 $(M+H)^+$
97	3-OCF_3	7-Chloro-6-(3-trifluoromethoxy-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	85	371 $(M+H)^+$
98	3-Cl,4-OCH_3	7-Chloro-6-(3-chloro-4-methoxy-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	100	351 $(M+H)^+$

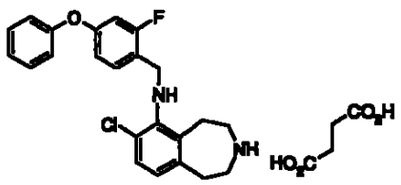
Examples 99-106 may be prepared essentially as described in Example 91 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. The yields for the Step 1 (General Procedure 5-3) and MS (ES+) data are shown in the Table below.



Ex.	R	Compound	Yield (%)	MS (ES+) m/z
99		7-Chloro-6-(4-benzyloxy-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	87	393 $(M+H)^+$
100		7-Chloro-6-[4-(3,3-dimethyl-2-oxo-butoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	20	401 $(M+H)^+$
101		7-Chloro-6-[4-(2,2-dimethylpropoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	23	373 $(M+H)^+$
102		7-Chloro-6-[4-(2-cyclohexylethoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	61	413 $(M+H)^+$
103		7-Chloro-6-[4-(1*H*-pyrazol-1-yl)benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	36	353 $(M+H)^+$
104		7-Chloro-6-[4-(pyridin-3-yloxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	42	380 $(M+H)^+$
105		6-(4-Benzylthio-benzylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	21	409 $(M+H)^+$

Example 106

7-Chloro-6-(2-fluoro-4-phenoxy-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

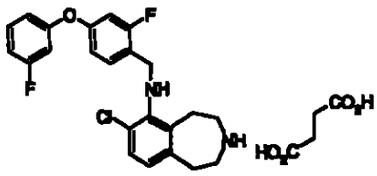


Using a method similar to the General Procedure 5-3, couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.1 g, 2.5 mmol) with 2-fluoro-4-phenoxy-benzylamine (550 mg, 2.5 mmol). Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) and then SCX chromatography to obtain 7-chloro-6-(2-fluoro-4-phenoxy-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. MS (ES+) *m/z*: 493 $(M+H)^+$.

Use a method similar to the General Procedure 1-1 to deprotect 7-chloro-6-(2-fluoro-4-phenoxy-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (95:5) to give the free base of the title compound (468 mg, 47% overall). MS (ES+) *m/z*: 397 $(M+H)^+$. Use a method similar to the General Procedure 2-1 to obtain the title compound.

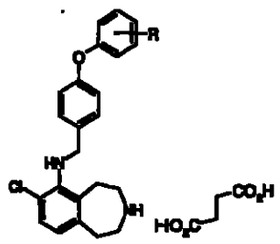
Example 107

7-Chloro-6-[2-fluoro-4-(3'-fluorophenoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Use a method similar to the Example 106, using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (426 mg, 1.0 mmol) and 2-fluoro-4-(3'-fluorophenoxy)-benzylamine (340 mg, 1.4 mmol) to give the free base of the title compound (162 mg, 39%). MS (ES+) *m/z*: 415 $(M+H)^+$. Use a method similar to the General Procedure 2-1 to obtain the title compound.

Examples 108-121 may be prepared essentially as described in Example 107 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. The yields for the Step 1 (General Procedure 5-3) and MS (ES+) data are shown in the Table below.



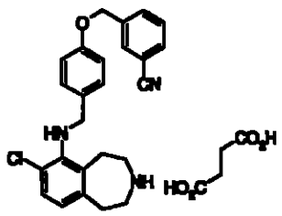
Ex.	R	Compound	Yield (%)	MS (ES+) *m/z*
108	2-F	7-Chloro-6-[4-(2'-fluorophenoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	44	397 $(M+H)^+$
109	3-F	7-Chloro-6-[4-(3'-fluorophenoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	23	397 $(M+H)^+$
110	4-F	7-Chloro-6-[4-(4'-fluorophenoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	50	397 $(M+H)^+$
111	3-Cl	7-Chloro-6-[4-(3'-chlorophenoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	45	413 $(M+H)^+$
112	3,5-diF	7-Chloro-6-[4-(3',5'-difluorophenoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	36	415 $(M+H)^+$
113	4-CH_3	7-Chloro-6-[4-(4'-methylphenoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	54	393 $(M+H)^+$
114	3-CH_3	7-Chloro-6-[4-(3'-methylphenoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	45	393 $(M+H)^+$
115	2-CH_3	7-Chloro-6-[4-(2'-methylphenoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	54	393 $(M+H)^+$
116	3-^{i}Pr	7-Chloro-6-[4-(3'-isopropylphenoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	49	421 $(M+H)^+$
117	2-^{i}Pr	7-Chloro-6-[4-(2'-	40	421

		isopropylphenoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate		$(M+H)^+$
118	2-CN	7-Chloro-6-[4-(2'-cyanophenoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	79	404 $(M+H)^+$

Ex.	R	Compound	Yield (%)	MS (ES+) *m/z*
119	3-CN	7-Chloro-6-[4-(3'-cyanophenoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	37	404 $(M+H)^+$
120	2-CF_3	7-Chloro-6-[4-(2'-trifluoromethyl-phenoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	30	447 $(M+H)^+$
121	3-CF_3	7-Chloro-6-[4-(3'-trifluoromethyl-phenoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	37	447 $(M+H)^+$

Example 122

7-Chloro-6-[4-(3'-cyanobenzyloxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

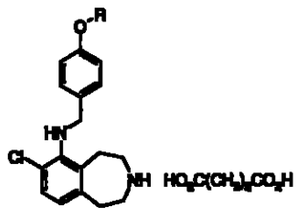


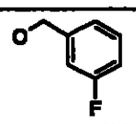
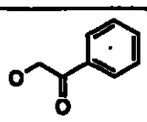
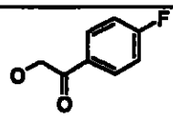
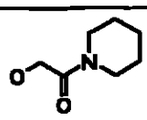
Mix 7-chloro-6-(4-hydroxy-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (150 mg, 0.38 mmol), 3-cyanobenzyl bromide (90 mg, 0.46 mmol), podwered potassium carbonate (105 mg, 0.76 mmol), powdered potassium iodide (6.6 mg, 0.04 mmol) and acetone (30 mL). Stir and heat to reflux under nitrogen for 16 hr. Dilute with acetone, filter, concentrate *in vacuo* and purify by chromatography on silica gel eluting with hexane/EtOAc (1:0 and 4:1) to obtain 7-chloro-6-[4-(3'-cyanobenzyloxy)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (72.4 mg, 37%). MS (ES+) *m/z* 514 $(M+H)^+$.

Use a method similar to the General Procedure 1-1 to deprotect 7-chloro-6-[4-(3'-cyanobenzyloxy)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (95:5) to give the free base of the title compound (42 mg, 71%). MS (ES+)

m/z: 418 $(M+H)^+$. Use a method similar to the General Procedure 2-1 to obtain the title compound.

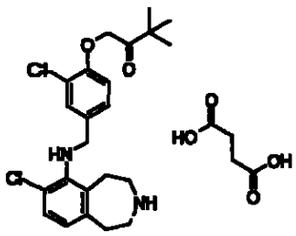
Examples 123-126 may be prepared essentially as described in Example 122 by using 7-chloro-6-(4-hydroxy-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropiate bromide. Overall yields and MS (ES+) data are shown in the Table below.



Ex.	O-R	Compound	Yield (%)	MS (ES+) *m/z*
123		7-Chloro-6-[4-(3'-fluorobenzyloxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	75	411 $(M+H)^+$
124		7-Chloro-6-[4-(2-oxo-2-phenyl-ethoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	45	421 $(M+H)^+$
125		7-Chloro-6-[4-(2-oxo-2-(4-fluorophenyl)-ethoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	17	439 $(M+H)^+$
126		7-Chloro-6-[4-(2-oxo-2-piperidin-1-yl-ethoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	44	428 $(M+H)^+$

Example 127

7-Chloro-6-[3-chloro-4-(3,3-dimethyl-2-oxo-butoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

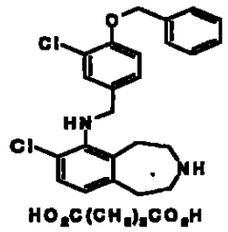


Use a method similar to the General Procedure 4-1 to react 7-chloro-6-(3-chloro-4-hydroxy-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (438 mg, 1.01 mmol) and 1-bromopinacolone (217 mg, 1.21 mmol). Purify by chromatography on silica gel eluting with EtOAc/hexane (1:4) to give 7-chloro-6-[3-chloro-4-(3,3-dimethyl-2-oxo-butoxy)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a colorless oil (441 mg, 82%). MS (ES+) *m/z*: 531 $(M+H)^+$.

Use a method similar to the General Procedure 1-1 to deprotect 7-chloro-6-[3-chloro-4-(3,3-dimethyl-2-oxo-butoxy)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (441 mg, 0.83 mmol). Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (93:7) to give the free base of the title compound (278 mg, 95%). MS (ES+) *m/z*: 435 $(M+H)^+$. Use a method similar to the General Procedure 2-1 to give the title compound.

Example 128

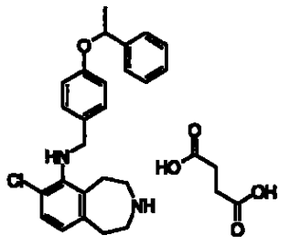
7-Chloro-6-(3-chloro-4-benzyloxy-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



The title compound may be prepared essentially as described in Example 127, using 7-chloro-6-(3-chloro-4-hydroxy-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and benzyl bromide (64%). MS (ES+) *m/z*: 427 $(M+H)^+$.

Example 129

(±)-7-Chloro-6-[4-(1-phenyl-ethoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

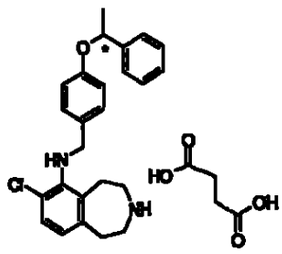


Use a method similar to the General Procedure 5-3, to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (851 mg, 2.0 mmol) and (±)-4-(1-phenyl-ethoxy)-benzylamine (721 mg, 2.6 mmol). Purify by chromatography on silica gel eluting with EtOAc/hexane (1:8) to give (±)-7-chloro-6-[4-(1-phenyl-ethoxy)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (702 mg, 69%). MS (ES+) *m/z*: 503 $(M+H)^+$.

Use a method similar to the General Procedure 1-1 to deprotect (±)-7-chloro-6-[4-(1-phenyl-ethoxy)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (702 mg, 1.40 mmol). Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (92:8) to give the free base of the title compound (368 mg, 65 %). MS (ES+) *m/z*: 407 $(M+H)^+$. Use a method similar to the General Procedure 2-1 to obtain the title compound.

Examples 130 and 131

(-)-7-Chloro-6-[4-(1-phenyl-ethoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate and (+)-7-Chloro-6-[4-(1-phenyl-ethoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

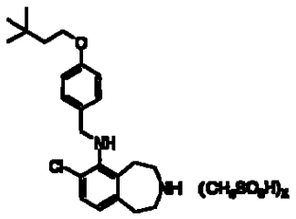


Separate the two enantiomers of Example 129 by chiral HPLC [Chiralcel OJ-H column, acetonitrile/methanol (20:80) with 0.2% DMEA; flow rate 1 mL/min; Isomer 1: t_R=5.0 min, Isomer 2: t_R=6.5 min].

Use a method similar to the General Procedure 2-1 to prepare the succinate of each enantiomer: (-)-7-chloro-6-[4-(1-phenyl-ethoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate, $[\alpha]^{20}_D$ –17.4° (c 0.5, CH_3OH), and (+)-7-chloro-6-[4-(1-phenyl-ethoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate, $[\alpha]^{20}_D$ +18.2° (c 0.5, CH_3OH).

Example 132

7-Chloro-6-[4-(3,3-dimethylbutoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Mesylate

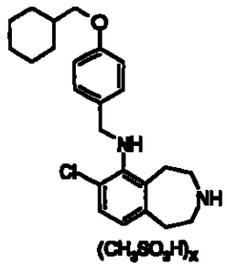


Use a method similar to the General Procedure 5-3 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (426 mg, 1.0 mmol) and 4-(3,3-dimethylbutoxy)-benzylamine (325 mg, 1.5 mmol). Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0 and 9:1) and then SCX chromatography to obtain 7-chloro-6-[4-(3,3-dimethylbutoxy)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. MS (ES+) *m/z*: 483 $(M+H)^+$.

Use a method similar to the General Procedure 1-1 to deprotect 7-chloro-6-[4-(3,3-dimethylbutoxy)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (95:5) to give the free base of the title compound (161 mg, 42% overall). MS (ES+) *m/z*: 387 $(M+H)^+$. Use a method similar to the General Procedure 2-4 to obtain the title compound.

Example 133

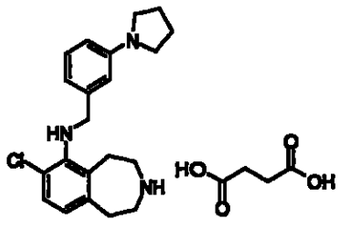
7-Chloro-6-(4-cyclohexylmethoxy-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Mesylate



The title compound may be prepared essentially as described in Example 132, using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 4-cyclohexylmethoxy-benzylamine (27% yield, MS (ES+) *m/z* 399 $(M+H)^+$).

Example 134

7-Chloro-6-(3-pyrrolidinyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

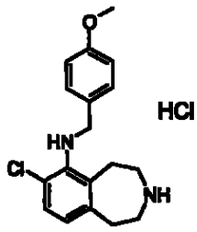


Use a method similar to the General Procedure 5-1, using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (300 mg, 0.7 mmol) and 3-(pyrrolidin-1-yl)benzylamine (300 mg, 1.7 mmol) to give, after chromatography on silica gel eluting with hexane/EtOAc (19:1, 9:1, 4:1 and 3:2), 7-chloro-6-(3-pyrrolidinyl-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow oil (195 mg, 62%). MS (ES+) *m/z*: 452 $(M+H)^+$.

Use a method similar to the General Procedure 1-1 to deprotect 7-chloro-6-(3-pyrrolidinyl-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (195 mg, 0.43 mmol). Purify by SCX chromatography to give the free base of the title compound (136 mg, 89%). Use a method similar to the General Procedure 2-1, using 7-chloro-6-(3-pyrrolidinyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (130 mg, 0.37 mmol), to give the title compound as an off-white gum (111 mg, 61%). MS (ES+) *m/z*: 356 $(M+H)^+$.

Example 135

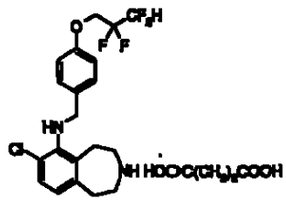
6-(4-Methoxybenzylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a similar method to the General Procedure 1-1, using 6-(4-methoxybenzylamino)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.1 g, 0.24 mmol) to give the free base of the title compound. Use a similar method to the General Procedure 2-2 to give the title compound (75 mg, 80%). HRMS calcd for $C_{18}H_{21}ClN_2O$ 317.1421, found 317.1410.

Example 136

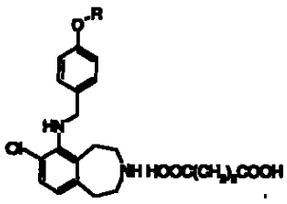
7-Chloro-6-[4-(2,2,3,3-tetrafluoropropoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (500 mg, 1.2 mmol) with 4-(2,2,3,3-tetrafluoropropoxy)-benzylamine (835 mg, 3.5 mmol) in toluene (10 mL). Purify by chromatography on silica gel eluting with hexane/EtOAc (10:1, 5:1 and 3:1) followed by SCX chromatography [pre-wash column with methanol followed by DCM, load material dissolved in DCM, then elute with DCM/2M ammonia in methanol (1:1) and concentrate *in vacuo*] to obtain 7-chloro-6-[4-(2,2,3,3-tetrafluoropropoxy)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (600 mg, 99%).

Use a method similar to the the General Procedure 1-3 to deprotect 7-chloro-6-[4-(2,2,3,3-tetrafluoropropoxy)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (600 mg, 1.2 mmol). Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (99:1 to 90:10) to give the free base of the title compound. Use a method similar to the General Procedure 2-1 to give the title compound (390 mg, 62 %). MS (ES+) *m/z*: 417 $(M+H)^+$.

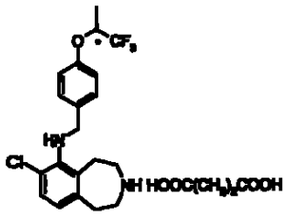
Examples 137-138 may be prepared essentially as described in Example 136 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. Overall yields and MS (ES+) data are shown in the Table below.



Ex.	O-R	Compound	Yield (%)	MS (ES+) *m/z*
137		7-Chloro-6-[4-(2,2,3,3,3-pentafluoropropoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	45	435 $(M+H)^+$
138		7-Chloro-6-[4-(2,2,2-trifluoro-1,2-dimethyl-ethoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	66	413 $(M+H)^+$

Examples 139 and 140

(-)-7-Chloro-6-[4-(2,2,2-trifluoro-1-methyl-ethoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate and (+)-7-Chloro-6-[4-(2,2,2-trifluoro-1-methyl-ethoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (500 mg, 1.2 mmol) with (±)-4-(2,2,2-trifluoro-1-methyl-ethoxy)-benzylamine (515 mg, 2.3 mmol) in toluene (10 mL). Purifyby chromatography on silica gel eluting with hexane/EtOAc (10:1, 5:1 and 3:1) followed by SCX chromatography [pre-wash column with methanol followed by DCM, load material dissolved in DCM, then elute with DCM/2M ammonia in methanol (1:1) and concentrate *in vacuo*] to give (±)-7-chloro-6-[4-(2,2,2-trifluoro-1-methyl-ethoxy)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (530 mg, 90%). GC-MS *m/z*: 494 (M^+).

Use a method similar to the General Procedure 1-3 to deprotect (±)-7-chloro-6-[4-(2,2,2-trifluoro-1-methyl-ethoxy)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (520 mg, 1.1 mmol). Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (99:1 to 90:10) to give (±)-7-chloro-6-[4-(2,2,2-trifluoro-1-methyl-ethoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Use a method similar to the General Procedure 2-1 to obtain (±)-7-chloro-6-[4-(2,2,2-trifluoro-1-methyl-ethoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate.

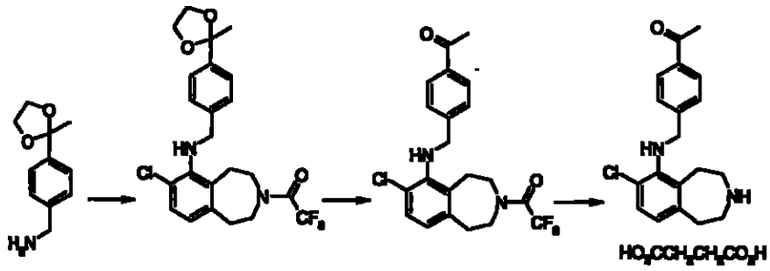
Separate the two enantiomers of (±)-7-chloro-6-[4-(2,2,2-trifluoro-1-methyl-ethoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine succinate by normal phase chiral chromatography (Chiralpak AD 8x30 cm, elute with 85:15 heptane/3A ethanol with 0.2% DMEA).

Use a method similar to the General Procedure 2-1 to obtain (-)-7-chloro-6-[4-(2,2,2-trifluoro-1-methyl-ethoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate [137 mg, 71% recovery, 98% ee (Chiralpak AD, 4.6x150 mm, eluent: 85:15 heptane/isopropanol with 0.2% DMEA., 0.6 mL/min)]. MS (ES+) *m/z*: 399 $(M+H)^+$. $[\alpha]^{20}_D$ –7.9° (c 0.5, MeOH).

Use a method similar to the General Procedure 2-1 to obtain (+)-7-chloro-6-[4-(2,2,2-trifluoro-1-methyl-ethoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate [133 mg, 69% recovery, 97% ee (Chiralpak AD, 4.6x150 mm, eluent: 85:15 heptane/isopropanol with 0.2% DMEA., 0.6 mL/min)]. MS (ES+) *m/z*: 399 $(M+H)^+$. $[\alpha]^{20}_D$ +9.2° (c 0.5, MeOH).

Example 141

6-(4-Acetyl-benzylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Use a method similar to the General Procedure 5-3 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (200 mg, 0.47 mmol) with 4-(2-methyl-[1,3]dioxolan-2-yl)-benzylamine (prepared by following the procedure described in *J. Med. Chem.* 1978, *21*, 507) (182 mg, 0.94 mmol). Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 19:1 and 9:1) to give 6-{4-(2-methyl-[1,3]dioxolan-2-yl)benzylamino}-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (150 mg, 68%). GC-MS *m/z* 468 (M^+).

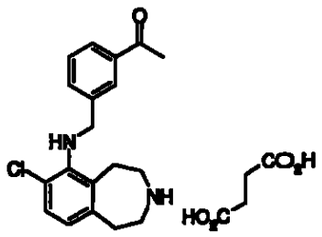
Dissolve 6-{4-(2-methyl-[1,3]dioxolan-2-yl)benzylamino}-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (150 mg, 0.32 mmol) in methanol (5 mL) and add 1N aqueous HCl (1 mL). Stir the solution at ambient temperature for 2 h. Remove the solvent, dissolve the residue in DCM and wash with saturated aqueous $NaHCO_3$. Dry the organic phase over Na_2SO_4, filter and concentrate. Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 9:1, 17:3 and 4:1) to obtain 6-(4-acetyl-benzylamino)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (107 mg, 79%). GC-MS *m/z* 424 (M^+).

Use a method similar to the General Procedure 1-2, using 6-(4-acetyl-benzylamino)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (100 mg, 0.23 mmol), to give the free base of the title compound as an oil (76 mg, 99%) that was used without further purification.

Use a method similar to the General Procedure 2-1, using 6-(4-acetyl-benzylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (76 mg, 0.23 mmol), to give the title compound as a white solid (102 mg, 97%). MS (ES+) *m/z*: 329 $(M+H)^+$.

Example 142

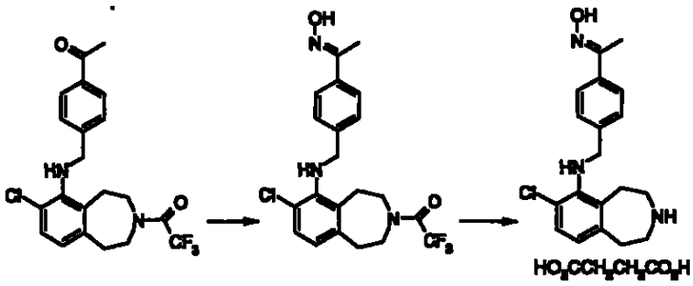
6-(3-Acetylbenzylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Use a method similar to Example 141, using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 3-(2-methyl-[1,3]dioxolan-2-yl)-benzylamine (prepared by following the procedure described in *J. Med. Chem.* 2000, *43*, 3315), to give the title compound as a solid. MS (ES+) *m/z*: 329 $(M+H)^+$.

Example 143

7-Chloro-6-[4-(1-hydroxyiminoethyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Add hydroxylamine hydrochloride (19 mg, 0.27 mmol) and pyridine (0.04 mL, 0.54 mmol) to a solution of 6-(4-acetylbenzylamino)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (115 mg, 0.27 mmol) in ethanol (10 mL). Heat the mixture to reflux for 2 h. Remove the solvent *in vacuo* and partition the residue between DCM and 0.1N aqueous HCl. Dry the organic phase over Na_2SO_4, filter and concentrate. Dissolve the oil into the minimum amount of ether and add hexane to precipitate the solid. Filter to obtain 7-chloro-6-[4-(1-hydroxyiminoethyl)-benzylamino]-

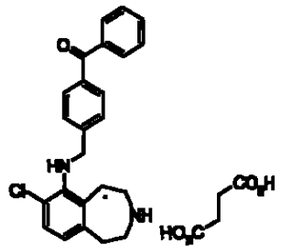
3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a solid (112 mg, 94%) that was used without further purification. MS (ES+) *m/z*: 440 $(M+H)^+$.

Use a method similar to the General Procedure 1-2, using 7-chloro-6-[4-(1-hydroxyiminoethyl)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (100 mg, 0.23 mmol), to give 7-chloro-6-[4-(1-hydroxyiminoethyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (61 mg, 78%) that was used without further purification.

Use a method similar to the General Procedure 2-1, using 7-chloro-6-[4-(1-hydroxyiminoethyl)benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine(58 mg, 0.17 mmol) to give the title compound as a white solid (68 mg, 87%). MS (ES+) *m/z*: 344 $(M+H)^+$.

Example 144

6-(4-Benzoyl-benzylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



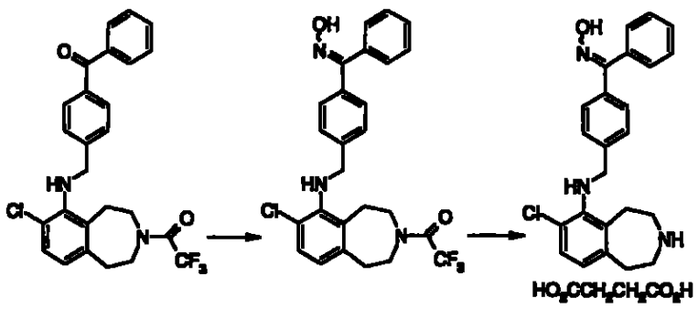
Use a method similar to the General Procedure 5-3 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (272 mg, 0.64 mmol) with 4-(aminomethyl)benzophenone (prepared by following the procedure described in *J. Biol. Chem.* 1993, *268 (19)*, 14230) (270 mg, 1.3 mmol). Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 9:1, 17:3 and 4:1) to give 6-(4-benzoyl-benzylamino)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (300 mg, 96%).

Use a method similar to the General Procedure 1-2, using 6-(4-benzoyl-benzylamino)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (80 mg, 0.16 mmol), to give 6-(4-benzoyl-benzylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (47 mg, 73%) that was used without further purification.

Use a method similar to the General Procedure 2-1, using -(4-benzoyl-benzylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (45 mg, 0.11 mmol), to give the title compound as a white solid (37 mg, 63%). MS (ES+) *m/z*: 391 $(M+H)^+$.

Example 145

7-Chloro-6-[4-(1-hydroxyiminobenzyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Add hydroxylamine hydrochloride (52 mg, 0.75 mmol) and pyridine (0.1 mL) to a solution of 6-(4-benzoyl-benzylamino)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (91 mg, 0.19 mmol) in ethanol (10 mL). Heat the mixture to reflux overnight. Remove the solvent *in vacuo* and partition the residue between DCM and 0.1N aqueous HCl. Dry the organic phase over Na_2SO_4, filter and concentrate. Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 4:1 and 3:1) to give 7-chloro-6-[4-(1-hydroxyiminobenzyl)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a mixture of E/Z isomers (93 mg, 99%).

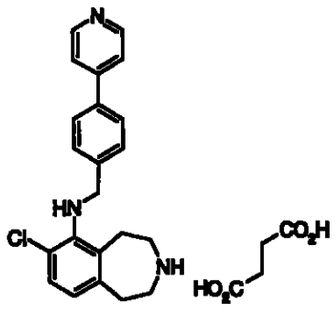
Use a method similar to the General Procedure 1-2, using 7-chloro-6-[4-(1-hydroxyiminobenzyl)benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (97 mg, 0.19 mmol), to give 7-chloro-6-[4-(1-hydroxyiminobenzyl)-

benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (68 mg, 87%) that was used without further purification.

Use a method similar to the General Procedure 2-1, using 7-chloro-6-[4-(1-hydroxyiminobenzyl)benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (65 mg, 0.16 mmol), to give the title compound as a white solid (67 mg, 80%). MS (ES+) *m/z*: 406 $(M+H)^+$.

Example 146

7-Chloro-6-[4-(pyridin-4-yl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



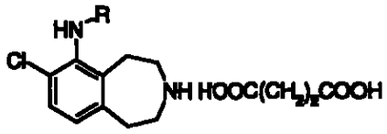
Use a method similar to the General Procedure 5-3, using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (178 mg, 0.426 mmol) and a solution of 4-(pyridin-4-yl)-benzylamine (116 mg, 0.63 mmol) in THF/toluene (1:1, 8 mL). Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 7:3 and 1:1) to give 7-chloro-6-[4-(4-pyridin-4-yl)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (120 mg, 63%). MS (ES+) *m/z*: 460 $(M+H)^+$.

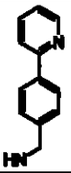
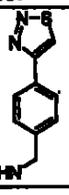
Use a method similar to the General Procedure 1-2, using 7-chloro-6-[4-(pyridin-4-yl)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (153 mg, 0.33 mmol), to give 7-chloro-6-[4-(pyridin-4-yl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (110 mg, 91%) that was used without further purification.

Use a method similar to the General Procedure 2-1, using 7-chloro-6-[4-(pyridin-4-yl)-

benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (105 mg, 0.289 mmol) to give the title compound as a white solid (123 mg, 88%). MS (ES+) *m/z*: 364 $(M+H)^+$.

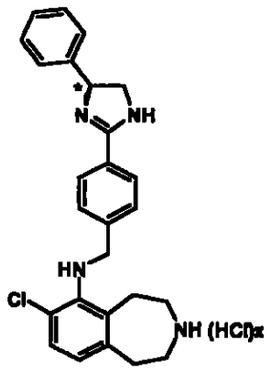
Examples 147-149 may be prepared essentially as described in Example 146 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. Overall yields and MS (ES+) data are shown in the Table below.



Ex.	NH-R	Compound	Yield (%)	MS (ES+) *m/z*
147		7-Chloro-6-[4-(pyridin-2-yl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	32	364 $(M+H)^+$
148		7-Chloro-6-[4-(1,2,3-thiadiazol-4-yl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	23	371 $(M+H)^+$
149		7-Chloro-6-[4-(2-methylthiazol-4-yl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	22	384 $(M+H)^+$

Example 150

(-)-7-Chloro-6-[4-(4-phenyl-4,5-dihydro-1*H*-imidazol-2-yl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

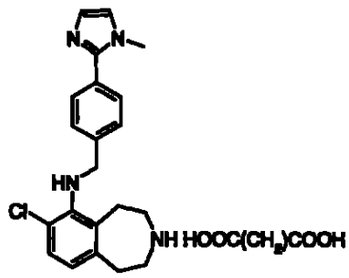


Mix 7-chloro-6-(4-cyanobenzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (200mg, 0.49 mmol, 1.0 equiv.), 1-(*R*)-phenyl-ethane-1,2-diamine (600 mg, 4.4 mmol, prepared as described in *J. Org. Chem.* 1997, 62, 3586) and *p*-toluenesulfonic acid monohydrate (102 mg, 0.53 mmol) in a sealed tube equipped with a magnetic stirrer. Heat the mixture to 200°C for 16 h. Cool the mixture to ambient temperature. Dilute with DCM (50 mL) and wash with saturated aqueous $NaHCO_3$ (10 mL). Collect the organic fraction and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (98:2 to 80:20).

Use a method similar to the General Procedure 2-3 to give title compound as the hydrochloride. Use reverse phase HPLC [Column: Symmetry C18, 10x300 mm, flow = 25 mL/min, water with 0.1% TFA / Acetonitrile (9:1 to 2:3)] followed by SCX chromatography to obtain the free base of the title compound. Use a method similar to the General Procedure 2-3 to obtain the title compound (38 mg, 16%). MS (ES+) *m/z*: 431 $(M+H)^+$. $[\alpha]^{20}_D$ -20° (c 0.5, MeOH).

Example 151

7-Chloro-6-[4-(1-methyl-1*H*-imidazol-2-yl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

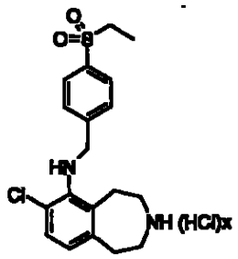


Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (455 mg, 1.1 mmol) with 4-(1-methyl-1*H*-imidazol-2-yl)-benzylamine (240 mg, 1.3 mmol) in toluene (8 mL). Purify by chromatography on silica gel eluting with hexane/EtOAc (10:1, 5:1 and 3:1) followed by SCX chromatography [pre-wash column with methanol followed by DCM, load material dissolved in DCM, then elute with DCM/2M ammonia in methanol (1:1) and concentrate *in vacuo*] to obtain 7-chloro-6-[4-(1-methyl-1*H*-imidazol-2-yl)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (429 mg, 93%). MS (ES+) *m/z*: 463 $(M+H)^+$.

Use a method similar to the General Procedure 1-3 to deprotect 7-chloro-6-[4-(1-methyl-1*H*-imidazol-2-yl)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (99:1 to 90:10) to give the free base of the title compound. Use a method similar to the General Procedure 2-1 to give the title compound (350 mg, 73 %). MS (ES+) *m/z*: 367 $(M+H)^+$.

Example 152

7-Chloro-6-(4-ethanesulfonyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



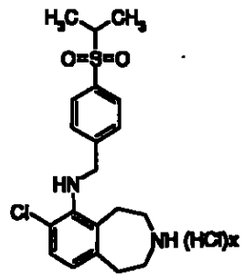
Use a method similar to the General Procedure 5-2, using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.2 g, 0.35 mmol) and 4-ethanesulfonyl-benzylamine (0.2 g, 1.06 mmol) to give 7-chloro-6-(4-ethanesulfonyl-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a colorless oil.

Use a method similar to the General Procedure 1-1 to obtain the free base of the title compound as a yellow oil. Use a method similar to the General Procedure 2-2 to form the hydrochloride salt. Purify by reverse phase preparative HPLC (Zorbax SB-Phenyl 21.2x250 mm, 5 micron, 22 mL/min of 0.1% HCl in water/acetonitrile (9:1 to 1:1) over 30 min, detector at 230 nm) to obtain the title compound as a white solid (57 mg, 36%).

MS (ES+) *m/z*: 379 $(M+H)^+$.

Example 153

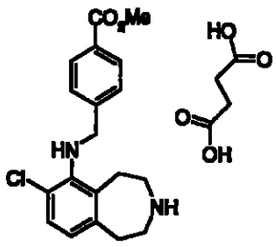
7-Chloro-6-[4-(2-propanesulfonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



The title compound may be prepared essentially as described in Example 152, using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 4-(2-propanesulfonyl)-benzylamine(11% yield, MS (ES+) *m/z* 393 $(M+H)^+$).

Example 154

7-Chloro-6-(4-methoxycarbonyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

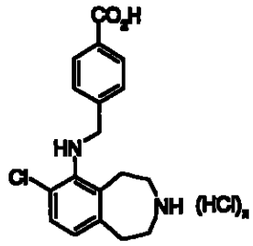


Treat 4-aminomethyl-benzoic acid methyl ester hydrochloride (0.2 g, 0.71 mmol) with K_2CO_3 (1.0 g, 0.71 mmol) in a mixture of toluene/water (1:1, 2 mL). Separate the organic layer, dry over anhydrous Na_2SO_4 and use as a toluene solution for the next step. Use a method similar to the General Procedure 5-2, using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.1 g, 0.24 mmol) and 4-aminomethyl-benzoic acid methyl ester (0.2 g, 0.71 mmol) to give 7-chloro-6-(4-methoxycarbonyl-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a colorless oil.

Use a method similar to the General Procedure 1-1 to obtain the free base of the title compound as a yellow oil. Use a method similar to the General Procedure 2-1 to obtain the title compound as a white solid (20 mg, 18%). MS (ES+) *m/z*: 345 $(M+H)^+$.

Example 155

6-(4-Carboxy-benzylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



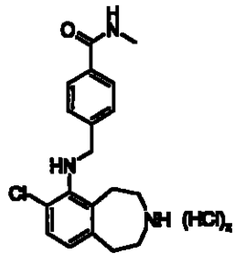
Combine 7-chloro-6-(4-methoxycarbonyl-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (70 mg, 0.16 mmol), potassium carbonate (0.87 g, 6.3 mmol), methanol (2 mL), water (2 mL) and heat at 50°C for 3 h. Purify by SCX

chromatography to obtain 6-(4-carboxy-benzylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow oil.

Use a method similar to the General Procedure 2-2 to form the hydrochloride salt. Purify by reverse phase preparative HPLC [Zorbax SB-Phenyl 21.2x250 mm, 5 micron, 22 mL/min of 0.1% HCl in water/acetonitrile (9:1 to 1:1) over 30 min, detector at 230 nm] to obtain the title compound as a white solid (30 mg, 46%). MS (ES+) *m/z*: 331 $(M+H)^+$.

Example 156

7-Chloro-6-(4-methylcarbamoyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

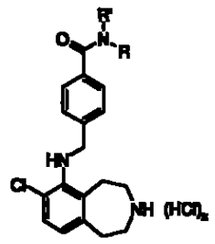


Combine 3-(*tert*-butoxycarbonyl)-6-(4-carboxy-benzylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.1 g, 0.3 mmol), methylamine hydrochloride (31 mg, 0.46 mmol), triethylamine (0.1 g, 0.9 mmol), HATU (0.2 g, 0.5 mmol), anhydrous DMF (3 mL) and stir at ambient temperature for 17 h. Partition the reaction mixture between brine (5 mL) and diethyl ether (5 mL), separate the organic layer and dry over anhydrous Na_2SO_4. Evaporate the solvent to obtain 3-(*tert*-butoxycarbonyl)-7-chloro-6-(4-methylcarbamoyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow oil (0.1 g, 93%). MS (ES+) *m/z*: 344 $(M+H\text{-}Boc)^+$.

Use a method similar to the General Procedure 1-5 and purify the residue by SCX chromatography to obtain the free base of the title compound as a yellow oil. Use a method similar to the General Procedure 2-2 to form the hydrochloride salt. Purify by reverse phase preparative HPLC [Zorbax SB-Phenyl 21.2x250 mm, 5 micron, 22 mL/min

of 0.1% HCl in water/acetonitrile (9:1 to 1:1) over 30 min, detector at 230 nm] to obtain the title compound as a white solid (0.9 g, 65%). MS (ES+) *m/z*: 344 $(M+H)^+$.

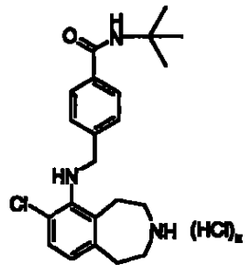
Examples 157-158 may be prepared essentially as described in Example 156 by using 3-(*tert*-butoxycarbonyl)-6-(4-carboxy-benzylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. Overall yields and MS (ES+) data are shown in the Table below.



Ex.	R	R'	Compound	Yield (%)	MS (ES+) *m/z*
157	Me	Me	7-Chloro-6-(4-dimethylcarbamoyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	51	358 $(M+H)^+$
158	*i*-Pr	H	7-Chloro-6-(4-isopropylcarbamoyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	56	372 $(M+H)^+$

Example 159

6-(4-*tert*-Butylcarbamoyl-benzylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

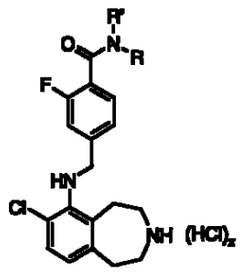


Use a method similar to the General Procedure 5-2, using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.2 g, 0.35 mmol) and 4-aminometyl-N-*tert*-butyl-benzamide (0.2 g, 1.06 mmol), to give

6-(4-*tert*-butylcarbamoyl-benzylamino)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a colorless oil.

Use a method similar to the General Procedure 1-1 to obtain the free base of the title compound as a yellow oil. Use a method similar to the General Procedure 2-2 to form the hydrochloride salt and purify by reverse phase preparative HPLC [Zorbax SB-Phenyl 21.2x250 mm, 5 micron, 22 mL/min of 0.1% HCl in water/acetonitrile (9:1 to 1:1) over 30 min, detector at 230 nm] to obtain the title compound as a white solid (65 mg, 41%). MS (ES+) *m/z*: 386 $(M+H)^+$.

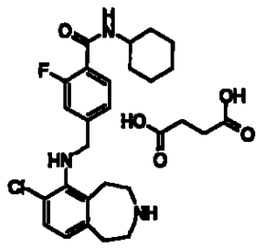
Examples 160-161 may be prepared essentially as described in Example 159 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. Overall yields and MS (ES+) data are shown in the Table below.



Ex.	R	R'	Compound	Yield (%)	MS (ES+) *m/z*
160	*t*-Bu	Me	6-(4-*tert*-Butylcarbamoyl-3-fluoro-benzylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo [*d*]azepine Hydrochloride	48	404 $(M+H)^+$
161	*n*-Pr	Me	7-Chloro-6-[3-fluoro-4-(*N*-methyl-*N*-propyl-carbamoyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	48	404 $(M+H)^+$

Example 162

7-Chloro-6-[4-(cyclohexylaminocarbonyl-)3-fluoro-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



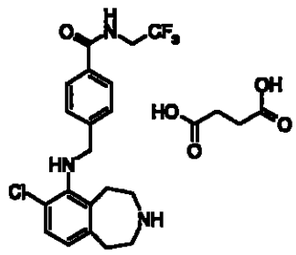
Use a method similar to the General Procedure 5-2 to react 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (500 mg, 1.17 mmol) with 4-aminomethyl-*N*-cyclohexyl-2-fluoro-benzamide (441 mg, 1.76 mmol). Purify by chromatography on silica gel eluting with hexane/EtOAc (20:1, 10:1, 7:1 and 5:1) to give 7-chloro-6-[4-(cyclohexylaminocarbonyl-)3-fluoro-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil.

Use a method similar to the General Procedure 1-3 and purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (1:0, 20:1. 10:1 and 7:1) followed by reverse phase semi-prep HPLC [SymmetryPrep C18, 7 □m, 19x300 mm column eluting with acetonitrile/0.1 % trifluoroacetic acid in water (1:9 to 8:2) at 20 mL/min] and SCX chromatography to give the free base of the title compound.

Use a method similar to the General Procedure 2-1 to give the title compound as a yellow solid (97 mg, 15%). MS (ES+) *m/z*: 430 $(M+H)^+$.

Example 163

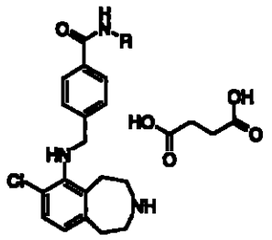
7-Chloro-6-[4-(2,2,2-trifluoroethylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



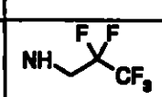
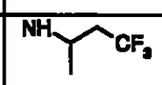
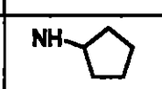
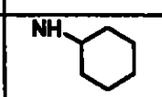
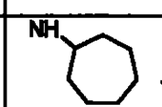
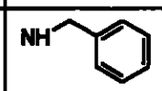
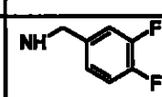
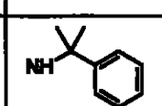
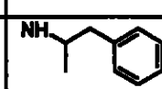
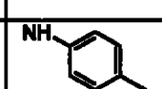
Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (250 mg, 0.59 mmol) with 4-aminomethyl-*N*-(2,2,2-trifluoroethyl)-benzamide (273 mg, 1.17 mmol). Purify by chromatography on silica gel eluting with hexane/EtOAc (20:1, 10:1, 7:1 and 5:1) to give 7-chloro-3-(2,2,2-trifluoroacetyl)-6-[4-(2,2,2-trifluoroethyl-aminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil.

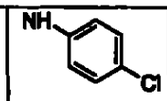
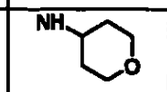
Use a method similar to the General Procedure 1-3 and purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (1:0, 20:1. 10:1 and 7:1) to give the free base of the title compound. Use a method similar to the General Procedure 2-1 to give the title compound as a white solid (191 mg, 61%). MS (ES+) *m/z*: 412 $(M+H)^+$.

Examples 164-177 may be prepared essentially as described in Example 163 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. Overall yields and MS (ES+) data are shown in the Table below.



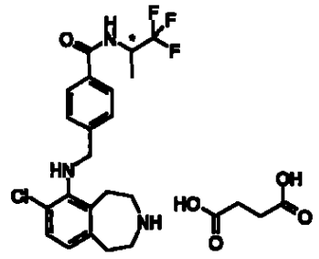
Ex.	NH-R	Compound	Yield (%)	MS (ES+) *m/z*

164		7-Chloro-6-[4-(3,3,3-trifluoro-propylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	38	426 $(M+H)^+$
165		7-Chloro-6-[4-(2,2,3,3,3-pentafluoro-propylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	41	462 $(M+H)^+$
166		(±)-7-Chloro-6-[4-(2,2,2-trifluoro-1-methyl-ethylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	46	426 $(M+H)^+$
167		(±)-7-Chloro-6-[4-(1-methyl-3,3,3-trifluoro-propylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	28	440 $(M+H)^+$
168		7-Chloro-6-[4-(cyclopentylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	55	398 $(M+H)^+$
169		7-Chloro-6-[4-(cyclohexylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	82	412 $(M+H)^+$
170		7-Chloro-6-[4-(cycloheptylcarbamoyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	65	426 $(M+H)^+$
171		6-[4-(Benzylaminocarbonyl)-benzylamino]-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	33	420 $(M+H)^+$
172		7-Chloro-6-[4-(3,4-difluoro-benzylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	55	456 $(M+H)^+$
173		7-Chloro-6-[4-(1-methyl-1-phenyl-ethylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	12	448 $(M+H)^+$
174		(±)-7-Chloro-6-[4-(1-methyl-2-phenyl-ethylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	36	448 $(M+H)^+$
175		7-Chloro-6-[4-(*p*-tolylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	60	420 $(M+H)^+$

176		7-Chloro-6-[4-(4-chloro-phenylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	28	440 $(M+H)^+$
177		7-Chloro-6-[4-(tetrahydro-pyran-4-yl-aminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	13	414 $(M+H)^+$

Examples 178 and 179

(-)-7-Chloro-6-[4-(2,2,2-trifluoro-1-methyl-ethylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate and (+)-7-Chloro-6-[4-(2,2,2-trifluoro-1-methyl-ethylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Dissolve (±)-7-chloro-6-[4-(2,2,2-trifluoro-1-methyl-ethylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (472 mg, 1.11 mmol) in DCM (50 mL) and add di-*tert*-butyl-dicarbonate (300 mg, 1.34 mmol) and a solution of sodium carbonate (2 g) in water (50 mL). Stir the reaction at room temperature for 2 h then dilute with DCM, wash with water, dry over Na_2SO_4, filter and concentrate. Purify by chromatography on silica gel eluting with hexane/EtOAc (10:1, 5:1 and 3:1) to give (±)-3-*tert*-butoxycarbonyl-7-chloro-6-[4-(2,2,2-trifluoro-1-methyl-ethylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-benzo[*d*]azepine (330 mg, 57%).

Separate the two enantiomers by chiral HPLC [Chiralpak AD column, 8x30 cm, eluting with 0.2% DMEA in heptane/isopropanol (9:1)].

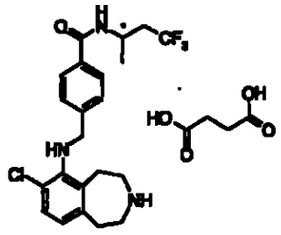
Use a method similar to the General Procedure 1-5 to deprotect the first eluting compound and purify by SCX chromatography to give (-)-7-chloro-6-[4-(2,2,2-trifluoro-

1-methyl-ethylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Use a method similar to the General Procedure 2-1 to give (-)-7-chloro-6-[4-(2,2,2-trifluoro-1-methyl-ethylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine succinate as a white solid (50 mg, 15%). MS (ES+) *m/z*: 426 $(M+H)^+$; $[\alpha]^{20}_D$ –3.3° (c 0.5, CH_3OH).

Use a method similar to the General Procedure 1-5 to deprotect the second eluting compound and purify by SCX chromatography to give (+)-7-chloro-6-[4-(2,2,2-trifluoro-1-methyl-ethylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Use a method similar to the General Procedure 2-1 to give (+)-7-chloro-6-[4-(2,2,2-trifluoro-1-methyl-ethylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine succinate as a white solid (55 mg, 16%). MS (ES+) *m/z*: 426 $(M+H)^+$; $[\alpha]^{20}_D$ +4.4° (c 0.5, CH_3OH).

Examples 180 and 181

(+)-7-Chloro-6-[4-(1-methyl-3,3,3-trifluoro-propylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate and (-)-7-Chloro-6-[4-(1-methyl-3,3,3-trifluoro-propylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Dissolve (±)-7-chloro-3-(2,2,2-trifluoroacetyl)-6-[4-(1-methyl-3,3,3-trifluoro-propylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (985 mg, 2.24 mmol) in DCM (50 mL) and add di-*tert*-butyl-dicarbonate (605 mg, 3.36 mmol) and a solution of sodium carbonate (2 g) in water (50 mL). Stir the mixture at room temperature for 1 h then dilute with DCM, wash with water, dry over Na_2SO_4, filter and concentrate. Purify by chromatography on silica gel eluting with hexane/EtOAc (10:1,

5:1 and 3:1) to give (±)-3-*tert*-butoxycarbonyl-7-chloro-6-[4-(1-methyl-3,3,3-trifluoro-propylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-benzo[*d*]azepine.

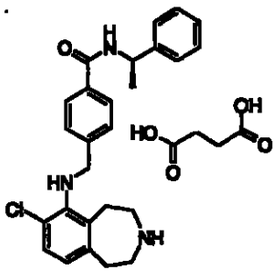
Separate the two enantiomers by chiral HPLC [Chiralpak AD column, 8x30 cm, eluting with heptane/isopropanol/0.2% DMEA in methanol (90:5:5)].

Use a method similar to the General Procedure 1-5 to deprotect the first eluting compound and purify by SCX chromatography to give (+)-7-chloro-6-[4-(1-methyl-3,3,3-trifluoro-propylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Use a method similar to the General Procedure 2-1 to give (+)-7-chloro-6-[4-(1-methyl-3,3,3-trifluoro-propylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine succinate as a white solid (186 mg, 15%). MS (ES+) *m/z*: 440 $(M+H)^+$; $[\alpha]^{20}_D$ +6.5° (c 0.5, CH_3OH).

Use a method similar to the General Procedure 1-5 to deprotect the second eluting compound and purify by SCX chromatography to give (-)-7-chloro-6-[4-(1-methyl-3,3,3-trifluoro-ptopylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Use a method similar to the General Procedure 2-1 to give (-)-7-chloro-6-[4-(1-methyl-3,3,3-trifluoro-propylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine succinate as a white solid (191 mg, 15%). MS (ES+) *m/z*: 440 $(M+H)^+$; $[\alpha]^{20}_D$ –5.2° (c 0.5, CH_3OH).

Example 182

(*R*)-(+)-7-Chloro-6-[4-(1-phenyl-ethylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

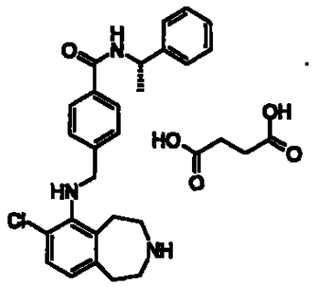


Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (250 mg, 0.59 mmol) with (*R*)-4-aminomethyl-*N*-(1-phenyl-ethyl)-benzamide (298 mg, 1.17 mmol) in toluene (15 mL). Purify by chromatography on silica gel eluting with hexane/EtOAc (20:1, 10:1, 7:1 and 5:1) to give (*R*)-(+)-7-chloro-6-[4-(1-phenyl-ethylcaminocarbonyl)-benzylamino]-3-(2,2,2-trifluoroacetyl)- 2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil.

Use a method similar to the General Procedure 1-3 and purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (1:0, 20:1. 10:1 and 7:1) to give the free base of the title compound. Use a method similar to the General Procedure 2-1 to give the title compound as a yellow solid (158 mg, 49%). MS (ES+) *m/z*: 434 $(M+H)^+$; $[\alpha]^{20}_D$ +18.7° (c 0.5, CH_3OH).

Example 183

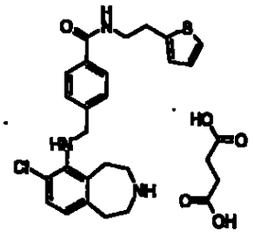
(*S*)-(-)-7-Chloro-6-[4-(1-phenyl-ethylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Use a method similar to the Example 182, using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (250 mg, 0.59 mmol) and (*S*)-4-aminomethyl-*N*-(1-phenyl-ethyl)-benzamide (298 mg, 1.17 mmol) to give the title compound as a white solid (95 mg, 29%). MS (ES+) *m/z*: 434 $(M+H)^+$; $[\alpha]^{20}_D$ -20.1° (c 0.5, CH_3OH).

Example 184

7-Chloro-6-{4-[(2-thiophen-2-yl-ethyl)-carbamoyl]-benzylamino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

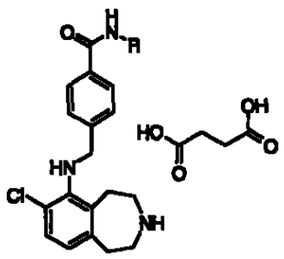


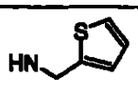
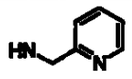
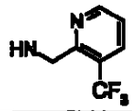
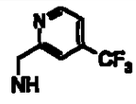
Use a method similar to the General Procedure 5-3, react 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (250 mg, 0.588 mmol) with 4-aminomethyl-*N*-(2-thiophen-2-yl-ethyl)-benzamide (306 mg, 1.176 mmol) using palladium(II) acetate (26 mg, 0.118 mmol), tris(dibenzylideneacetone)dipalladium(0) (53 mg, 0.059 mmol), BINAP (220 mg, 0.353 mmol) and cesium carbonate (383 mg, 1.176 mmol) in dioxane (6 mL). Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 7:3 and 1:1) to give 7-chloro-6-{4-[(2-thiophen-2-yl-ethyl)-carbamoyl]-benzylamino}-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (233 mg, 91%). MS (ES+) *m/z*: 535 $(M+H)^+$.

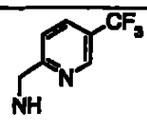
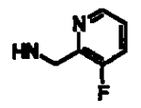
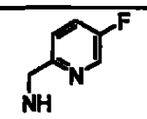
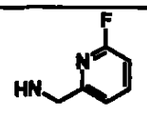
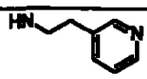
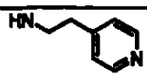
Use a method similar to the General Procedure 1-2, using 7-chloro-6-{4-[(2-thiophen-2-yl-ethyl)-carbamoyl]-benzylamino}-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (223 mg, 0.416 mmol), to give 7-chloro-6-{4-[(2-thiophen-2-yl-ethyl)-carbamoyl]-benzylamino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (145 mg, 79%) that was used without any further purification.

Use a method similar to the General Procedure 2-1, using 7-chloro-6-{4-[(2-thiophen-2-yl-ethyl)-carbamoyl]-benzylamino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (145 mg, 0.330 mmol), to give the title compound as a solid (123 mg, 67%). MS (ES+) *m/z*: 440 $(M+H)^+$.

Examples 185-194 may be prepared essentially as described in Example 184 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. Overall yields and MS (ES+) data are shown in the Table below.

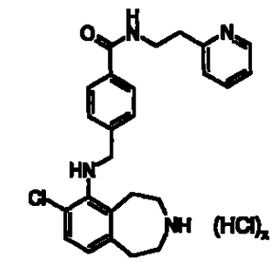


Ex.	NH-R	Compound	Yield (%)	MS (ES+) *m/z*
185		7-Chloro-6-{4-[(thiophen-2-ylmethyl)-carbamoyl]-benzylamino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	46	426 $(M+H)^+$
186		7-Chloro-6-{4-[(pyridin-2-ylmethyl)-carbamoyl]-benzylamino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	49	421 $(M+H)^+$
187		7-Chloro-6-{4-[(3-trifluoromethyl-pyridin-2-ylmethyl)-carbamoyl]-benzylamino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	39	489 $(M+H)^+$
188		7-Chloro-6-{4-[(4-trifluoromethyl-pyridin-2-ylmethyl)-carbamoyl]-benzylamino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	26	489 $(M+H)^+$

Ex.	NH-R	Compound	Yield (%)	MS (ES+) m/z
189		7-Chloro-6-{4-[(5-trifluoromethyl-pyridin-2-ylmethyl)-carbamoyl]-benzylamino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	29	489 $(M+H)^+$
190		7-Chloro-6-{4-[(3-fluoro-pyridin-2-ylmethyl)-carbamoyl]-benzylamino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	37	439 $(M+H)^+$
191		7-Chloro-6-{4-[(5-fluoro-pyridin-2-ylmethyl)-carbamoyl]-benzylamino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	51	439 $(M+H)^+$
192		7-Chloro-6-{4-[(6-fluoro-pyridin-2-ylmethyl)-carbamoyl]-benzylamino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	54	439 $(M+H)^+$
193		7-Chloro-6-[4-(2-pyridin-3-yl-ethylcarbamoyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	46	435 $(M+H)^+$
194		7-Chloro-6-[4-(2-pyridin-4-yl-ethylcarbamoyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	27	435 $(M+H)^+$

Example 195

7-Chloro-6-[4-(2-pyridin-2-yl-ethylcarbamoyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the General Procedure 5-3 to react 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine

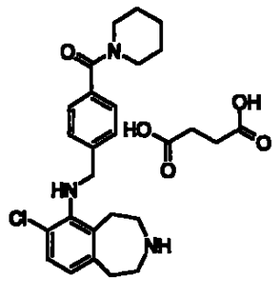
(200 mg, 0.471 mmol) and 4-aminomethyl-*N*-(2-pyridin-2-yl-ethyl)-benzamide (241 mg, 0.942 mmol) using palladium(II) acetate (21 mg, 0.094 mmol), tris(dibenzylideneacetone)dipalladium(0) (43 mg, 0.047 mmol), BINAP (176 mg, 0.283 mmol) and cesium carbonate (307 mg, 0.942 mmol) in dioxane (5 mL). Purify by chromatography on silica gel eluting with hexane and hexane/EtOAc/DCM/methanol (7:1:1:1) to give 7-chloro-6-[4-(2-pyridin-2-yl-ethylcarbamoyl)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (107 mg, 43%). MS (ES+) *m/z*: 531 $(M+H)^+$.

Use a method similar to the General Procedure 1-2, using 7-chloro-6-[4-(2-pyridin-2-yl-ethylcarbamoyl)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (107 mg, 0.202 mmol), to give 7-chloro-6-[4-(2-pyridin-2-yl-ethylcarbamoyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (85 mg, 97%) that was used without any further purification.

Use a method similar to the General Procedure 2-2, using 7-chloro-6-[4-(2-pyridin-2-yl-ethylcarbamoyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (85 mg, 0.195 mmol), to give the title compound as a solid (103 mg, 97 %). MS (ES+) *m/z*: 435 $(M+H)^+$.

Example 196

7-Chloro-6-[4-(piperidine-1-carbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



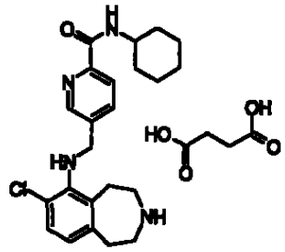
Using a method similar to the General Procedure 5-2, react 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine

(500 mg, 1.17 mmol) with 4-(piperidin-1-ylcarbonyl)-benzylamine (308 mg, 1.41 mmol). Purify by chromatography on silica gel eluting with hexane/EtOAc (20:1, 10:1, 7:1 and 5:1) to give 7-chloro-6-[4-(piperidine-1-carbonyl)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil.

Use a method similar to the General Procedure 1-3 and purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (1:0, 20:1. 10:1 and 7:1) to give the free base of the title compound. Use a method similar to the General Procedure 2-1 to give the title compound as a yellow solid (284 mg, 47%). MS (ES+) *m/z*: 398 $(M+H)^+$.

Example 197

7-Chloro-6-[2-(cyclohexylaminocarbonyl-pyridin-5-ylmethyl)-amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



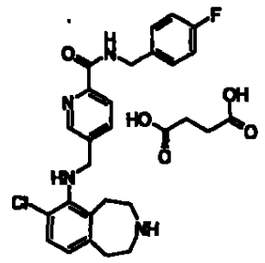
Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (348 mg, 0.82 mmol) with 5-aminomethyl-pyridine-2-carboxylic acid cyclohexylamide (200 mg, 0.86 mmol). Purify by chromatography on silica gel eluting with hexane/EtOAc (20:1, 10:1, 7:1 and 5:1) to give 7-chloro-6-[2-(cyclohexylaminocarbonyl-pyridin-5-ylmethyl)-amino]-3-(2,2,2-trifluoroacetyl)- 2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as oil.

Use a method similar to the General Procedure 1-3 and purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (1:0, 20:1. 10:1 and 7:1) to give the free base of the title compound.

Use a method similar to the General Procedure 2-1 to give the title compound as a yellow solid (147 mg, 34%). MS (ES+) *m/z*: 413 $(M+H)^+$.

Example 198

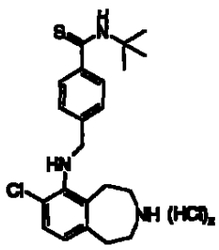
7-Chloro-6-[2-(4-fluoro-benzylaminocarbonyl)-pyridin-5-ylmethyl]-amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



The title compound may be prepared essentially as described in Example 197, using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 5-aminomethyl-pyridine-2-carboxylic acid 4-fluoro-benzylamide (28% yield, MS (ES+) m/z 439).

Example 199

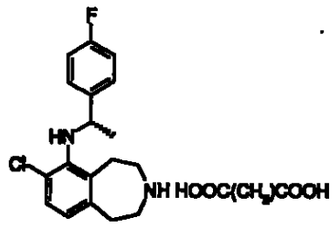
7-Chloro-6-(4-*tert*-butylthiocarbamoyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Combine 6-(4-*tert*-butylcarbamoyl-benzylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo-[*d*]azepine (0.3 g, 0.67 mmol), 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4- diphosphetane-2,4-disulfide (Lawesson's reagent) (0.3, g, 0.67 mmol) and anhydrous 1,4-dioxane (10 mL) in a sealed tube and heat at 100°C for 5 h. Cool the reaction mixture to ambient temperature, evaporate the solvent and purify the residue by SCX

Example 200

(*S*)-(-)-7-Chloro-6-[1-(4-fluorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

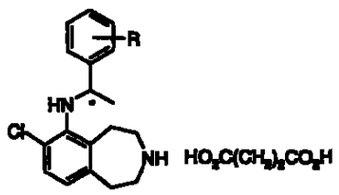


Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (7.0g, 16.4mmol) with (*S*)-1-(4-fluorophenyl)ethylamine (6.9 g, 49.3 mmol) in toluene (175 mL). Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1 to 1:1) followed by SCX chromatography [pre-wash column with methanol followed by DCM, load material dissolved in DCM, then elute with DCM/2M ammonia in methanol (1:1) and concentrate *in vacuo*] to give 7-chloro-6-[1-(*S*)-(4-fluorophenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (3.96 g, 58%). GC-MS *m/z*: 414 (M^+).

Use a method similar to the General Procedure 1-3 to deprotect 7-chloro-6-[1-(*S*)-(4-fluorophenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (3.92 g, 9.5 mmol) and purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (99:1 to 80:20) to give the free base of the title compound. Use a method similar to the General Procedure 2-1 and crystallize the solid from ethanol and methyl-*t*-butyl ether. Filter and dry the solid in a vacuum oven at 60°C overnight to obtain the title compound (3.4 g, 83 %). MS (ES+) *m/z*: 319 $(M+H)^+$; $[\alpha]^{20}_D$ –102.8° (c 0.5, MeOH).

Examples 201-209 may be prepared essentially as described in Example 200 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. The yields for the Step 1

(General Procedure 5-2), optical rotation and MS (ES+) data are shown in the Table below.

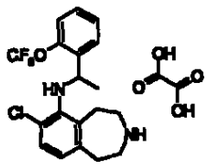


Ex.	R	Compound	Yield (%)	$[\alpha]^{20}_D$ (c, solvent)	MS
201	4-F	(*R*)-(+)-7-Chloro-6-[1-(4-fluorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	69	+89.2° (c 0.5, MeOH)	319 $(M+H)^+$
202	2-F	(+)-7-Chloro-6-[1-(2-fluorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	62	+105° (c 0.5, MeOH)	319 $(M+H)^+$
203	4-CN	(+)-7-Chloro-6-[1-(4-cyanophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	60	+142.1° (c 0.5, MeOH)	326 $(M+H)^+$
204	4-CN	(-)-7-Chloro-6-[1-(4-cyanophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	52	-149.3° (c 0.5, MeOH)	326 $(M+H)^+$
205	2,3-diF	(+)-7-Chloro-6-[1-(2,3-difluorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	14	+99.3° (c 0.5, MeOH)	337 $(M+H)^+$
206	2,3-diF	(-)-7-Chloro-6-[1-(2,3-difluorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	80	-107.9° (c 0.5, MeOH)	337 $(M+H)^+$
207	2,4-diF	(+)-7-Chloro-6-[1-(2,4-difluorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	94	+101.4° (c 0.5, MeOH)	337 $(M+H)^+$
208	2,4-diF	(-)-7-Chloro-6-[1-(2,4-difluorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	96	-107.9° (c 0.5, MeOH)	337 $(M+H)^+$

Ex.	R	Compound	Yield (%)	$[\alpha]^{20}_D$ (c, solvent)	MS
209	3,5-diCF_3	(-)-7-Chloro-6-[1-(3,5-bis-trifluoromethyl-phenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	99	-93° (c 0.5, MeOH)	437 $(M+H)^+$

Example 210

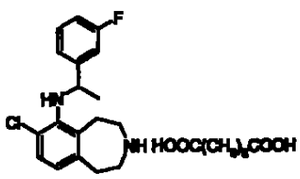
(+)-7-Chloro-6-[(2-trifluoromethoxy-phenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Oxalate



Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.15 g, 0.35 mmol) with 1-(2-trifluoromethoxyphenyl)-ethylamine Isomer 2 at 90°C for 15 h. Use a method similar to the General Procedure 1-2 and purify by reverse phase preparative HPLC to give the free base of the title compound. Use a method similar to the General Procedure 2-5 to give the title compound (27 mg, 16 %). HPLC t_R = 4.2 min (Chiralpak AD 4.6x150 mm, 3 micron column, 1.0 mL/min of 94.8/5/0.2 heptane/ethanol/dimethyethylamine isocratic; detector is at 225 nm); HRMS calcd for $C_{19}H_{20}ClF_3N_2O$ 385.1294, found 385.1285; $[\alpha]^{20}_D$ +95.4° (c 0.5, MeOH).

Example 211

(±)-7-Chloro-6-[1-(3-fluorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

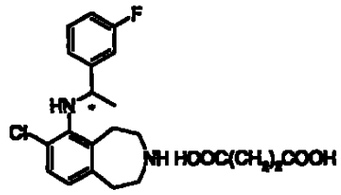


Add palladium(II) acetate (27 mg, 0.12 mmol), BINAP (146 mg, 0.24 mmol), cesium carbonate (270 mg, 0.8 mmol) and (±)-1-(3-fluorophenyl)-ethylamine (230 mg, 1.6 mmol) to a solution of 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (250 mg, 0.6 mmol) in toluene (9 mL). Degas the slurry and fill with nitrogen. Heat the mixture to 95°C for 16 h. Add additional palladium(II) acetate (0.1 equiv.) and BINAP (0.2 equiv.) and continue heating the reaction for an additional 24 h. Cool the mixture, dilute with EtOAc (50 mL) then filter through Celite®. Concentrate the filtrate and purify by chromatography on silica gel eluting with hexane/EtOAc (9:1 to 1:1) followed by SCX chromatography to obtain (±)-7-chloro-6-[1-(3-fluorophenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (138 mg, 56%). GC-MS *m/z*: 414 (M^+).

Use a method similar to the General Procedure 1-3 to deprotect (±)-7-chloro-6-[1-(3-fluorophenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (132 mg, 0.3 mmol) and purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (99:1 to 90:10) to give the free base of the title compound. Use a method similar to the General Procedure 2-1 to give the title compound (98 mg, 70 %). MS (ES+) *m/z*: 319 $(M+H)^+$.

Example 212

(+)-7-Chloro-6-[1-(3-fluorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

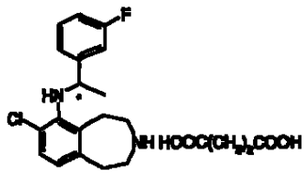


Separate the two enantiomers of (±)-7-chloro-6-[1-(3-fluorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine succinate by normal phase chromatography (Chiralpak AD 2x25 cm, elute with 95:5 heptane/isopropanol with 0.2 % DMEA).

Use a method similar to the General Procedure 2-1 to obtain the title compound [23 mg, 30% recovery, 99% ee (Chiralpak AD, 4.6x250 mm, eluent: 95:5 heptane/isopropanol, with 0.2% DMEA, 1.0 mL/min)]. MS (ES+) *m/z*: 319 $(M+H)^+$; $[\alpha]^{20}_D$ +64° (c 0.5, MeOH).

Example 213

(-)-7-Chloro-6-[1-(3-fluorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



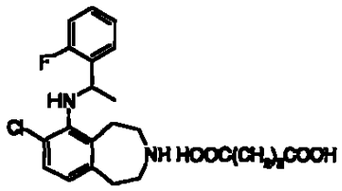
Add tris(dibenzylideneacetone)dipalladium(0) (3.4 g, 3.8 mmol), BINAP (4.7 g, 7.5 mmol), cesium carbonate (8.6 g, 26.3 mmol) and 1-(3-fluorophenyl)-ethylamine Isomer 2 (5.8 g, 41.3 mmol) to a solution of 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (8.0 g, 18.8 mmol) in toluene(225 mL). Degas the slurry and fill with nitrogen. Heat the mixture to 95 °C for 8 h. Add additional tris(dibenzylideneacetone)dipalladium(0) (0.1 equiv.), and BINAP (0.2 equiv.). Continue heating the reaction for an additional 16 h. Cool the mixture, dilute with EtOAc (200 mL) then filter thru Celite®. Concentrate *in vacuo* and purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) followed by SCX chromatography to obtain 7-chloro-6-[1-(3-fluorophenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (6.0 g, 78%). GC-MS *m/z*: 414 (M^+).

Use a method similar to the General Procedure 1-3 to deprotect 7-chloro-6-[1-(3-fluorophenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (6.0 g, 14.4 mmol). Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (99:1 to 90:10) to give the free base of the title compound. Use a method similar to the General Procedure 2-1 and crystallize the solid from ethanol and methyl-*t*-butyl ether. Filter and dry the solid under vacuum at 60°C

overnight to obtain the title compound [5.3 g, 84 % yield, 99% ee (Chiralpak AD, 4.6x250 mm, eluent: 95:5 heptane/EtOH, with 0.2% DMEA, 1.0 mL/min)]. MS (ES+) *m/z*: 319 $(M+H)^+$; $[\alpha]^{20}_D$ –90.6° (c 0.5, MeOH).

Example 214

(±)-7-Chloro-6-[1-(2-fluorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

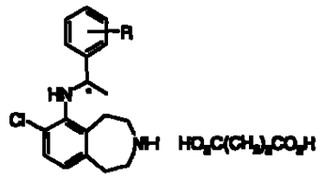


Use a method similar to the General Procedure 5-1 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (250 mg, 0.6 mmol) with (±)-1-(2-fluorophenyl)-ethylamine (206 mg, 1.5 mmol) in toluene (5 mL). Purify the residue by chromatography on silica gel eluting with hexane/EtOAc (9:1 to 1:1) followed by SCX chromatography [pre-wash column with methanol followed by DCM, load material dissolved in DCM, then elute with DCM/2M ammonia in methanol (1:1) and concentrate *in vacuo*] to obtain (±)-7-chloro-6-[1-(2-fluorophenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (86 mg, 35%). GC-MS *m/z*: 414 (M^+).

Use a method similar to the General Procedure 1-3 to deprotect (±)-7-chloro-6-[1-(2-fluorophenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (85 mg, 0.2 mmol) and purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (99:1 to 90:10) to give the free base of the title compound. Use a method similar to the General Procedure 2-1 to give the title compound (70 mg, 80 %). MS (ES+) *m/z*: 319 $(M+H)^+$.

Examples 215-216 may be prepared essentially as described in Example 214 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. The yields for the Step 1

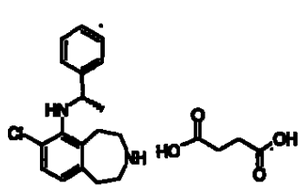
(General Procedure 5-1), optical rotation and MS (ES+) data are shown in the Table below.



Ex.	R	Compound	Yield (%)	$[\alpha]^{20}_D$ (c, solvent)	MS (ES+) *m/z*
215	3-CN	(+)-7-Chloro-6-[1-(3-cyanophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	58	+100.7° (c 0.5, MeOH)	326 $(M+H)^+$
216	3-CN	(-)-7-Chloro-6-[1-(3-cyanophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	90	-109.7° (c 0.5, MeOH)	326 $(M+H)^+$

Example 217

(*S*)-(-)-7-Chloro-6-(1-phenyl-ethylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

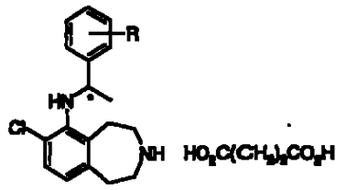


Add palladium(II) acetate (396 mg, 1.8 mmol), BINAP (2.2 g, 3.5 mmol), cesium carbonate (8.0 g, 24.6 mmol), and 1*S*-(-)-methylbenzylamine (6.4 g, 52.9 mmol) to a solution of 7-chloro-6-trifluoromethanesulfonyloxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1H-benzo[*d*]azepine (7.5 g, 17.6 mmol) in toluene(173 ml). Degas the slurry and fill with nitrogen. Heat the mixture to 95°C for 16 h. GC/MS shows some starting material still present after 16 h, so add additional palladium(II) acetate (0.1 equiv.), BINAP, and 1*S*-(-)-methylbenzylamine (1.0 equiv..). Continue heating the reaction for an additional 24 h. Cool the mixture, dilute with EtOAc (250 ml) then filter through Celite®. Concentrate *in vacuo* and purify by chromatography on silica gel eluting with hexane/EtOAc/methanol (84:15:1) followed by SCX chromatography to give (*S*)-7-

chloro-6-(1-phenyl-ethylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1H-benzo[*d*]azepine (4.38 g, 63%). GC-MS *m/z*: 396 (M^+).

Use a method similar to the General Procedure 1-1 to deprotect (*S*)-7-chloro-6-(1-phenyl-ethylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1H-benzo[*d*]azepine (4.3 g, 10.8 mmol). Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (99/1 to 80/20) to give the free base of the title compound. Use a method similar to the General Procedure 2-1 and crystallize the solid from ethanol and methyl-*t*-butyl ether. Filter and dry the solid in a vacuum oven at 70°C overnight to obtain the title compound (3.6 g, 80%). MS (ES+) *m/z*: 301 $(M+H)^+$. $[\alpha]^{20}_D$ –95.6° (c 0.5, MeOH).

Examples 218-227 may be prepared essentially as described in Example 217 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. The yields for the Step 1, optical rotation or enantiomeric excess (determined by chiral HPLC) and MS (ES+) data are shown in the Table below.



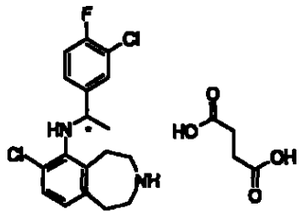
Ex.	R	Compound	Yield (%)	$[\alpha]^{20}_D$ (c, solvent) or ee (%)	MS (ES+) *m/z*
218	H	(*R*)-(+)-7-Chloro-6-(1-phenyl-ethylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	47	+100.5° (c 0.5, MeOH)	301 $(M+H)^+$
219	4-CF_3	(+)-7-Chloro-6-[1-(4-trifluoromethyl-phenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	55	+95.7° (c 0.5, MeOH)	369 $(M+H)^+$

Ex.	R	Compound	Yield (%)	$[\alpha]^{20}_D$ (c, solvent) or ee (%)	MS (ES+) *m/z*
220	3-CF_3	7-Chloro-6-[1-(3-trifluoromethyl-phenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate, Isomer 1	90	95% ee	369 $(M+H)^+$
221	3,4-diF	7-Chloro-6-[1-(3,4-trifluorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[d]azepine Succinate, Isomer 1	28	94 % ee	337 $(M+H)^+$
222	3,4-diF	(+)-7-Chloro-6-[1-(3,4-trifluorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[d]azepine Succinate	81	+89.0° (c 0.5, MeOH)	337 $(M+H)^+$
223	3,4,5-triF	7-Chloro-6-[1-(3,4,5-trifluorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[d]azepine Succinate, Isomer 2	40	ND	355 $(M+H)^+$
224	3-OCH_3	7-Chloro-6-[1-(3-methoxy-phenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride, Isomer 1	53	ND	331 $(M+H)^+$
225	4-OCH_3	7-Chloro-6-[1-(4-methoxy-phenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride, Isomer 1	53	>99 % ee	331 $(M+H)^+$
226	4-OPh	7-Chloro-6-[1-(4-phenoxyphenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[d]azepine Succinate, Isomer 1	27	ND	393 $(M+H)^+$
227	4-OPh	7-Chloro-6-[1-(4-phenoxyphenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[d]azepine Succinate, Isomer 2	27	ND	393 $(M+H)^+$

ND = Not determined

Example 228

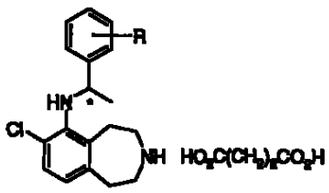
(-)-7-Chloro-6-[1-(3-chloro-4-fluoro-phenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Use a method similar to the General Procedure 5-3 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (426 mg, 1.0 mmol) with 1-(3-chloro-4-fluoro-phenyl)-ethylamine Isomer 1 (226 mg, 1.3 mmol). Purify by chromatography on silica gel eluting with EtOAc/hexane (1:7) to give 7-chloro-6-[1-(3-chloro-4-fluoro-phenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow oil (293 mg, 65%).

Use a method similar to the General Procedure 1-1 to deprotect 7-chloro-6-[1-(3-chloro-4-fluoro-phenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 1 (293 mg, 0.65 mmol). Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (94:6) to give the free base of the title compound as an oil (157 mg, 68%). MS (ES+) *m/z*: 353 $(M+H)^+$. Use a method similar to preparation E-1 to convert the free base to the title compound. $[\alpha]^{20}_D$ –115.9° (c 0.5, MeOH).

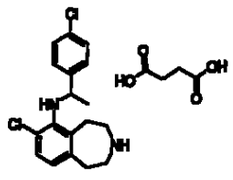
Examples 229-235 may be prepared essentially as described in Example 228 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. The yields for the Step 1 (General Procedure 5-3), optical rotation and MS (ES+) data are shown in the Table below.



Ex.	R	Compound	Yield (%)	$[\alpha]^{20}_D$ (c, solvent)	MS
229	3-Cl	(+)-7-Chloro-6-[1-(3-chlorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	17	+119.6° (c 0.5, CH_3OH)	335 $(M+H)^+$
230	2-Cl	(+)-7-Chloro-6-[1-(2-chlorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	30	+45.0° (c 0.5, CH_3OH)	335 $(M+H)^+$
231	4-CH_3	(*R*)-(+)-7-Chloro-6-(1-*p*-tolylethylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	57	+107° (c 0.5, MeOH)	315 $(M+H)^+$
232	4-CH_3	(*S*)-(-)-7-Chloro-6-(1-*p*-tolylethylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	54	-97.2° (c 0.5, MeOH)	315 $(M+H)^+$
233	3-Cl,4-F	(+)-7-Chloro-6-[1-(3-chloro-4-fluorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	84	+115.0° (c 0.5, CH_3OH)	353 $(M+H)^+$
234	3,5-diF	(-)-7-Chloro-6-[1-(3,5-difluorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	50	-97.6° (c 0.5, MeOH)	337 $(M+H)^+$
235	3,5-diF	(+)-7-Chloro-6-[1-(3,5-difluorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	41	+91.0° (c 0.5, MeOH)	337 $(M+H)^+$

Example 236

(±)-7-Chloro-6-[1-(4-chlorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

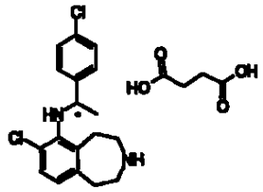


Use a method similar to the General Procedure 5-3 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (852 mg, 2.0 mmol) and (±)-4-chloro-(α-methyl)benzylamine (622 mg, 4.0 mmol). Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0 and 9:1) to obtain (±)-7-chloro-6-[1-(4-chlorophenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (326 mg, 38%). MS (ES+) *m/z*: 431 $(M+H)^+$.

Use a method similar to the General Procedure 1-1 to deprotect (±)-7-chloro-6-[1-(4-chlorophenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (95:5) to give the free base of the title compound (61 mg, 100%). MS (ES+) *m/z*: 335 $(M+H)^+$. Use a method similar to the General Procedure 2-1 to obtain the title compound.

Examples 237 and 238

(-)-7-Chloro-6-[1-(4-chlorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate and (+)-7-Chloro-6-[1-(4-chlorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



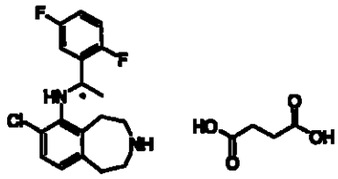
Submit (±)-7-chloro-6-[1-(4-chlorophenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (326 mg, 0.76 mmol) to chiral chromatography (Chiralpak AD, 4.6x150 mm, eluting with heptane/ethanol (9:1) with 0.2% DMEA, 1mL/min) to provide the two enantiomers: 7-chloro-6-[1-(4-chlorophenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 1 (102 mg, t_R = 5.25 min) and 7-chloro-6-[1-(4-chlorophenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 2 (110 mg, t_R = 6.40 min).

Use a method similar to the General Procedure 1-1 to deprotect 7-chloro-6-[1-(4-chlorophenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 1. Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (95:5) to give 7-chloro-6-[1-(4-chlorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 1 (Example 237, 82 mg, 100%). MS (ES+) *m/z*: 335 $(M+H)^+$. Use a method similar to the General Procedure 2-1 to obtain the title compound. $[\alpha]^{20}_D$ –127.7° (c 0.5, CH_3OH).

Use a method similar to the General Procedure 1-1 to deprotect 7-chloro-6-[1-(4-chlorophenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 2. Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (95:5) to give 7-chloro-6-[1-(4-chlorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 2 (Example 238, 68 mg, 78%). MS (ES+) *m/z*: 335 $(M+H)^+$. Use a method similar to the General Procedure 2-1 to obtain the title compound. $[\alpha]^{20}_D$ +133.6° (c 0.5, CH_3OH).

Examples 239 and 240

7-Chloro-6-[1-(2,5-difluorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate Isomer 1, and 7-chloro-6-[1-(2,5-difluorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate Isomer 2



Use a method similar to the General Procedure 5-1 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[d]azepine (550 mg, 1.27 mmol) and crude (±)-α-methyl-(2',5'-difluoro)benzylamine (400 mg).

Separate the two enantiomers by chiral chromatography (eluent: 75:20:5 heptane/isopropanol/methanol, 4.6x250 mm Chiralpak AD, 1 mL/min, uv 260 nm) to obtain 7-chloro-6-[1-(2,5-difluorophenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-

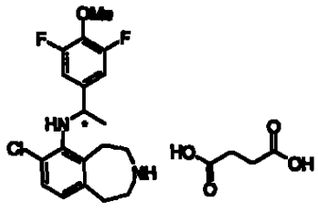
tetrahydro-1*H*-benzo[*d*]azepine Isomer 1 [150 mg, 29%; chiral HPLC: t_R = 4.5 min; MS (ES+) *m/z*: 433 $(M+H)^+$] and 7-chloro-6-[1-(2,5-difluorophenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 2 [130 mg, 25%; chiral HPLC: t_R = 5.5 min; MS (ES+) *m/z*: 433 $(M+H)^+$], both as opaque oils which solidify upon standing to off-white waxy solids.

Use a method similar to the General Procedure 1-1 to deprotect 7-chloro-6-[1-(2,5-difluorophenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 1 (140 mg, 0.32 mmol). Purify by SCX chromatography to give 7-chloro-6-[1-(2,5-difluorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 1 (102 mg, 95%) as a yellow oil. Use a method similar to the General Procedure 2-1 to obtain the Isomer 1 of the title compound (130 mg, 95%) as an off-white solid. MS (ES+) *m/z*: 337 $(M+H)^+$.

Use a method similar to the General Procedure 1-1 to deprotect 7-chloro-6-[1-(2,5-difluorophenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 2 (125 mg, 0.29 mmol). Purify by SCX chromatography to give 7-chloro-6-[1-(2,5-difluorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 2 (87.7 mg, 90%) as a yellow oil. Use a method similar to the General Procedure 2-1 to obtain the Isomer 2 of the title compound (117 mg, 99%) as an off-white solid. MS (ES+) *m/z*: 337 $(M+H)^+$.

Example 241

(-)-7-Chloro-6-[1-(3,5-difluoro-4-methoxy-phenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

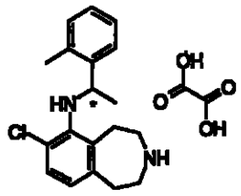


Use a method similar to the General Procedure 5-1 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[d]azepine

(300 mg, 0.7 mmol) and crude α-methyl-(3',5'-difluoro-4'-methoxy)benzylamine (380 mg). Purify by chromatography on silica gel eluting with hexane/EtOAc (95:5) followed by chiral chromatography [heptane/isopropanol/dimethylethylamine (90:10:0.2), 4.6x250 mm Chiralpak AD, 1 mL/min, uv 250 nm] to give 7-chloro-6-[1-(3,5-difluoro-4-methoxy-phenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 1 [59 mg, 18% yield, 99% ee, chiral HPLC: t_R = 6.0 min; MS (ES-) *m/z*: 461 (M-H)$^-$] and 7-chloro-6-[1-(3,5-difluoro-4-methoxy-phenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 2 [50 mg, 15% yield, 99% ee, chiral HPLC: t_R = 7.7 min; MS (ES-) *m/z*: 461 (M-H)$^-$]. Use a method similar to the General Procedure 1-1 to deprotect 7-chloro-6-[1-(3,5-difluoro-4-methoxy-phenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 2 (50 mg, 0.14 mmol). Purify by SCX chromatography to give 7-chloro-6-[1-(3,5-difluoro-4-methoxy-phenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 2 (35 mg, 70%) as a yellow oil. Use a method similar to the General Procedure 2-1, using 7-chloro-6-[1-(3,5-difluoro-4-methoxy-phenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 2 (35 mg, 0.10 mmol), to give the title compound (44 mg, 97%) as an off-white powder. MS (ES+) *m/z*: 367 $(M+H)^+$; $[\alpha]^{20}_D$ –107.0° (c 0.5, CH_3OH).

Example 242

(+)-7-Chloro-6-[(2-methylphenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Oxalate

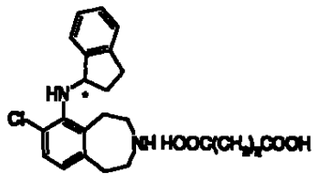


Usa a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.15 g, 0.35 mmol) with (*R*)-1-(2-methyl)-ethylamine (162 mg, 1.2 mmol) at 90°C for 17 h. Deprotect according to the General Procedure 1-2. Purify by reverse phase preparative HPLC and form the oxalate salt according to the General Procedure 2-5 to give the title compound (72 mg, 51 %). HPLC t_R = 4.0 min (Chiralpak AD 4.6x150 mm, 3 micron

column, 1.0 mL/min of 89.8:10:0.2 heptane/isopropanol/DMEA, isocratic; detector is at 225 nm); HRMS calcd for $C_{19}H_{23}ClN_2$ 315.1628, found 315.1623. $[\alpha]^{25}_D$ +67.2° (c 0.5, CH_3OH).

Example 243

(+)-7-Chloro-6-(indan-1-ylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

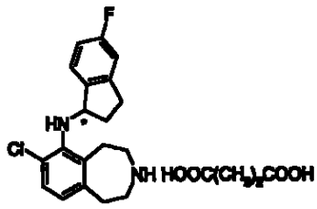


Use a method similar to the General Procedure 5-1 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (200 mg, 0.5 mmol) with (*R*)-1-aminoindan (188 mg, 1.4 mmol) in toluene (5 mL). Purify by chromatography on silica gel eluting with hexane / EtOAc (9:1 to 1:1) followed by SCX chromatography [pre-wash column with methanol followed by DCM, load material dissolved in DCM, then elute with DCM/2M ammonia in methanol (1:1) and concentrate *in vacuo*] to give 7-chloro-6-(indan-1-ylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (129 mg, 67%). GC-MS *m/z*: 408 (M^+).

Use a method similar to the General Procedure 1-1 to deprotect 7-chloro-6-(indan-1-ylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (125 mg, 0.3 mmol) and purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (99:1 to 80:20) to give the free base of the title compound. Use a method similar to the General Procedure 2-1 to give the title compound (104 mg, 78 %). MS (ES+) *m/z*: 313 $(M+H)^+$. $[\alpha]^{25}_D$ +73.9° (c 0.5, MeOH).

Example 244

(+)-7-Chloro-6-(5-fluoro-indan-1-ylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

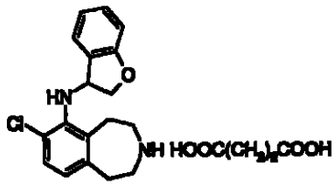


Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (210 mg, 0.5 mmol) with 5-fluoro-indan-ylamine Isomer 1 (161 mg, 1.1 mmol) in toluene (10 mL). Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1 to 1:1) followed by SCX chromatography to obtain 7-chloro-6-[1-(3,5-bis-trifluoromethyl-phenyl)-ethylamino]- 3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1H-benzo[*d*]azepine Isomer 1 (616 mg, 99%).

Use a method similar to the General Procedure 1-3 to deprotect 7-chloro-6-(5-fluoro-indan-ylamine)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1H-benzo[*d*]azepine Isomer 1 (200 mg, 0.5 mmol). Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (99/1 to 90/10) to give the free base of the title compound. Use Preparation E-1 to give the title compound (140 mg, 66 %). MS (ES+) *m/z*: 331 $(M+H)^+$. $[\alpha]^{20}_D$ + 80.0° (C, 0.5, MeOH)

Example 245

(±)-7-Chloro-6-(2,3-dihydro-benzofuran-3-ylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



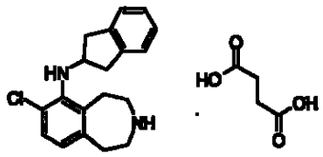
Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.15 g, 0.35 mmol) with 2,3-dihydro-benzofuran-3-ylamine (prepared as described in WO 0069816) (0.14 g, 1.1 mmol) at 90°C for 18 h.

Use a method similar to the General Procedure 1-2 and purify by reverse phase preparative HPLC [Zorbax SB-Phenyl 4.6x150 mm, 5 micron column, 1 mL/min of 0.1% TFA in water/ACN (9:1 to 1:9) over 30 min, detector at 230 and 254 nm].

Use a method similar to the General Procedure 2-1 to give the title compound (4.3 mg, 3%). HRMS calcd for $C_{18}H_{19}ClN_2O$ 315.1264, found 315.1256.

Example 246

7-Chloro-6-(indan-2-yl-amino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

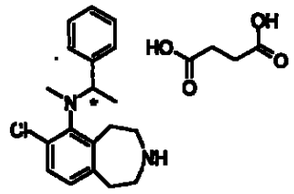


Use a method similar to the General Procedure 5-3, using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (426 mg, 1.0 mmol) and 2-aminoindane (400 mg, 3.0 mmol), to give 7-chloro-6-(indan-2-yl-amino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a slightly yellow oil (354 mg, 86%). MS (ES+) *m/z*: 409 $(M+H)^+$.

Using a method similar to the General Procedure 1-1, deprotect 7-chloro-6-(indan-2-yl-amino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (354 mg, 0.87 mmol) to obtain 7-chloro-6-(indan-2-yl-amino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a pale-yellow oil (166 mg, 61%). MS (ES+) *m/z*: 313 $(M+H)^+$. Use a method similar to the General Procedure 2-1 to give the title compound.

Example 247

(-)-7-Chloro-6-[(*N*-methyl)-1-phenylethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

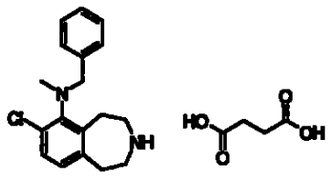


Dissolve (-)-7-chloro-6-(1-phenyl-ethylamine)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (192 mg) in DCE (5 mL) and add acetic acid (0.33 mL, 5.8 mmol), formaldehyde (37% solution; 0.5 mL) and sodium triacetoxyborohydride (570 mg, 2.7 mol) and stir the reaction at ambient temperature for 16 h. Dilute the reaction with DCM and wash with 1N aqueous NaOH. Dry the organic layers over Na_2SO_4, filter and concentrate. Purify by chromatography on silica gel eluting with hexane/EtOAc (20:1, 10:1 and 5:1) to give (-)-7-chloro-6-(methyl-1-phenylethylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil.

Use a method similar to the General Procedure 1-3 to deprotect (-)-7-chloro-6-(methyl-1-phenylethylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and purify by SCX chromatography to give the free base of the title compound. Use a method similar to the General Procedure 2-1 to give the title compound as a white solid (176 mg, 85%). MS (ES+) *m/z*: 315 $(M+H)^+$. $[\alpha]^{20}_D$ –5.4° (c 0.5, CH_3OH).

Example 248

7-Chloro-6-[(*N*-methyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

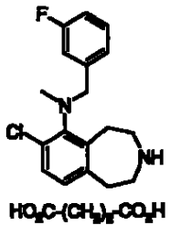


Dissolve 6-benzylamino-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (330 mg, 0.86 mmol) in DCM (3 mL) and add triethylamine (250 □L, 1.8 mmol) followed by di-*tert*-butyl-dicarbonate (260 mg, 1.2 mmol). Stir at ambient temperature for 1 h. Pour the mixture into water (250 mL), extract with DCM (3x25 mL) and concentrate *in vacuo* to give, after chromatography on silica gel eluting with hexane/EtOAc (9:1), 6-benzylamino-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a colorless oil (260 mg, 78%).

Dissolve 6-benzylamino-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (50 mg, 0.11 mmol) in acetonitrile (3 mL) and add a solution of formaldehyde in water (37%, 85 μL, 0.97 mmol) followed by sodium cyanoborohydride (16.5 mg, 0.26 mmol). Heat the solution to reflux 1 h, cool to ambient temperature, add glacial acetic acid (0.25 mL) and stir 72 h. Pour the mixture into water (100 mL) containing methanol (1 mL), extract with DCM (3x20 mL), wash the organic extracts with brine, dry over $MgSO_4$, filter and concentrate *in vacuo*. Dissolve the resulting residue in DCM (5 mL), and add trifluoroacetic acid (2 mL). Stir for 2 h at ambient temperature and evaporate the solvent. Purify by SCX chromatography. Use a method similar to the General Procedure 2-1 to give the title compound (45 mg, 95%). MS (ES+) *m/z*: 301 $(M+H)^+$.

Example 249

7-Chloro-6-[(*N*-methyl)-3-fluorobenzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

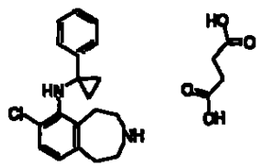


$HO_2C-(CH_2)_2-CO_2H$

The title compound may be prepared essentially as described in Example 248 by using 7-chloro-6-(3-fluorobenzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (85% yield and MS (ES+) *m/z* 319 $(M+H)^+$).

Example 250

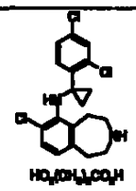
7-Chloro-6-(1-phenyl-cyclopropylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.2 g, 0.47 mmol) with 1-phenyl-cyclopropylamine (0.2 g, 1.41 mmol) using tris(dibenzylideneacetone)dipalladium(0) (43.0 mg, 0.05 mmol), BINAP (0.1 g, 0.15 mmol) and cesium carbonate (0.3 g, 0.97 mmol) at 90°C for 17 h to obtain 7-chloro-6-(1-phenyl-cyclopropylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a colorless oil.

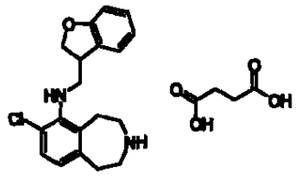
Use a method similar to the General Procedure 1-1 to obtain the free base of the title compound as a yellow oil. Use a method similar to the General Procedure 2-1 to obtain the title compound as a white solid (85 mg, 33%).

Example 251 may be prepared essentially as described in Example 250 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 1-(2,4-dichlorophenyl)-cyclopropylamine. The overall yield (3 steps) is shown in the Table below.

Ex.	Structure	Compound	Yield (%)
251		7-Chloro-6-[1-(2,4-dichlorophenyl)-cyclopropylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	19

Example 252

(±)-7-Chloro-6-(2,3-dihydro-benzofuran-3-yl-methylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

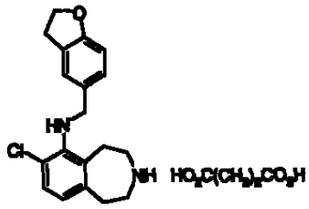


Use a method similar to the General Procedure 5-2 to couple 2,3-dihydro-benzofuran-3-yl-methylamine (prepared as described in WO 0069816) (0.14 g, 1.1 mmol) with 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.15 g, 0.35 mmol) at 90°C for 18 h.

Use a method similar to the General Procedure 1-2 to deprotect 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Purify by reverse phase preparative HPLC [Zorbax SB-Phenyl 4.6x150 mm 5 micron column, 1 mL/min of 1% TFA in water/ACN (9:1 to 1:9) over 30 min, detector at 230 and 254 nm]. Use a method similar to the General Procedure 2-1 to give the title compound (4.3 mg, 3%).

Example 253

7-Chloro-6-[(2,3-dihydrobenzo[b]furan-5-yl)-methylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



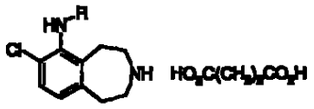
Suspend commercially available 2,3-dihydrobenzo[*b*]furan-5-yl-methylamine hydrochloride (1.0 g, 5.4 mmol) in DCM (100 mL). Add 1N aqueous NaOH (15 mL) and stir until all solids dissolve. Add two spatulas of NaCl. Stir the mixture and extract twice with DCM. Combine the organic layers, dry over Na_2SO_4, and concentrate in *vacuo* to

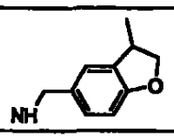
obtain 2,3-dihydrobenzo[*b*]furan-5-yl-methylamine (650 mg, 81%). MS (ES+) *m/z*: 133 $(M+H-NH_3)^+$.

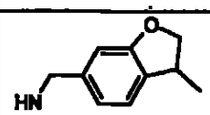
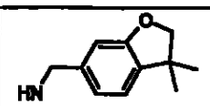
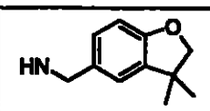
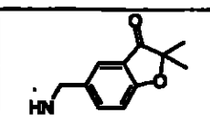
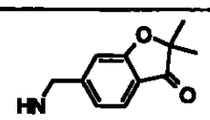
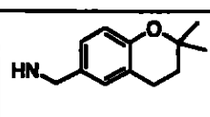
Use a method similar to the General Procedure 5-3 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (426 mg, 1.0 mmol) with 5-aminomethyl-2,3-dihydrobenzo[*b*]furane (223 mg, 1.5 mmol). Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0 and 9:1) to obtain 7-chloro-6-[(2,3-dihydrobenzo[b]furan-5-yl)-methylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (244 mg, 58%). MS (ES+) *m/z*: 425 $(M+H)^+$.

Use a method similar to the General Procedure 1-1 to deprotect 7-chloro-6-[(2,3-dihydrobenzo[b]furan-5-yl)-methylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (95:5) to give the free base of the title compound (105 mg, 32%). MS (ES+) *m/z*: 329 $(M+H)^+$. Use a method similar to the General Procedure 2-1 to obtain the title compound.

Examples 254-260 may be prepared essentially as described in Example 253 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. The yields for the Step 1 (General Procedure 5-3) and MS (ES+) data are shown in the Table below.

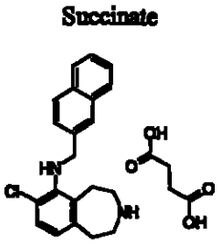


Ex.	NH-R	Compound	Yield (%)	MS (ES+) *m/z*
254		(±)-7-Chloro-6-[*C*-(3-methyl-2,3-dihydro-benzofuran-5-yl)-methylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	50	343 $(M+H)^+$

Ex.	NH-R	Compound	Yield (%)	MS (ES+) m/z
255		(±)-7-Chloro-6-[*C*-(3-methyl-2,3-dihydro-benzofuran-6-yl)-methylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	66	343 $(M+H)^+$
256		7-Chloro-6-[*C*-(3,3-dimethyl-2,3-dihydro-benzofuran-6-yl)-methylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	57	357 $(M+H)^+$
257		7-Chloro-6-[*C*-(3,3-dimethyl-2,3-dihydro-benzofuran-5-yl)-methylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	64	357 $(M+H)^+$
258		7-Chloro-6-[*C*-(2,2-dimethyl-3-oxo-2,3-dihydro-benzofuran-5-yl)-methylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	47	371 $(M+H)^+$
259		7-Chloro-6-[*C*-(2,2-dimethyl-3-oxo-2,3-dihydro-benzofuran-6-yl)-methylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	67	371 $(M+H)^+$
260		7-Chloro-6-[(2,2-dimethyl-chroman-6-yl)-methylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	24	371 $(M+H)^+$

Example 261

7-Chloro-6-(naphthalen-2-yl-methylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

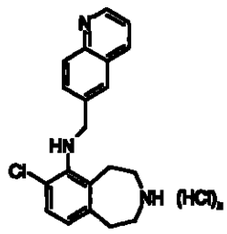


Use a method similar to the General Procedure 5-2 to couple 2-aminomethylnaphthalene (prepared as described in WO 9509159) (0.17 g, 1.1 mmol) with 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.15 g, 0.35 mmol) at 90°C for 18 h.

Use a method similar to the General Procedure 1-2 to give the free base of the title compound. HRMS calcd for $C_{21}H_{21}ClN_2$ 337.1471, found 337.1461. Use a method similar to the General Procedure 2-1 to give the title compound (104 mg, 66 % overall).

Example 262

7-Chloro-6-[(quinolin-6-yl-methyl)-amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

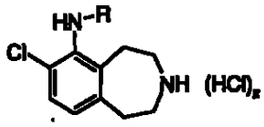


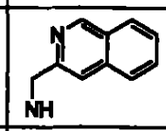
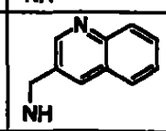
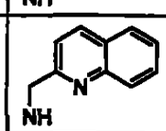
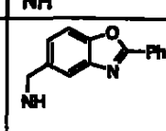
Use a method similar to the General Procedure 5-2, using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.2 g, 0.35 mmol) and 6-aminomethyl-quinoline (0.2 g, 1.06 mmol) with tris(dibenzylideneacetone)dipalladium(0) (32.0 mg, 0.04 mmol), BINAP (44.0 mg, 0.07 mmol) and cesium carbonate (0.2 g, 0.71 mmol) at 90°C for 17 h, to obtain 7-chloro-6-[(quinolin-6-yl-methyl)-amino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a colorless oil.

Use a method similar to the General Procedure 1-1 to obtain the free base of the title compound as a yellow oil. Use a method similar to the General Procedure 2-2 to form the hydrochloride salt and purify by reverse phase preparative HPLC [Zorbax SB-Phenyl 21.2x250 mm, 5 micron column, 22 mL/min of 0.1% HCl in water/acetonitrile (9:1 to 1:1) over 30 min, detector at 230 nm) to obtain the title compound as a white solid (50 mg, 56% overall). MS (ES+) *m/z*: 338 $(M+H)^+$.

Examples 263-266 may be prepared essentially as described in Example 262 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-

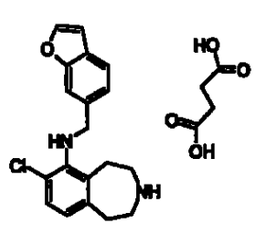
tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. Overall yields and MS (ES+) data are shown in the Table below.



Ex.	NH-R	Compound	Yield (%)	MS (ES+) *m/z*
263		7-Chloro-6-[(isoquinolin-3-yl-methyl)-amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	63	338 $(M+H)^+$
264		7-Chloro-6-[(quinolin-3-yl-methyl)-amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	35	338 $(M+H)^+$
265		7-Chloro-6-[(quinolin-2-yl-methyl)-amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	20	338 $(M+H)^+$
266		7-Chloro-6-[(2-phenyl-benzoxazol-6-yl-methyl)-amino]-2,3,4,5-tetrahydro-1*H*-benzo [*d*]azepine Hydrochloride	15	404 $(M+H)^+$

Example 267

6-[(Benzofuran-6-ylmethyl)-amino]-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

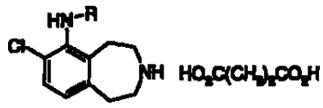


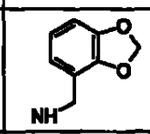
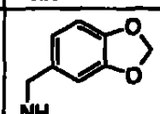
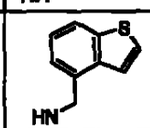
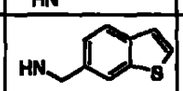
Use a method similar to the General Procedure 5-2, using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.2 g, 0.35 mmol) and 6-aminomethyl-benzofuran (0.2 g, 1.06 mmol) with tris(dibenzylideneacetone)dipalladium (0) (32.0 mg, 0.04 mmol), BINAP (88.0 mg, 0.11 mmol) and cesium carbonate (0.2 g, 0.71 mmol) at 90°C for 17 h, to obtain 6-

[(benzofuran-6-yl-methyl)-amino]-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a colorless oil.

Use a method similar to the General Procedure 1-1 to obtain the free base of the title compound as a yellow oil. Use a method similar to the General Procedure 2-1 to obtain the title compound as a white solid (72 mg, 46% overall). MS (ES+) *m/z*: 327 $(M+H)^+$.

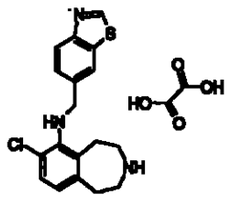
Examples 268-271 may be prepared essentially as described in Example 267 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. Overall yields and MS (ES+) data are shown in the Table below.



Ex.	NH-R	Compound	Yield (%)	MS (ES+) *m/z*
268		6-[(Benzo[1,3]dioxol-4-yl-methyl)-amino]-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	54	331 $(M+H)^+$
269		6-[(Benzo[1,3]dioxol-5-yl-methyl)-amino]-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	55	331 $(M+H)^+$
270		6-(Benzo[b]thiophen-4-yl-methylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	73	343 $(M+H)^+$
271		6-(Benzo[b]thiophen-6-yl-methylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	48	343 $(M+H)^+$

Example 272

6-[(Benzothiazol-6-yl-methyl)-amino]-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Oxalate

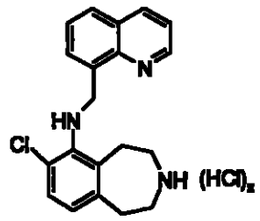


Using a method similar to the General Procedure 5-4, combine 6-amino-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[d] azepine (0.1 g, 0.35 mmol), 6-bromomethyl-benzothiazole (80 mg, 0.35 mmol), and potassium carbonate (47.0 mg, 0.35 mmol) in anhydrous DMF (1 mL) in a sealed tube. Heat at 150°C for 3 h to obtain 6-[(benzothiazol-6-yl-methyl)-amino]-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a colorless oil.

Use a method similar to the General Procedure 1-1 to obtain the free base of the title compound as a yellow oil. Use a method similar to the General Procedure 2-5 to obtain the title compound as a white solid (25 mg, 16% overall). MS (ES+) *m/z*: 344 $(M+H)^+$.

Example 273

7-Chloro-6-[(quinolin-8-yl-methyl)-amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



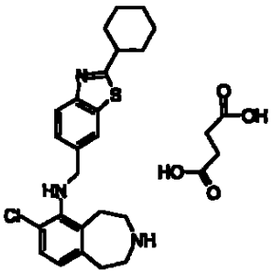
Using a method similar to the General Procedure 5-4, combine 6-amino-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*] azepine (0.1 g, 0.35 mmol), 8-bromomethyl-quinoline (83.6 mg, 0.038 mmol), cesium carbonate (0.2 g, 0.68 mmol) and anhydrous acetonitrile (1 mL) in a sealed tube and heat at 50°C for 12 h to obtain 7-

chloro-6-[(quinolin-8-yl-methyl)-amino)-amino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a colorless oil.

Use a method similar to the General Procedure 1-1 to obtain the free base of the title compound as a yellow oil. Use a method similar to the General Procedure 2-2 to form the hydrochloride salt and purify by reverse phase preparative HPLC [Zorbax SB-Phenyl 21.2x250 mm, 5 micron column, 22 mL/min of 0.1% HCl in water/acetonitrile (9:1 to 1:1) over 30 min, detector at 230 nm) to obtain the title compound as a white solid (13 mg, 8% overall). MS (ES+) *m/z*: 338 $(M+H)^+$.

Example 274

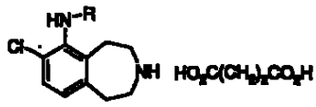
7-Chloro-6-[(2-cyclohexyl-benzothiazol-6-yl-methyl)-amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

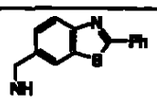
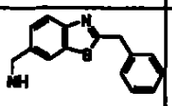
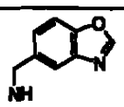


Using a method similar to the General Procedure 5-4, combine 6-amino-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*] azepine (60 mg, 0.21 mmol), 6-bromomethyl-2-cyclohexyl-benzothiazole (0.1 g, 0.31 mmol), potassium carbonate (58 mg, 0.42 mmol) and anhydrous toluene (2 mL) in a sealed tube and heat at 100°C for 72 h to obtain 7-chloro-6-[(2-cyclohexyl-benzothiazol-6-yl-methyl)-amino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a colorless oil.

Use a method similar to the General Procedure 1-1 to obtain the free base of the title compound as a yellow oil. Use a method similar to the General Procedure 2-1 to obtain the title compound as a white solid (40 mg, 35% overall). MS (ES+) *m/z*: 427 $(M+H)^+$.

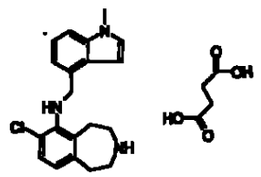
Examples 275-277 may be prepared essentially as described in Example 274 by using 6-amino-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[d] azepine and the appropriate bromide. Overall yields and MS (ES+) data are shown in the Table below.



Ex.	NH-R	Compound	Yield (%)	MS (ES+) *m/z*
275		7-Chloro-6-[(2-phenyl-benzothiazol-6-yl-methyl)-amino]-2,3,4,5-tetrahydro-1*H*-benzo [*d*]azepine Succinate	39	420 $(M+H)^+$
276		6-[(2-Benzyl-benzothiazol-6-yl-methyl)-amino]-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo [*d*]azepine Succinate	36	453 $(M+H)^+$
277		6-[(Benzoxazol-6-yl-methyl)-amino]-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	7	328 $(M+H)^+$

Example 278

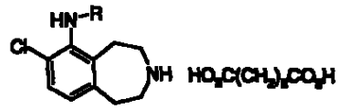
7-Chloro-6-[(1-methyl-indol-4-yl-methyl)-amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

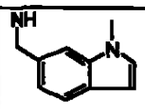
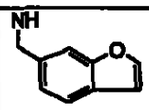


Using a method similar to the General Procedure 5-1, couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetra-hydro-1*H*-benzo[*d*]azepine (0.1 g, 0.24 mmol) with 4-aminomethyl-1-methylindole (0.1 g, 0.71 mmol) to obtain 7-chloro-6-[(1-methyl-indol-4-yl-methyl)-amino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a colorless oil.

Use a method similar to the General Procedure 1-1 to obtain the free base of the title compound as a yellow oil. Use a method similar to the General Procedure 2-1 to obtain the title compound as a white solid (0.1 g, 91% overall). MS (ES+) *m/z*: 340 $(M+H)^+$.

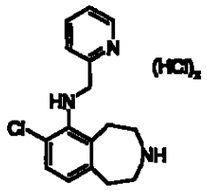
Examples 279-280 may be prepared essentially as described in Example 278 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine with the appropriate amine. Overall yields and MS (ES+) data are shown in the Table below.



Ex.	NH-R	Compound	Yield (%)	MS (ES+) *m/z*
279		7-Chloro-6-[(1-methyl-indol-6-yl-methyl)-amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	42	340 $(M+H)^+$
280		6-[(Benzofuran-6-ylmethyl)-amino]-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	46	327 $(M+H)^+$

Example 281

7-Chloro-6-(pyridin-2-ylmethylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



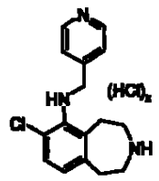
Use a method similar to the General Procedure 5-1 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (500 mg, 1.17 mmol) with pyridin-2-ylmethylamine (254 mg, 2 equiv.) using palladium acetate (0.1 equiv.), BINAP (0.3 equiv.) and cesium carbonate (1.4 equiv.) in toluene (5

mL). Purify the residue by chromatography on silica gel eluting with hexane/EtOAc (10:1, 5:1, 3:1, and 1:1) to give 7-chloro-6-(pyridin-2-ylmethylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil.

Use a method similar to the General Procedure 1-3 to deprotect 7-chloro-6-(pyridin-2-ylmethylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Purify by SCX chromatography followed by silica gel chromatography eluting with DCM/2M ammonia in methanol (1:0, 40:1, 20:1 and 10:1) to give the free base of the title compound. Use a method similar to the General Procedure 2-2 to give the title compound as an off white solid (207 mg, 55% overall). MS (ES+) *m/z*: 288 $(M+H)^+$.

Example 282

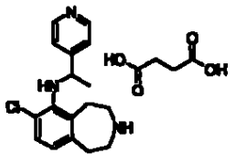
7-Chloro-6-(pyridin-4-ylmethylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



may be prepared essentially as described in Example 281 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and pyridin-4-ylmethylamine (28% yield, and MS (ES+) 288 $(M+H)^+$).

Example 283

(±)-7-Chloro-6-[(1-pyridin-4-yl-ethyl)-amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

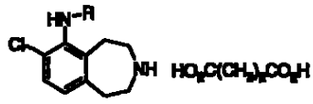


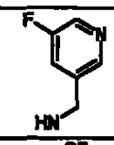
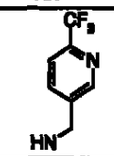
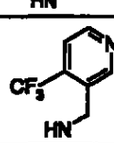
Use a method similar to the General Procedure 5-3 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine

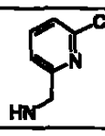
(400 mg, 0.94 mmol) and (±)-1-pyridin-4-yl-ethylamine (prepared as described in *Bull. Kor. Chem. Soc.* 1998, *19* (8), 891-893) (172 mg, 1.41 mmol). Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 4:1 and 1:1) to give (±)-7-chloro-6-[(1-pyridin-4-yl-ethyl)-amino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine.

Use a method similar to the General Procedure 1-1 to give the free base of the title compound (73 mg, 26%). Use a method similar to the General Procedure 2-1, using (±)-7-chloro-6-[(1-pyridin-4-yl-ethyl)-amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (73 mg, 0.243 mmol), to give the title compound (31 mg, 31%). MS (ES+) *m/z*: 302 $(M+H)^+$.

Examples 284-287 may be prepared essentially as described in Example 283 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. The yields for the Step 1 (General Procedure 5-3) and MS (ES+) data are shown in the Table below.

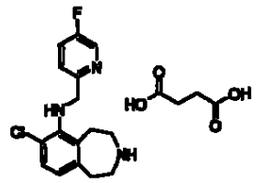


Ex.	NH-R	Compound	Yield (%)	MS (ES+) *m/z*
284		7-Chloro-6-(5-fluoro-pyridin-3-ylmethylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	88	306 $(M+H)^+$
285		7-Chloro-6-(6-trifluoromethyl-pyridin-3-yl-methylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	83	356 $(M+H)^+$
286		7-Chloro-6-(4-trifluoromethyl-pyridin-3-yl-methylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	60	356 $(M+H)^+$

Ex.	NH-R	Compound	Yield (%)	MS (ES+) *m/z*
287		7-Chloro-6-[(6-trifluoromethyl-pyridin-2-ylmethyl)-amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	84	356 $(M+H)^+$

Example 288

7-Chloro-6-[(5-fluoro-pyridin-2-ylmethyl)-amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

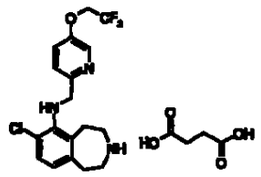


Use a method similar to the General Procedure 5-1 to couple 2-aminomethyl-5-fluoro-pyridine (230 mg, 1.8 mmol) and a solution of 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (500 mg, 1.2 mmol) in toluene (4 mL). Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1 to 1:1) followed by SCX chromatography to give 7-chloro-6-[(5-fluoro-pyridin-2-ylmethyl)-amino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (302 mg, 64%). GC-MS *m/z*: 402 (M^+).

Dissolve 7-chloro-6-[(5-fluoro-pyridin-2-ylmethyl)-amino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (297 mg, 0.74 mmol) in ethanol (5 mL). Add 5N aqueous NaOH (10 equiv.) and stir for 1 h at ambient temperature. Concentrate *in vacuo* and purify by SCX chromatography followed by chromatography on silica gel eluting with DCM/2M ammonia in methanol (99:1 to 9:1) to obtain the free base of the title compound. Use a method similar to the General Procedure 2-1 and crystallize the solid from methanol and diethyl ether. Dry the solid in a vacuum oven at 60°C overnight to obtain the title compound (181 mg, 58%). MS (ES+) *m/z*: 306 $(M+H)^+$.

Example 289

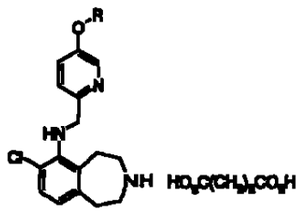
7-Chloro-6-{[5-(2,2,2-trifluoro-ethoxy)-pyridin-2-ylmethyl]-amino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Use a method similar to the General Procedure 5-2 to couple 7-chloro-6-trifluoromethanesulfonyloxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (370 mg, 0.9 mmol) with 2-aminomethyl-5-(2,2,2-trifluoroethoxy)-pyridine (180 mg, 0.9 mmol) in toluene (8 mL). Purify by chromatography on silica gel eluting with hexane/EtOAc (10:1, 5:1 and 3:1) followed by SCX chromatography [pre-wash column with methanol followed by DCM, load material dissolved in DCM, then elute with DCM/2M ammonia in methanol (1:1) and concentrate *in vacuo*] to obtain 7-chloro-6-{[5-(2,2,2-trifluoro-ethoxy)-pyridin-2-ylmethyl]-amino}-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1H-benzo[*d*]azepine.

Use a method similar to the General Procedure 1-3 to deprotect 7-chloro-6-{[5-(2,2,2-trifluoro-ethoxy)-pyridin-2-ylmethyl]-amino}-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1H-benzo[*d*]azepine. Purify by chromatography on silica gel elutin with DCM/2M ammonia in methanol (99/1 to 90/10) to obtain the free base of the title compound. Use a method similar to the General Procedure 2-1 to give the title compound (184 mg, 42 %). MS (ES+) *m/z*: 386 $(M+H)^+$.

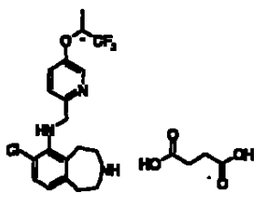
Examples 290-291 may be prepared essentially as described in Example 289 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. Overall yields and MS (ES+) data are shown in the Table below.



Ex.	O-R	Compound	Yield (%)	MS (ES+) m/z
290		7-Chloro-6-{[5-(2,2,2-trifluoro-1,1-dimethyl-ethoxy)-pyridin-2-ylmethyl]-amino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	48	414 $(M+H)^+$
291		(±)-7-Chloro-6-{[5-(2,2,2-trifluoro-1-methyl-ethoxy)-pyridin-2-ylmethyl]-amino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepin Succinate	49	400 $(M+H)^+$

Examples 292 and 293

(-)-7-Chloro-6-{[5-(2,2,2-trifluoro-1-methyl--ethoxy)-pyridin-2-ylmethyl]-amino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate and (+)-7-Chloro-6-{[5-(2,2,2-trifluoro-1-methyl-ethoxy)-pyridin-2-ylmethyl]-amino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

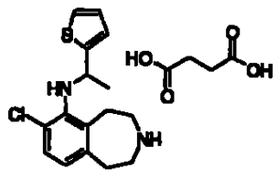


Separate the two enantiomers of (±)-7-chloro-6-{[5-(2,2,2-trifluoro-1-methyl-ethoxy)-pyridin-2-ylmethyl]-amino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine succinate by normal phase chiral HPLC (Chiralcel OD 8x35 cm, elute with 4:1 heptane/3A-ethanol with 0.2 % DMEA). Purify each enantiomer by chromatography on silica gel eluting with DCM/2M ammonia in methanol (20:1). Use a method similar to the General Procedure 2-1 to obtain the title compounds: (-)-7-Chloro-6-{[5-(2,2,2-trifluoro-1-methyl-ethoxy)-pyridin-2-ylmethyl]-amino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine succinate

(Example 292, 75 mg, 38%), 95% ee [Chiralpak AD, 4.6x150 mm, eluent: 85/15 heptane/3A ethanol with 0.2% DMEA, 0.6 mL/min)]; MS (ES+) *m/z*: 400 $(M+H)^+$. $[\alpha]^{20}_D$ -12.1° (c 0.5, MeOH). (+)-7-Chloro-6-{[5-(2,2,2-trifluoro-1-methyl-ethoxy)-pyridin-2-ylmethyl]-amino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine succinate (Example 293, 72 mg, 37%), 93% ee [Chiralpak AD, 4.6x150 mm, eluent: 85/15 heptane/3A ethanol with 0.2% DMEA, 0.6 mL/min)]. MS (ES+) *m/z*: 400 $(M+H)^+$. $[\alpha]^{20}_D$ +7.4° (c 0.5, MeOH).

Example 294

(±)-7-Chloro-6-[(1-thiophen-2-yl-ethyl)-amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

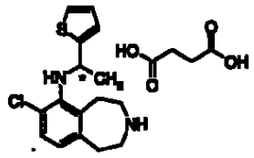


Use a method similar to the General Procedure 5-3 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (200 mg, 0.47 mmol) with (±)-1-thiophen-2-yl-ethylamine (prepared as described in *J. Amer. Chem. Soc.* 1942, *64*, 477-479) (200 mg, 1.57 mmol). Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 9:1 and 4:1) to give (±)-7-chloro-6-[(1-thiophen-2-yl-ethyl)-amino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (126 mg, 67%).

Use a method similar to the General Procedure 1-1, using (±)-7-chloro-6-[(1-thiophen-2-yl-ethyl)-amino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (126 mg, 0.313 mmol), to give the free base of the title compound (73 mg, 77%). Use a method similar to the General Procedure 2-1, using (±)-7-chloro-6-[(1-thiophen-2-yl-ethyl)-amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (73 mg, 0.241 mmol) to give the title compound (100 mg, 50% overall). MS (ES+) *m/z*: 307 $(M+H)^+$.

Example 295

(+)-7-Chloro-6-[(1-thiophen-2-yl-ethyl)-amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate, Isomer 1

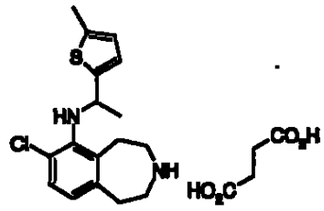


Separate the two enantiomers of (±)-7-chloro-6-[(1-thiophen-2-yl-ethyl)-amino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine by chiral preparative HPLC (Chiralpak AD, 8x30 cm; eluent: 9:1 heptane/isopropanol with 0.2% DMEA; flow: 350 mL/min at 240 nm (UV), ~650 mg load] to obtain 7-chloro-6-[(1-thiophen-2-yl-ethyl)-amino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 1, ee=100% [Analytical Column: Chiralpak AD, 4.6x250mm; eluent: 9:1 heptane/isopropanol with 0.2% DMEA; flow: 1 mL/min at 250nm (UV).

Use a method similar to the General Procedure 1-1, using 7-chloro-6-[(1-thiophen-2-yl-ethyl)-amino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 1, to give 7-chloro-6-[(1-thiophen-2-yl-ethyl)-amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 1. Use a method similar to the General Procedure 2-1, using 7-chloro-6-[(1-thiophen-2-yl-ethyl)-amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 1 (73 mg, 0.241 mmol) to give the title compound (100 mg, 98%). MS (ES+) *m/z*: 307 $(M+H)^+$. $[\alpha]^{20}_D$ +115.0° (c 0.5, MeOH).

Example 296

(±)-7-Chloro-6-[1-(5-methylthiophen-2-yl)ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

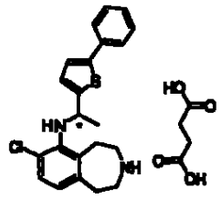


Use a method similar to the General Procedure 5-1 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (96 mg, 0.227 mmol) with (±)-2-(1-aminoethyl)-5-methylthiophene (48 mg, 0.34 mmol) using palladium(II) acetate (10 mg, 0.0454 mmol), BINAP (60 mg, 0.0908 mmol) and cesium carbonate (148 mg, 0.454 mmol) in toluene (10 mL). Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 19:1) to give (±)-7-chloro-6-[1-(5-methylthiophen-2-yl)ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (47 mg, 50%). GC-MS *m/z* 416 (M^+).

Use a method similar to the General Procedure 1-2, using (±)-7-chloro-6-[1-(5-methylthiophen-2-yl)ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (47 mg, 0.113 mmol) to give (±)-7-chloro-6-[1-(5-methylthiophen-2-yl)ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (30 mg, 83%) that was used without further purification. Use a method similar to the General Procedure 2-1 to give the title compound as a white solid (36 mg, 88%). MS (ES+) *m/z*: 321 $(M+H)^+$.

Example 297

(+)-7-Chloro-6-[1-(5-phenyl-thiophen-2-yl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



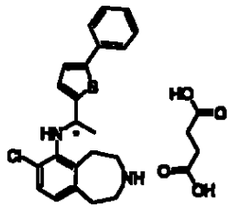
Use a method similar to the General Procedure 5-3 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.328 g, 0.773 mmol) with 1-(5-phenyl-thiophen-2-yl)ethylamine Isomer 1 (0.236 g, 1.16 mmol) using palladium(II) acetate (69 mg, 0.309 mmol), tris(dibenzylideneacetone)-dipalladium(0) (142 mg, 0.155 mmol), BINAP (578 mg, 0.928 mmol) and cesium carbonate (504 mg, 1.546 mmol) in toluene (10 mL). Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0 and 19:1) to give 7-chloro-6-[1-(5-phenyl-thiophen-

2-yl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 1 (89 mg, 34%).

Use a method similar to the General Procedure 1-2, using 7-chloro-6-[1-(5-phenyl-thiophen-2-yl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 1 (89 mg, 0.186 mmol) to give 7-chloro-6-[1-(5-phenyl-thiophen-2-yl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 1 (65 mg, 92%) as an oil that was used without further purification. Use a method similar to the General Procedure 2-1, using 7-chloro-6-[1-(5-phenyl-thiophen-2-yl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 1 (65 mg, 0.17 mmol), to give the title compound as a white solid (58 mg, 68%). MS (ES+) *m/z*: 383 $(M+H)^+$; $[\alpha]^{20}_D$ +159.0° (c 0.5, MeOH).

Example 298

(-)-7-Chloro-6-[1-(5-phenyl-thiophen-2-yl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

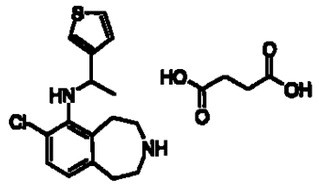


Use a method similar to the General Procedure 5-3 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.484 g, 1.138 mmol) with 1-(5-phenyl-thiophen-2-yl)ethylamine Isomer 2 (0.347 g, 1.71 mmol) using palladium(II) acetate (102 mg, 0.45 mmol), tris(dibenzylideneacetone)-dipalladium(0) (209 mg, 0.228 mmol), BINAP (851 mg, 1.366 mmol) and cesium carbonate (741 mg, 2.276 mmol) in toluene (12 mL). Purify by chromatography on silica gel eluting with hexane:EtOAc (1:0 and 19:1) to give 7-chloro-6-[1-(5-phenyl-thiophen-2-yl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 2 (247 mg, 63 %).

Use a method similar to the General Procedure 1-2, using 7-chloro-6-[1-(5-phenyl-thiophen-2-yl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 2 (247 mg, 0.516 mmol) to give 7-chloro-6-[1-(5-phenyl-thiophen-2-yl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 2 (184 mg, 93%) as an oil that was used without further purification. Use a method similar to the General Procedure 2-1, using 7-chloro-6-[1-(5-phenyl-thiophen-2-yl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 2 (184 mg, 0.48 mmol) to give the title compound as a white solid (200 mg, 83%). MS (ES+) *m/z*: 383 $(M+H)^+$; $[\alpha]^{20}_D$ -196.5° (c 0.5, MeOH).

Example 299

(±)-7-Chloro-6-[(1-thiophen-3-yl-ethyl)-amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

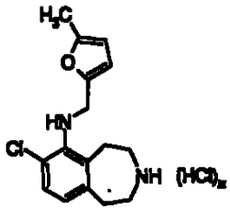


Use a method similar to the General Procedure 5-3 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (200 mg, 0.47 mmol) with (±)-1-thiophen-3-yl-ethylamine (prepared as described in *J. Heterocycl. Chem.* 1988, *25*, 1571-1581) (90 mg, 0.70 mmol). Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 9:1 and 4:1) to give (±)-7-chloro-6-(1-thiophen-3-yl-ethylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (100 mg, 53%).

Use a method similar to the General Procedure 1-1, using (±)-7-chloro-6-(1-thiophen-3-yl-ethylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (100 mg, 0.248 mmol), to give the free base of the title compound (74 mg, 98%). Use a method similar to the General Procedure 2-1, using (±)-7-chloro-6-(1-thiophen-3-yl-ethylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (74 mg, 0.242 mmol) to give the title compound (108 mg, 54% overall). MS (ES+) *m/z*: 307 $(M+H)^+$.

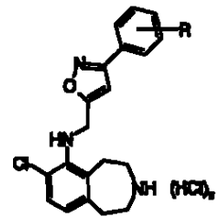
Example 300

7-Chloro-6-[(5-methylfuran-2-ylmethyl)-amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Combine 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (100 mg, 0.24 mmol), 2-(di-*tert*-butylphosphino)-biphenyl (6.8 mg, 0.023 mmol), tris(dibenzylideneacetone)dipalladium (11 mg, 0.012 mmol) and potassium phosphate (70 mg, 0.33 mmol) in a pressure tube and degas. Dissolve the mixture in dry toluene (2 mL) and degas. Add a solution of 5-methylfurfurylamine (30 mg, 0.27 mmol) in toluene (1 mL) and degas. Stir at 90°C for 24 h. Cool to ambient temperature, dilute with ethyl ether and filter through Celite®. Concentrate and purify by chromatography on silica gel eluting with hexane/EtOAc (20:1). Remove the solvent and add 7M ammonia in methanol (4 mL). Stir at ambient temperature for 24 h. Concentrate and purify by SCX chromatography to give the free base of the title compound. Use a method similar to the General Procedure 2-2 to obtain the title compound as a solid (56 mg, 66%). MS (ES+) *m/z*: 291 $(M+H)^+$.

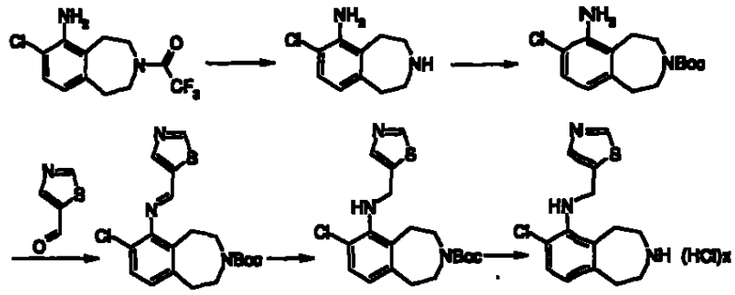
Examples 301-302 may be prepared essentially as described in Example 300 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. Overall yields and MS (ES+) data are shown in the Table below.



Ex.	R	Compound	Yield (%)	MS (ES+) m/z
301	4-Cl	7-Chloro-6-{[3-(4-chlorophenyl)-isoxazol-5-ylmethyl]-amino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	30	389 $(M+H)^+$
302	4-OMe	7-Chloro-6-{[3-(4-methoxyphenyl)-isoxazol-5-ylmethyl]-amino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	54	384 $(M+H)^+$

Example 303

7-Chloro-6-(thiazol-5-ylmethyl-amino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Thiazole-5-carbaldehyde: Add DMSO slowly to a solution of oxalyl chloride (1.6 g, 13 mmol) in anhydrous DCM (30 mL) under nitrogen at –78 °C and stir for 10 min. Add dropwise a solution of 5-hydroxymethylthiazole (1.15 g, 10 mmol) in DCM (10 mL) and stir the mixture for 40 min. Add triethylamine and stir for 5 min and then quench the reaction with water. Extract the mixture three times with ether, combine the organic extracts, wash with brine, dry over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with EtOAc/hexane (2:5) to give thiazole-5-carbaldehyde (337 mg, 29%).

3-(*tert*-Butoxycarbonyl)-7-chloro-6-(thiazol-5-ylmethyleneamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Dissolve 6-amino-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (285 mg, 0.97 mmol) in methanol (10 mL). Add 7N ammonia in methanol (10 mL) and stir overnight at ambient temperature. Concentrate *in vacuo* and dissolve the residue in THF (10 mL). Add saturated aqueous $NaHCO_3$ (5 mL)

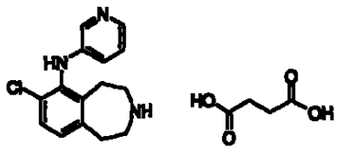
and di-*tert*-butyl-dicarbonate (254 mg, 1.16 mmol). Stir the reaction mixture at ambient temperature for 4 h. Dilute the mixture with water, extract three times with EtOAc, combine the organic extracts, dry over Na_2SO_4, filter and concentrate *in vacuo* to give crude material. Mix thiazole-5-carbaldehyde (165 mg, 1.45 mmol) with above crude residue (0.97 mmol, assuming 100% conversion), acetic acid (87 mg, 1.45 mmol) and 1,2-dichloroethane (10 mL). Stir at ambient temperature for 20 min. Add sodium triacetoxyborohydride and stir under nitrogen overnight. Quench the reaction with saturated aqueous $NaHCO_3$, separate the organic layer and extract the aqueous layer three times with DCM. Combine the organic extracts, dry over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with EtOAc/hexane (1:3) to afford the desired intermediate as a yellow oil (228 mg, 60% three steps). MS (ES+) *m/z*: 392 $(M+H)^+$.

3-(*t*-Butoxycarbonyl)-7-chloro-6-(thiazol-5-ylmethyl-amino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Dissolve 3-(*t*-butoxycarbonyl)-7-chloro-6-(thiazol-5-ylmethyleneamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (228 mg, 0.58 mmol) in methanol (10 mL), add sodium borohydride (263 mg, 7 mmol) and reflux for 28 h. Cool to ambient temperature, dilute with EtOAc and add slowly water. Separate the organic layer, extract the aqueous layer three times with EtOAc. Combine the organic extracts, dry over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with EtOAc/hexane (1:3) to give the desired intermediate as a colorless oil (134 mg, 58%). MS (ES+) *m/z*: 394 $(M+H)^+$.

7-Chloro-6-(thiazol-5-ylmethyl-amino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride: Use a method similar to the General Procedure 1-6 to deprotect 3-(*tert*-butoxycarbonyl)-7-chloro-6-(thiazol-5-ylmethyl-amino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (134 mg, 0.34 mmol). Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (94:6) to give 7-chloro-6-(thiazol-5-ylmethyl-amino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (90 mg, 90%). MS (ES+) *m/z*: 294 $(M+H)^+$. Use a method similar to the General Procedure 2-2 to obtain the title compound.

Example 304

7-Chloro-6-[(3-pyridyl)amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

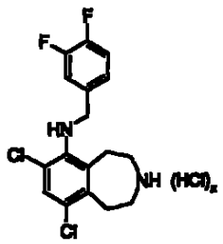


Use a method similar to the General Procedure 5-1 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (300 mg, 0.7 mmol) with 3-aminopyridine (75 mg, 0.85 mmol). Purify by chromatography on silica gel eluting with hexane/EtOAc (4:1) to give 7-chloro-6-[(3-pyridyl)amino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an off-white solid (20 mg, 8%). MS (ES+) *m/z*: 370 $(M+H)^+$.

Use a method similar to the General Procedure 1-1 to deprotect 7-chloro-6-[(3-pyridyl)amino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (20 mg, 0.05 mmol). Purify by SCX chromatography to give 7-chloro-6-[(3-pyridyl)amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow oil (15 mg, 99%). Use a method similar to the General Procedure 2-1, using 7-chloro-6-[(3-pyridyl)amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (15.1 mg, 0.05 mmol), to give the title compound as a light yellow solid (20 mg, 97%). MS (ES+) *m/z*: 319 $(M+H)^+$.

Example 305

7,9-Dichloro-6-(3,4-difluorobenzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



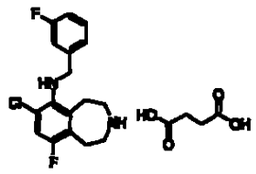
Dissolve 7-dichloro-6-(3,4-difluorobenzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (150 mg, 0.36 mmol) in anhydrous toluene (20 mL). Add *N*-chlorosuccinimide (140 mg, 1 mmol) and heat at 60°C for 4 h. Cool to room

temperature, pour reaction mixture into water (250 mL) and extract with EtOAc (3x50 mL). Wash combined organic extracts with water, brine, dry over Na_2SO_4, filter, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (4:1) to give 7,9-dichloro-6-(3,4-difluorobenzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (110 mg, 67%). MS (ES+) *m/z*: 453 $(M+H)^+$.

Use a method similar to the General Procedure 1-1 to deprotect 7,9-dichloro-6-(3,4-difluorobenzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (120 mg, 0.26 mmol). Purify by SCX chromatography to give 7,9-dichloro-6-(3,4-difluorobenzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow oil (81 mg, 88%). Use a method similar to the General Procedure 2-2, using 7,9-dichloro-6-(3,4-difluorobenzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (75 mg, 0.21 mmol), to give the title compound as a yellow gum (80 mg, 96%). MS (ES+) *m/z*: 357 $(M+H)^+$.

Example 306

7-Chloro-9-fluoro-6-(3-fluorobenzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



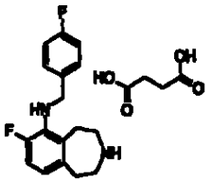
Use a method similar to the General Procedure 5-1 to couple 7-chloro-9-fluoro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (130 mg, 0.3 mmol) with 3-fluorobenzylamine (100 □L, 0.89 mmol). Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1 and 4:1) followed by SCX chromatography to give 7-chloro-9-fluoro-6-(3-fluorobenzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow oil (35 mg, 28%). MS (ES+) *m/z*: 401 $(M+H)^+$.

Use a method similar to the General Procedure 1-1 to deprotect 7-chloro-9-fluoro-6-(3-fluorobenzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (32 mg, 0.08 mmol). Purify by SCX chromatography to give 7-chloro-9-fluoro-6-(3-

fluorobenzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow oil (10 mg, 45%). Use a method similar to the General Procedure 2-1, using 7-chloro-9-fluoro-6-(3-fluorobenzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (10 mg, 0.033 mmol), to give the title compound as a light yellow solid (14 mg, 97%). MS (ES+) *m/z*: 323 $(M+H)^+$.

Example 307

7-Fluoro-6-(4-fluorobenzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

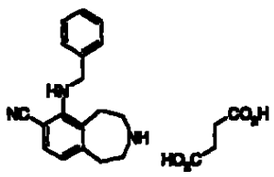


Use a method similar to the General Procedure 5-1 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (250 mg, 0.61 mmol) with 4-fluorobenzylamine (92 mg, 1.2 equiv.) using palladium(II) acetate (0.1 equiv.), BINAP (0.3 equiv.) and cesium carbonate (1.4 equiv.) in toluene (5 mL). Purify by chromatography on silica gel eluting with hexane/EtOAc (10:1, 5:1, 3:1 and 1:1) to give 7-fluoro-6-(4-fluorobenzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil.

Use a method similar to the General Procedure 1-3 to deprotect 7-fluoro-6-(4-fluorobenzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Purify by SCX chromatography to give the free base of the title compound. Use a method similar to the General Procedure 2-1 to give the title compound as an off white solid (14 mg, 6%). MS (ES+) *m/z*: 289 $(M+H)^+$.

Example 308

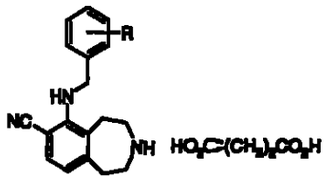
6-Benzylamino-7-cyano-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Use a method similar to the General Procedure 5-1 to couple 7-cyano-3-(2,2,2-trifluoroacetyl)-6- trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (125 mg, 0.3 mmol) with benzylamine (0.1 mL, 0.9 mmol) using palladium(II) acetate (7 mg, 0.03 mmol), BINAP (37 mg, 0.06 mmol) and cesium carbonate (137 mg, 0.4 mmol) in toluene (3 mL). Purify by chromatography on silica gel eluting with heptane/EtOAc (4:1 to 1:1) to give 6-benzylamino-7-cyano-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a clear oil (60 mg, 54%). MS (ES+) *m/z*: 374 $(M+H)^+$.

Use a method similar to the General Procedure 1-2, using 6-benzylamino-7-cyano-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (56 mg, 0.15 mmol), to give 6-benzylamino-7-cyano-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a clear oil (38 mg, 93%). MS (ES+) *m/z*: 278 $(M+H)^+$. Use a method similar to the General Procedure 2-1 to give the title compound as a white powder (39 mg, 71%). MS (ES+) *m/z*: 278 $(M+H)^+$.

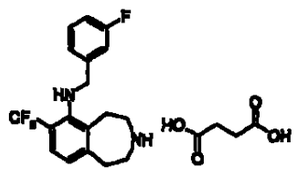
Examples 309-310 may be prepared essentially as described in Example 308 by using 7-cyano-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. Overall yields and MS (ES+) data are shown in the Table below.



Ex.	R	Compound	Yield (%)	MS (ES+) *m/z*
309	4-F	7-Cyano-6-(4-fluorobenzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	46	296 $(M+H)^+$
310	2-F	7-Cyano-6-(2-fluorobenzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	43	296 $(M+H)^+$

Example 311

6-(3-Fluorobenzylamino)-7-trifluoromethyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

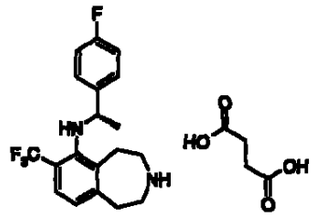


Use a method similar to the General Procedure 5-1 to couple 3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-7-trifluoromethyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (110 mg, 0.24 mmol) and 3-fluorobenzyl amine (90 μL, 0.7 mmol). Purify by chromatography on silica gel eluting with hexane/EtOAc (95:5) followed by SCX chromatography to give 6-(3-fluorobenzylamino)-3-(2,2,2-trifluoroacetyl)-7-trifluoromethyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow oil (55 mg, 53%). MS (ES+) *m/z*: 435 $(M+H)^+$.

Use a method similar to the General Procedure 1-1 to deprotect 6-(3-fluorobenzylamino)-3-(2,2,2-trifluoroacetyl)-7-trifluoromethyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (55 mg, 0.13 mmol). Purify by SCX chromatography to give 6-(3-fluorobenzylamino)-7-trifluoromethyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow oil (34 mg, 81%). Use a method similar to the General Procedure 2-1 to give the title compound as an off-white solid (33 mg, 72%). MS (ES+) *m/z*: 339 $(M+H)^+$.

Example 312

(*S*)-(-)-6-[1-(4-Fluorophenyl)-ethylamino]-7-trifluoromethyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

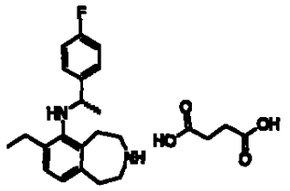


Use a method similar to the General Procedure 5-3 to couple 3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-7-trifluoromethyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (430 mg, 0.94 mmol) with (*S*)-1-(4-fluorophenyl)ethylamine (195 mg, 1.40 mmol). Purify by chromatography on silica gel eluting with EtOAc/hexane (1:8) to give (*S*)-6-[1-(4-fluorophenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-7-trifluoromethyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (279 mg, 66%). MS (ES+) *m/z*: 449 $(M+H)^+$.

Use a method similar to the General Procedure 1-1 to deprotect (*S*)-6-[1-(4-fluorophenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-7-trifluoromethyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (279 mg, 0.62 mmol). Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (94:6) to obtain (*S*)-6-[1-(4-fluorophenyl)-ethylamino]-7-trifluoromethyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a colorless oil (190 mg, 87%). MS (ES+) *m/z*: 353 $(M+H)^+$. Use a method similar to the General Procedure 2-1 to give the title compound. $[\alpha]^{20}_D$ -96.7° (c 0.5, MeOH).

Example 313

(*S*)-7-Ethyl-6-[1-(4-fluorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



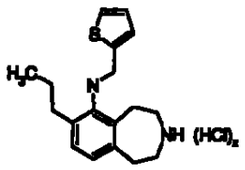
Use a method similar to the General Procedure 5-3 to couple 7-ethyl-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (335 mg, 0.8 mmol) and (*S*)-1-(4-fluorophenol)ethyl amine (557 mg, 4.0 mmol). Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 9:1 and 17:3) to give (*S*)-7-ethyl-6-[1-(4-fluorophenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (127 mg, 39%). MS (ES+) *m/z*: 409 $(M+H)^+$.

Use a method similar to the General Procedure 1-1 to deprotect (*S*)-7-ethyl-6-[1-(4-fluorophenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-

benzo[*d*]azepine. Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (93:7) to give (*S*)-7-ethyl-6-[1-(4-fluorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (70 mg, 72%). MS (ES+) *m/z*: 313 $(M+H)^+$. Use a method similar to the General Procedure 2-1 to obtain the title compound.

Example 314

7-Propyl-6-[(2-thienyl)methylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the General Procedure 5-1 to couple 7-propyl-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 2-(aminomethyl)-thiophene. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1 and 4:1) to give 7-propyl-6-[(2-thienyl)methylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow solid. MS (ES+) *m/z*: 397 $(M+H)^+$.

Use a method similar to the General Procedure 1-1 to deprotect 7-propyl-6-[(2-thienyl)methylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Purify by SCX chromatography to give the free base of the title compound as a yellow oil. Use a method similar to the General Procedure 2-2 to give the title compound as a light yellow solid. MS (ES+) *m/z*: 301 $(M+H)^+$.

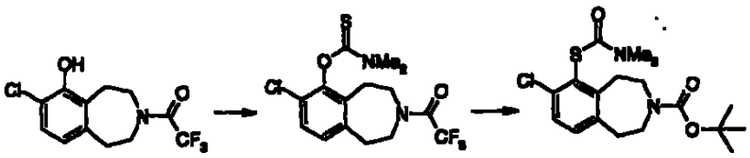
General Procedure 7

Dissolve the appropriate substituted 3-*tert*-butoxycarbonyl-6-dimethylcarbamoyl-thio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.0 equiv) in methanol (0.1-0.2 M solution). Add potassium hydroxide (32 equiv.) and heat the mixture at 50°C for 2-8 h. Cool the reaction to ambient temperature and add the appropriate halide (1.0-5.0 equiv.). Stir the mixture at ambient temperature for 0.5-16 h. Remove the solvent *in vacuo* and partition the residue between DCM and water. Extract the aqueous phase with DCM, combine the

organic extracts, dry over Na_2SO_4, filter and concentrate. Purify by chromatography in silica gel eluting with hexane/EtOAc mixtures to obtain the desired compound.

Preparation 172

3-*tert*-Butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine



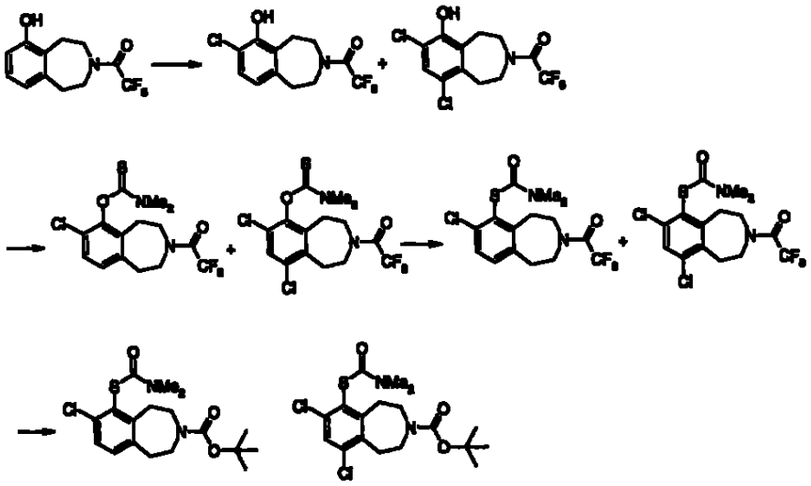
7-Chloro-6-dimethylthiocarbamoyloxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Place 7-chloro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (64.3 g, 219 mmol) in acetone (450 mL) and water (200 mL) with K_2CO_3 (91.8 g, 664 mmol) and dimethylthiocarbamoyl chloride (31.5 g, 255 mmol). Stir at ambient temperature for 1.25 h. Add additional dimethylthiocarbamoyl chloride (3 g, 24 mmol) and stir for an additional 1.75 h at ambient temperature. Add more dimethylthiocarbamoyl chloride (0.7 g, 5.7 mmol) and water (150 mL) to the mixture and stir for 0.5 h at ambient temperature. Slowly add water (500 mL) to the reaction over 2 h to promote crystallization and stir the resulting slurry at ambient temperature for 1.5 h. Collect the solid by filtration to give the desired intermediate (76 g, 91%).

3-*tert*-Butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Dissolve 7-chloro-6-dimethylthiocarbamoyloxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (155 g, 407 mmol) in diphenyl ether (1500 mL) and heat to 250°C for 2.5 h. Cool the reaction and dilute with methanol (308 mL). Add 1N aqueous NaOH (616 mL) and stir at 60°C for 4 h. Cool the reaction to ambient temperature and extract between DCM (3 x 500 mL) and water (500 mL). Combine the organic extracts and add to 1N aqueous HCl (1 L). Stir the reaction at ambient temperature for 0.25 h then wash with hexane (5 x 400 mL). Adjust the pH of the aqueous layer to 7.0 with 5N aqueous NaOH and mix the aqueous solution with DCM (2.5 L). Cool the mixture in an ice bath and add K_2CO_3 (169 g, 1221 mmol) and di-*t*-

butyl dicarbonate (67.5 g, 390 mmol) and stir the reaction at ambient temperature for 0.5 h. Add di-*t*-butyl dicarbonate (16.35 g, 75 mmol) and stir for 0.3 h at ambient temperature. Add di-*t*-butyl dicarbonate (0.1 g, 0.46 mmol) and stir for 0.25 h at ambient temperature. Concentrate the mixture *in vacuo* to remove the volatiles and warm to 45°C. Seed the mixture with a small amount of the title compound and stir for 1 h at 45°C. Cool the reaction in an ice bath and stir for an additional 2 h. Collect the resultant solid by filtration and rinse with cold hexane (100 mL). Concentrate the filtrate *in vacuo*, recrystallize from DCM/heptane, and isolate the solids by filtration. Combine the solids and dry *in vacuo* to give the title compound as a white crystalline solid (142 g, 91%). MS (ES+) *m/z* 385 $(M+H)^+$.

Preparation 173

3-*tert*-Butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 3-*tert*-butoxycarbonyl-7,9-dichloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine



7-Chloro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 7,9-dichloro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine:

To a solution of 6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.961 g, 3.71 mmol) in toluene (30 mL) at 70 °C, add diisobutylamine (52 μL, 0.30 mmol) followed by slow addition of neat sulfuryl chloride (343 μL,

4.27 mmol). Stir for 1 h at 70 °C and concentrate *in vacuo*. Dilute the residue with water, extract three times with EtOAc, dry over anhydrous Na_2SO_4 and concentrate *in vacuo* to afford a 4:1 mixture of 7-chloro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 7,9-dichloro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a white solid (1.07 g, 98%).

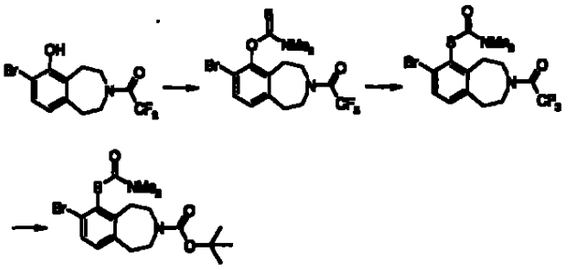
7-Chloro-6-dimethylthiocarbamoyloxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 7,9-dichloro-6-dimethylthiocarbamoyloxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: To a mixture of 4:1 7-chloro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 7,9-dichloro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.513 g, 1.75 mmol) in anhydrous dioxane (10 mL) under nitrogen, add dimethyl thiocarbamoyl chloride (0.432 g, 3.50 mmol), 4-dimethylaminopyridine (21 mg, 0.18 mmol) and triethylamine (731 µL, 5.24 mmol) and heat under reflux overnight. Cool the reaction mixture to ambient temperature and dilute with water, extract three times with EtOAc, dry over anhydrous Na_2SO_4 and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (17:1) to afford a mixture of 4:1 7-chloro-6-dimethylthiocarbamoyloxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 7,9-dichloro-6-dimethylthiocarbamoyloxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow oil (0.64 g, 95%)

7-Chloro-6-dimethylcarbamoylthio-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 7,9-dichloro-6-dimethylcarbamoylthio-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Heat the mixture of 4:1 7-chloro-6-dimethylthiocarbamoyloxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 7,9-dichloro-6-dimethylthiocarbamoyloxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.630 g, 1.66 mmol) in diphenyl ether (4.5 mL) at 250 °C for 4 h under nitrogen. Cool to ambient temperature. Purify by chromatography on silica gel eluting with hexane/EtOAc (7:3) to give a mixture of 4:1 7-chloro-6-dimethylcarbamoylthio-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 7,9-dichloro-6-dimethylcarbamoylthio-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow oil (0.54 g, 85%).

3-*tert*-Butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 3-*tert*-butoxycarbonyl-7,9-dichloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: To the mixture of 4:1 7-chloro-6-dimethylcarbamoylthio-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 7,9-dichloro-6-dimethylcarbamoylthio-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.536 g, 1.47 mmol) in methanol (7 mL), add aqueous potassium carbonate (0.812 g, 5.88 mmol in 1.5 mL of water). Stir for 5 h at ambient temperature, add di-*tert*-butyl dicarbonate (418 mg, 1.91 mmol) and stir for an additional 30 min. Dilute with EtOAc and water. Separate the layers and extract the aqueous layer three times with EtOAc. Dry over anhydrous Na_2SO_4, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (7:3) to give a mixture of 4:1 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 3-*tert*-butoxycarbonyl-7,9-dichloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a white solid (0.52 g, 96%).

Preparation 174

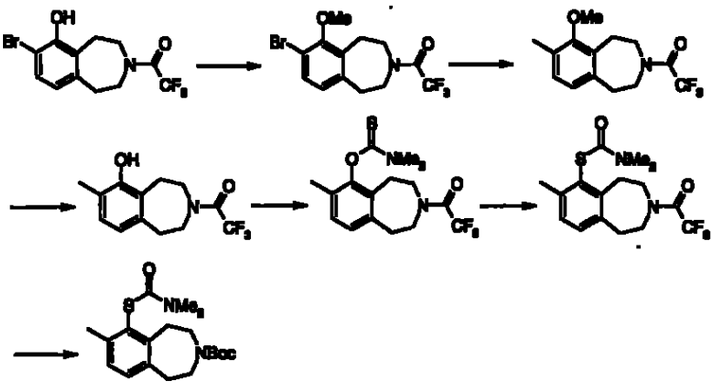
7-Bromo-3-*tert*-butoxycarbonyl-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine



Use a method similar to the Preparation 172, using 7-bromo-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine to give the title compound.

Preparation 175

3-*tert*-Butoxycarbonyl-6-dimethylcarbamoylthio-7-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine



7-Bromo-6-methoxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Add potassium carbonate (10.214 g, 73.9 mmol) to a solution of 7-bromo-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (5.0 g, 14.8 mmol) in acetone (50 mL) and stir for 10 min. Add methyl iodide (4.2 g, 1.5 mL, 29.6 mmol) and stir the mixture overnight at room temperature. Remove the solvent *in vacuo* and partition the residue between water and DCM. Extract the aqueous phase twice with DCM. Combine the organic extracts, dry over Na_2SO_4, filter and concentrate *in vacuo* to obtain the desired intermediate as a solid (5.15 g, 99%). MS (ES+) *m/z*: 352 $(M+H)^+$.

6-Methoxy-7-methyl-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Add potassium carbonate (5.65 g, 40.91 mmol), tetrakis(triphenylphosphine)palladium (1.576 g, 1.363 mmol) and trimethylboroxine (2.053 g, 2.3 mL, 16.35 mmol) to a solution of 7-bromo-6-methoxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (4.8 g, 13.63 mmol) in dimethylformamide (40 mL) under nitrogen. Heat the mixture to 115°C for 6 h. Add water and extract the aqueous phase twice with EtOAc. Combine the organic extracts, dry over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0 and 19:1) to obtain the desired intermediate as a solid (3.23 g, 83%). GC-MS *m/z* 287 (M^+).

6-Hydroxy-7-methyl-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Add borontribromide (21.6 mL, 1.0 M solution in DCM) to a solution of 6-methoxy-7-methyl-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (3.1 g, 10.8 mmol) in DCM (200 mL) at 0°C under nitrogen. Warm to room temperature and stir overnight. Dilute with DCM and wash with water. Dry the organic layer over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0 and 9:1) to obtain the desired intermediate as a solid (2.74 g, 93%). MS (ES+) *m/z*: 274 $(M+H)^+$.

6-Dimethylthiocarbamoyloxy-7-methyl-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Dissolve 6-hydroxy-7-methyl-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.0 g, 3.66 mmol) in acetone (50 mL). Add potassium carbonate (1.517 g, 10.98 mmol) and dimethylthiocarbamoyl chloride (0.904 g, 7.32 mmol). Heat the mixture at reflux overnight. Remove the solvent *in vacuo* and partition the residue between water and DCM. Dry the organic phase over Na_2SO_4, filter and concentrate. Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0 and 9:1) to obtain the desired intermediate as a solid (1.18 g, 90%). MS (ES+) *m/z*: 361 $(M+H)^+$.

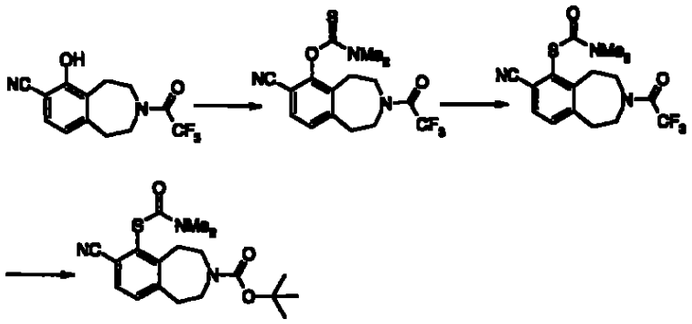
6-Dimethylcarbamoylthio-7-methyl-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Dissolve 6-dimethylthiocarbamoyloxy-7-methyl-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.15 g, 3.19 mmol) in diphenyl ether (20 mL) and heat to 265°C for 3 h in a sealed tube. Cool the reaction to room temperature. Purify by chromatography on silica gel eluting with hexane/EtOAc (4:1 and 7:3) to obtain the desired intermediate as a solid (1.10 g, 96%). MS (ES+) *m/z*: 361 $(M+H)^+$.

3-*tert*-Butoxycarbonyl-6-dimethylcarbamoylthio-7-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Dissolve 6-dimethylcarbamoylthio-7-methyl-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.048 g, 2.9 mmol) in methanol (40 mL). Add a solution of potassium carbonate (1.6 g, 11.6 mmol) in water (10 mL). Stir at room temperature overnight. Remove the solvent and partition the residue between water and

DCM. Extract the aqueous phase twice with DCM. Combine the organic extracts, dry over Na_2SO_4, filter and concentrate. Dissolve the residue (0.756 g, 2.86 mmol) in DCM (50 mL). Add triethylamine (0.579 g, 0.8 mL, 2.0 equiv) and di-*tert*-butyl dicarbonate (0.624 g, 2.86 mmol) and stir at room temperature overnight. Dilute with DCM and wash with water. Dry the organic phase over Na_2SO_4, filter and concentrate to obtain the title compound as foam (1.038 g, 99%). MS (ES+) *m/z*: 264 $(M+H\text{-}Boc)^+$.

Preparation 176

3-*tert*-Butoxycarbonyl-7-cyano-6-dimethylcarbamoylsulfanyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine



<u>7-Cyano-6-dimethylthiocarbamoyloxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine</u>: Add dimethylthiocarbamoyl chloride (197 mg, 1.58 mmol) to a stirred solution of 7-cyano-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (150 mg, 0.53 mmol), DMAP (6 mg, 0.05 mmol) and dry triethylamine (300 µL) in dry 1,4-dioxane (5 mL) under an atmosphere of nitrogen and heat at 120 °C for 6 h. Cool and continue stirring for 2 days at ambient temperature. Dilute with EtOAc, wash with 1N aqueous HCl, water, saturated aqueous Na_2CO_3 and brine. Dry over $MgSO_4$ then concentrate *in vacuo*. Purify by chromatography on silica gel eluting with EtOAc:heptane (0:1 to 3:10) to give the desired intermediate as a white solid (158 mg, 81%).

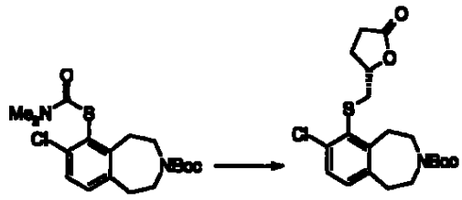
<u>7-Cyano-6-dimethylcarbamoylsulfanyl-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine</u>: Heat a round bottom flask containing a solution of 7-cyano-6-dimethylthiocarbamoyloxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (786 mg, 2.12 mmol) in diphenyl ether (21 mL) in a preheated oil bath at

230°C for 2 h. Cool and purify by chromatography on silica gel eluting with EtOAc:heptane (0:1 to 1:1) to give the desired intermediate as a yellow foam (740 mg, 94%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60-7.56 (d, 1H), 7.36-7.30 (d, 1H), 3.88-3.68 (m, 4H), 3.34-3.03 (m, 10H).

3-*tert*-Butoxycarbonyl-7-cyano-6-dimethylcarbamoylsulfanyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Add potassium carbonate (4.13 g, 30 mmol) to a stirred solution of 7-cyano-6-dimethylcarbamoylsulfanyl-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (740 mg, 2.0 mmol) in methanol (40 mL)/water (15 mL) and stir for 1.5 h. Add DCM (10 mL), di-*tert*-butyl dicarbonate (480 mg, 2.2 mmol) and stir at ambient temperature for 3 days. Concentrate *in vacuo* and dilute with DCM, wash with water and extract with DCM. Combine the organic layers, wash with brine, dry over $MgSO_4$ and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with EtOAc:heptane (0:1 to 1:1) to give the title compound as a colourless foam (370 mg, 50%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, *J* 8 Hz, 1H), 7.29 (d, *J* 8 Hz, 1H), 3.69-3.48 (m, 4H), 3.26-3.02 (m, 10H), 1.45 (s, 9H).

Preparation 177

(*S*)-3-*tert*-Butoxycarbonyl-7-chloro-6-(5-oxo-tetrahydro-furan-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine

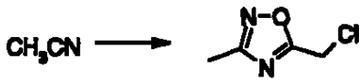


To a solution of 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-benzo[*d*]azepine (137 mg, 0.356 mmol) in methanol (2 mL) add potassium hydroxide pellets (640 mg, 11.4 mmol) and heat for 3 h at 50 °C. Cool to ambient temperature, add saturated aqueous NH_4Cl, extract three times with EtOAc, dry over anhydrous Na_2SO_4, and concentrate *in vacuo*. Dissolve the crude thiophenol thus obtained in dry DMF (2 mL), and add with stirring sodium hydride (18 mg, 0.713 mmol,

95% dispersion), followed by (*S*)-(+)-dihydro-5-(*p*-tolylsulfonyloxymethyl)-2-(3*H*)-furanone (144 mg, 0.533 mmol). Continue stirring overnight at ambient temperature, then dilute cautiously with EtOAc and cold saturated aqueous NH_4Cl. Extract three times with EtOAc, dry over anhydrous Na_2SO_4, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (7:3) to give the title compound as a colorless oil.

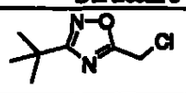
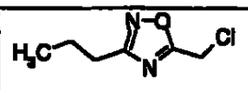
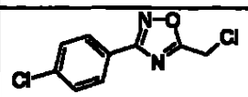
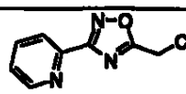
Preparation 178

5-Chloromethyl-3-methyl-[1,2,4]oxadiazole



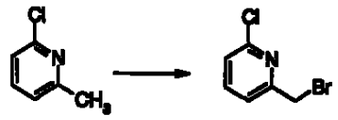
Add with stirring hydroxylamine (50 % in water, 25.0 mL, 0.380 mol) to a solution of acetonitrile (5.0 mL, 95.0 mmol) and ethanol (500 mL). Heat at 70 °C for 18 h. Concentrate *in vacuo* to provide crude *N*-hydroxyacetamidine (7.0 g, 100 %). Add slowly with stirring vinyl chloroacetate (2.1 mL) to *N*-hydroxyacetamidine (*J. Org. Chem.* 1971, *36*, 1306-1307) (1.00 g, 13.5 mmol) and heat at 90 °C for 5 h. Cool to ambient temperature, dilute with DCM, wash with aqueous 1N aqueous NaOH, dry over anhydrous Na_2SO_4 and concentrate *in vacuo* to give the title compound (904 mg, 50%).

The compounds of Preparation 179-182 were prepared essentially as described in Preparation 178.

Prep.	Structure	Compound
179		3-*tert*-Butyl-5-chloromethyl-[1,2,4]oxadiazole
180		5-Chloromethyl-3-propyl-[1,2,4]oxadiazole
181		5-Chloromethyl-3-(4-chloro-phenyl)-[1,2,4]oxadiazole
182		2-(5-Chloromethyl-[1,2,4]oxadiazol-3-yl)-pyridine

Preparation 183

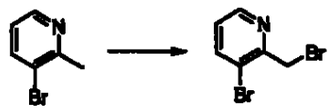
2-Bromomethyl-6-chloropyridine



Heat a mixture of 2-chloro-6-methylpyridine (5.46 g, 42.8 mmol), NBS (8.38 g, 47.08 mmol), and benzoyl peroxide (500 mg, 2.06 mmol) in carbon tetrachloride (80 mL) for 20 h at 85 °C. Cool to ambient temperature, filter, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/toluene (4:3) to provide the title compound as a white solid (3.64 g, 41%).

Preparation 184

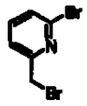
3-Bromo-2-bromomethyl-pyridine



Heat a mixture of 3-bromo-2-methylpyridine (*J. Med. Chem.* 1987, *30*, 871-880) (2.7 g, 15.8 mmol), NBS (3.10 g, 17.42 mmol), and benzoyl peroxide (190 mg, 0.78 mmol) in carbon tetrachloride (50 mL) overnight at 85 °C. Cool to ambient temperature, filter, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with toluene to provide the title compound as a white solid (1.81 g, 45%).

Preparation 185

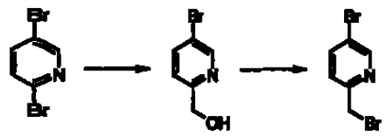
2-Bromo-6-bromomethyl-pyridine



Use a method similar to the Preparation 184, using 2-bromo-6-methylpyridine, to give the title compound.

Preparation 186

5-Bromo-2-bromomethylpyridine

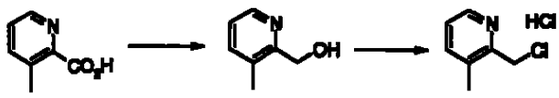


2-Hydroxymethyl-5-bromopyridine: Dissolve 2,5-dibromopyridine (10 g, 42 mmol) in toluene (500 mL) and cool to –78 °C. Add 2.5M *n*-butyllithium in hexane (20.3 mL, 50.6 mmol) and stir the mixture for 7 h at the same temperature. Add DMF (4.2 mL, 54.87 mmol) and stir for 1 h. Warm the solution to 0 °C and add sodium borohydride (3.2 g, 84.42 mmol). Stir the mixture at ambient temperature for 3 h. Dilute with EtOAc and saturated aqueous NH_4Cl. Separate the layers and extract the aqueous layer three times with EtOAc. Dry over anhydrous Na_2SO_4, filter and concentrate *in vacuo*. Recrystallization from hexane/EtOAc (9:1) gives the desired intermediate as a white solid (5.3 g, 66%).

5-Bromo-2-bromomethyl-pyridine : Dissolve 2-hydroxymethyl-5-bromopyridine (5.21 g, 27.7 mmol) in 48% aqueous hydrobromic acid (20 mL). Heat the mixture at 150 °C for 2 h. Cool to ambient temperature and remove excess hydrobromic acid under vacuum. Dilute with water, add cautiously saturated aqueous $NaHCO_3$ and extract three times with EtOAc. Dry over anhydrous Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to give the title compound as pink oil (6.0 g, 87%) that crystallizes in the freezer.

Preparation 187

2-Chloromethyl-3-methylpyridine Hydrochloride



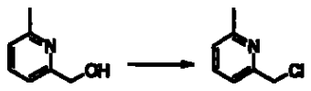
2-Hydroxymethyl-3-methylpyridine: Heat a mixture of 3-methylpicolinic acid (1.0 g, 7.3 mmol), potassium carbonate (4.1 g, 29.7 mmol), and iodomethane (4.4 g, 31.0 mmol) in acetone (35 mL) overnight under reflux. Filter, wash the residue with EtOAc, and concentrate *in vacuo*. Pass through a short plug of silica gel eluting with hexane/EtOAc (1:1) to provide 2-methoxycarbonyl-3-methylpyridine as a pale yellow liquid (630 mg, 57%). To a solution of 2-methoxycarbonyl-3-methylpyridine in anhydrous THF (10 mL)

at 0 °C, add with stirring a solution of 1M lithium aluminum hydride in THF (5 mL, 5 mmol), and continue stirring for 30 min at 0 °C. Allow the mixture to warm to ambient temperature and quench cautiously with 0.5M aqueous NaOH. Heat the mixture at 60 °C for 40 min, cool to ambient temperature, extract with EtOAc, dry over anhydrous Na_2SO_4 and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (4:3) to give the desired intermediate (90 mg, 18%).

2-Chloromethyl-3-methylpyridine hydrochloride: To 2-hydroxymethyl-3-methylpyridine (90 mg, 0.73 mmol) in dry DCM (10 mL) at ambient temperature, add with stirring thionyl chloride (0.53 mL, 7.3 mmol). Continue stirring overnight, concentrate *in vacuo*, and azeotrope three times with chloroform. Triturate the residue with dry ether, filter, and dry under vacuum to obtain the title compound as a beige solid (130 mg, 100%).

Preparation 188

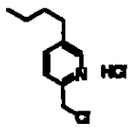
2-Chloromethyl-6-methylpryidine



Add with stirring a solution of thionyl chloride (0.77 mL, 10.6 mmol) in dry DCM (20 mL) to 2-hydroxymethyl-6-methylpyridine (1.0 g, 8.12 mmol) in dry DCM (20 mL) at 0 °C. Continue stirring at 0 °C for 1.25 h. Quench with isopropanol and concentrate *in vacuo*. Dissolve the residue in DCM, wash with saturated aqueous $NaHCO_3$, dry over anhydrous Na_2SO_4, and concentrate *in vacuo* to give the title compound. MS (ES+) *m/z* 142 $(M+H)^+$.

Preparation 189

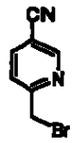
5-Butyl-2-chloromethylpyridine Hydrochloride



Use a method similar to the Preparation 187, using fusaric acid, to give the title compound. MS (APCI+) *m/z* 184 $(M+H)^+$.

Preparation 190

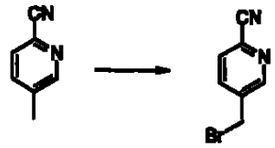
6-Bromomethylnicotinonitrile



Use a method similar to the Preparation 184, using 5-cyano-2-methylpyridine, to give the title compound.

Preparation 191

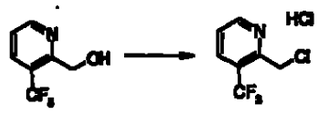
5-Bromomethyl-pyridine-2-carbonitrile



Use a method similar to the Preparation 184, using 5-methyl-picolinonitrile (*J. Chem. Soc.* 1962, 2637-2658), to give the title compound.

Preparation 192

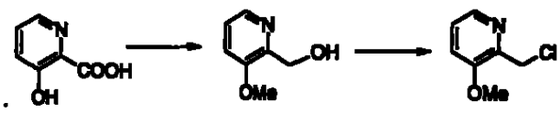
2-Chloromethyl-3-trifluoromethylpyridine Hydrochloride



Use the chlorination method described in Preparation 187, using 2-hydroxymethyl-3-trifluoromethylpyridine, to give the title compound. MS (APCI+) *m/z* 196 $(M+H)^+$.

Preparation 193

2-Chloromethyl-3-methoxypyridine

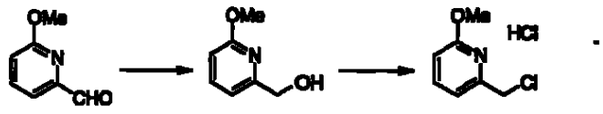


2-Hydroxymethyl-3-methoxypyridine: Heat a mixture of 3-hydroxypicolinic acid (5.3 g, 38 mmol), potassium carbonate (15.8 g, 114 mmol), and iodomethane (9.6 mL, 153 mmol) in acetone (100 mL) and DMF (10 mL) overnight at 60°C. Cool the reaction mixture to ambient temperature, pour into brine, extract three times with ethyl ether, dry over anhydrous $MgSO_4$ and concentrate *in vacuo*. Pass through a short plug of silica gel eluting with ether to provide 3-methoxy-2-methoxycarbonylpyridine as a pale yellow liquid (6.3 g, 100%). To a solution of 3-methoxy-2-methoxycarbonyl-pyridine (2.34 g, 14.0 mmol) in dry THF (25 mL) add slowly with stirring a solution of 1M lithium aluminum hydride in THF (10 mL, 10 mmol) and continue stirring overnight at ambient temperature. Quench cautiously with sodium sulfate decahydrate, filter under suction and rinse the solids with additional THF. Concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (3:1) to provide the desired intermediate as a white solid (350 mg, 18%).

2-Chloromethyl-3-methoxypyridine: Use a method similar to the Preparation 188, using 2-hydroxymethyl-3-methoxypyridine, to give the title compound. MS (APCI+) *m/z* 158 $(M+H)^+$.

Preparation 194

2-Chloromethyl-6-methoxypyridine Hydrochloride

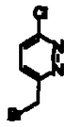


2-Hydroxymethyl-6-methoxypyridine: To 6-methoxy-pyridine-2-carbaldehyde (*J. Org. Chem.* 1990, *55*, 69-73) (11.0 g, 80.3 mmol) in wet THF (200 mL) add portion wise with stirring sodium borohydride (3.0 g, 79mmol) and continue stirring for 1 h at ambient temperature. Add brine, extract the reacton mixture twice with EtOAc, dry the organic layer over anhydrous Na_2SO_4 and concentrate *in vacuo*. Pass the residue through a small plug of silica gel eluting with hexane/EtOAc (3:1) to provide the desired intermediate as a clear liquid (9.0 g, 81%).

2-Chloromethyl-6-methoxypyridine hydrochloride: Use the chlorination method described in Preparation 187, using 2-hydroxymethyl-6-methoxypyridine, to give the title compound as a pale yellow solid. MS (APCI+) *m/z* 158 $(M+H)^+$.

Preparation 195

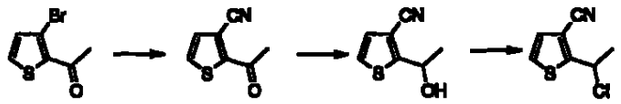
3-Bromomethyl-6-chloro-pyridazine



Use a method similar to the Preparation 184, using 3-chloro-6-methylpyridazine, to give the title compound as a red-orange liquid that darkens on standing.

Preparation 196

(±)-2-(1-Chloroethyl)-3-cyanothiophene



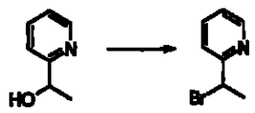
2-Acetyl-3-cyanothiophene: Heat a stirred solution of 2-acetyl-3-bromothiophene (1.49 g, 7.29 mmol) (*Chem. Pharm. Bull.* 2000, *48*, 1558-1566) in dry NMP (72 mL) for 10 h at 150 °C in the presence of copper cyanide (3.26 g, 36.5 mmol). Dilute the mixture with water, extract three times with diethyl ether, dry over anhydrous Na_2SO_4 and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (10:1) to give the desired intermediate as a dark oil (1.1 g, 99%).

(±)-2-(1-Hydroxyethyl)-3-cyanothiophene: Use a method similar to the reduction procedure described in Preparation 194, using 2-acetyl-3-cyanothiophene, to give the desired intermediate as dark oil.

(±)-2-(1-Chloroethyl)-3-cyanothiophene: Use a method similar to the Preparation 188, using (±)-2-(1-hydroxyethyl)-3-cyanothiophene, to give the title compound as dark oil. Use the crude material without further purification.

Preparation 197

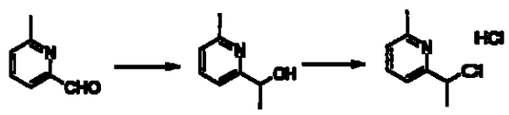
(±)-2-(1-Bromoethyl)-pyridine



To (±)-2-(1-hydroxyethyl)-pyridine (*Bull. Chem. Soc. Jpn.* 1990, *63*, 461-465) (10.0 g, 81.3 mmol) in DCM (120 mL) at 0° C, add with stirring triphenylphosphine (22.39 g, 85.365 mmol) followed by NBS (15.2 g, 85.4 mmol) in portions. Warm the reaction mixture to ambient temperature and continue stirring for 3 h. Concentrate *in vacuo* and purify by chromatography on silica gel eluting with hexane/EtOAc (19:1) to give the title compound.

Preparation 198

(±)-2-(1-Chloroethyl)-6-methylpyridine Hydrochloride

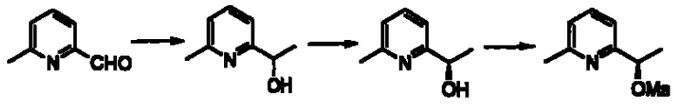


(±)-2-(1-Hydroxyethyl)-6-methylpyridine: To 6-methylpyridine-2-carboxaldehyde (2.0 g, 16.5 mmol) in dry THF (55 mL) at 0 °C under nitrogen, add a solution of 3M methyl magnesium bromide in ether (6.0 mL, 18.0 mmol,) dropwise with stirring. After 1 h at 0°C, quench with saturated aqueous NH_4Cl, extract three times with EtOAc, dry over anhydrous Na_2SO_4 and concentrate *in vacuo* to give the desired intermediate (crude, 2.3 g).

(±)-2-(1-Chloroethyl)-6-methylpyridine hydrochloride: To the crude 2-(1-hydroxyethyl)-6-methylpyridine (1.6 g, 11.7 mmol) in dry DCM (1.5 mL) add with stirring thionyl chloride (2.0 mL, 27 mmol) and continue stirring overnight. Concentrate *in vacuo*, azeotrope three times with dry chloroform and dry under high vacuum to provide the title compound as a tan solid (1.9 g, 85%). MS (APCI+) *m/z* 156 $(M+H)^+$.

Preparation 199

(*R*)-Methanesulfonic acid 1-(6-methyl-pyridin-2-yl)-ethyl ester



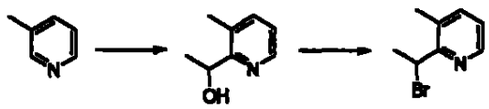
(±)-1-(6-Methyl-pyridin-2-yl)-ethanol: Use a method similar to the Preparation 198 (Step 1), using 6-methyl-2-pyridinecarboxaldehyde and methylmagnesium bromide, to give the desired intermediate.

(*R*)-1-(6-Methyl-pyridin-2-yl)-ethanol: Stir a mixture of 1-(6-methyl-pyridin-2-yl)-ethanol (2.9 g, 21 mmol), 4A molecular sieves powder (3 g), vinyl acetate (6 mL) and lipase Candida Antarctica acrylic resin (0.87 g) in *i*-Pr_2O (40 mL) at ambient temperature overnight (*J. Org. Chem.* 1998, *63*, 2481-2487; *Synlett* 1999, 41-44). Remove the solid residue by filtration. Evaporate the volatile substances and purify by chromatography eluting with hexane/EtOAc (7:3 to 1:1) to give the faster eluting (*R*)-acetic acid 1-(6-methyl-pyridin-2-yl)-ethyl ester as colorless oil (1.9 g, 50%), and the slower eluting (*S*)-alcohol as light yellow oil (1.258 g, 43%). Dissolve (*R*)-acetic acid 1-(6-methyl-pyridin-2-yl)-ethyl ester (1.72 g, 9.62 mmol) in methanol (50 mL) and add potassium carbonate (5.3 g, 38.5 mmol) in water (10 mL). Stir the mixture at ambient temperature for 4 h. Dilute with brine, extract three times with EtOAc, dry over anhydrous Na_2SO_4, filter through a short pad of silica gel and concentrate *in vacuo* to give the desired intermediate as a colorless oil (1.17 g, 89%).

(*R*)-Methanesulfonic acid 1-(6-methyl-pyridin-2-yl)-ethyl ester: To a stirred solution of (*R*)-1-(6-methyl-pyridin-2-yl)-ethanol (175 mg, 1.28 mmol) and triethylamine (355 µl, 2.56 mmol) in DCM (5 mL) at 0°C add methanesulfonyl chloride (148 µl, 1.92 mmol). Stir at 0 °C for 30 min and quench the reaction mixture with saturated aqueous $NaHCO_3$ at the same temperature. Extract the mixture three times with EtOAc, dry over anhydrous Na_2SO_4, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (8:2) to give the title compound as a colorless oil (274 mg, 100%).

Preparation 200

(±)-2-(1-Bromoethyl)-3-methyl-pyridine

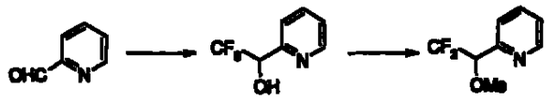


(±)-1-(3-Methyl-pyridin-2-yl)-ethanol: Dissolve *N,N*-dimethylethanolamine (70.45 mmol) in hexane (90 mL) at 0°C, add 2.5M *n*-butyl lithium in hexane (140.9 mmol,) and stir for 30 min at this temperature. Add a solution of 3-picoline (35.23 mmol) in hexane (10 mL) and continue stirring at 0° C for 1 h. Cool the resulting mixture to –78° C, add acetaldehyde (70.45 mmol) and continue stirring at –78° C for 1 h. Dilute with water, warm to ambient temperature, extract three times with EtOAc, dry over anhydrous Na_2SO_4, and concentrate *in vacuo*. Purify by chromatography eluting with hexane/EtOAc (85:15) to give the desired intermediate as a light yellow oil.

(±)-2-(1-Bromoethyl)-3-methyl-pyridine: Use a method similar to the Preparation 197, using 1-(3-fluoro-pyridin-2-yl)-ethanol, to give the title compound.

Preparation 201

(±)-2-[1-Methanesulfonyloxy-(2,2,2-trifluoroethyl)]pyridine

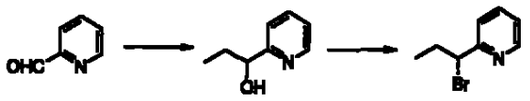


(±)-2-[1-Hydroxy-(2,2,2-trifluoroethyl)]-pyridine: To a stirred solution of 2-pyridine carboxaldehyde (2.09 g, 19.5 mmol) and (trifluoromethyl)trimethylsilane (3.33 g, 23.4 mmol) in THF (30 mL) at 0° C add 1M tetrabutylammonium fluoride in THF (956 µl, 0.956 mmol). Continue stirring for 30 min at 0° C and then at ambient temperature for 2 h. Add 1M aqueous HCl (20 mL) and stir 2 h at ambient temperature. Dilute with aqueous 1M aqueous NaOH to pH 8, extract the mixture three times with EtOAc, dry over anhydrous Na_2SO_4, and concentrate *in vacuo*. Purify by chromatography eluting with hexane/EtOAc (8:2) to give the desired intermediate as a yellow oil (3.22 g, 93%).

(±)-2-[1-Methanesulfonyloxy-(2,2,2-trifluoroethyl)]pyridine: Use a method similar to the Preparation 199 (Step 3), using (±)-2-[1-hydroxy-(2,2,2-trifluoroethyl)]pyridine, to give the title compound.

Preparation 202

(±)-2-(1-Bromopropyl)pyridine

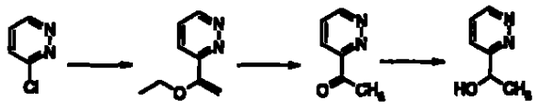


(±)-1-Pyridin-2-yl-propan-1-ol: To a stirred solution of 2-pyridine carboxaldehyde (4.0 g, 37.34 mmol) in THF (50 mL) at 0° C, add 3M ethyl magnesium bromide in ether (18.7 mL, 56.0 mmol), continue stirring for 30 min at 0°C and then at ambient temperature for 2 h. Add water (200 mL), extract three times with EtOAc, dry over anhydrous Na_2SO_4, filter through a short pad of silica gel and concentrate *in vacuo* to give the desired intermediate as a yellow oil (3.39 g, 66%).

(±)-2-(1-Bromopropyl)pyridine: Use a method similar to the Preparation 197, using 1-pyridin-2-yl-propan-1-ol, to give the title compound.

Preparation 203

(±)-1-Pyridazin-3-yl-ethanol



3-(1-Ethoxyvinyl)pyridazine: Heat pyridazine-3-chloride (WO 0107416) (2 g, 17.5 mmol) with tributyl-(1-ethoxyvinyl)tin (7.1 mL, 21.1 mmol) and dichlorobis(triphenylphosphine)palladium(II) (1.1 g, 1.6 mmol) in DMF (18 mL) at 110°C for 13 h. Cool the mixture, dilute with ether (175 mL) and add a solution of potassium fluoride (5.43 g, 94 mmol) in water (10 mL). After 1 h, filter the mixture through Celite®, and wash the filtrate with brine. Dry the combined organic extracts over Na_2SO_4 and evaporate. Purify by chromatography on silica gel eluting with EtOAc:hexane (0:1 to 6:4) to obtain the desired intermediate (1.7 g, 65%). HPLC t_R=3.7

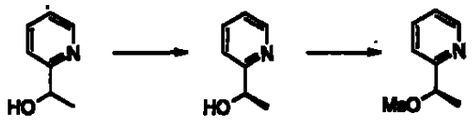
min (Zorbax Eclipse XBD-C8 4.6 x 150 mm 5 micron column, 1.5 mL/min of 90/10 to 10/90 0.1% TFA in water/acetonitrile over 10 min. Detector is at 230 and 254 nm.).

1-Pyridazin-3-yl-ethanone: Stir 3-(1-ethoxyvinyl)pyridazine (1.7 g, 11.3 mmol) in acetone (6.3 mL) and 2.5N aqueous HCl (3.1 mL) for 2 h at ambient temperature and evaporate. Dissolve the residue in DCM and wash the organic layer with saturated aqueous $NaHCO_3$, dry the organic layer over Na_2SO_4 and evaporate to obtain the desired intermediate (1.4 g, 99%). HPLC t_R=1.9 min (Zorbax Eclipse XBD-C8 4.6 x 150 mm 5 micron column, 1.5 mL/min of 90/10 to 10/90 0.1% TFA in water/acetonitrile over 10 min. Detector is at 230 and 254 nm.).

(±)-1-Pyridazin-3-yl-ethanol: To 1-pyridazin-3-yl-ethanone (1.4 g, 11.2 mmol) in methanol (112 mL) add sodium borohydride (0.85 g, 22.5 mmol) at 0 °C and stir for 1 h at ambient temperature. Evaporate the mixture and purify by chromatography on silica gel eluting with EtOAc:hexane (1:1 to 1:0) and methanol:EtOAc (0:1 to 1:9) to obtain the title compound (1.3 g, 93%).

Preparation 204

(*R*)-(-)-1-(2-Pyridinyl)ethanol methanesulfonate ester



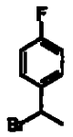
(*R*)-1-(Pyridin-2-yl)-ethanol: Stir a mixture of (±)-1-(pyridin-2-yl)-ethanol (21.2 mmol), 4A molecular sieves powder (3 g), vinyl acetate (6 mL) and lipase Candida Antarctica acrylic resin (0.87 g) in *i*-Pr_2O (40 mL) at ambient temperature overnight (*J. Org. Chem.* 1998, *63*, 2481-2487; *Synlett* 1999, 41-44). Remove the solid residue by filtration. Evaporate the volatile substances and purify by chromatography eluting with hexane/EtOAc (7:3 to 1:1) to give the faster eluting (*R*)-acetic acid 1-(pyridin-2-yl)-ethyl ester as colorless oil (50%) and the slower eluting (*S*)-alcohol as light yellow oil (43%). Dissolve (*R*)-acetic acid 1-(pyridin-2-yl)-ethyl ester (9.620 mmol) in methanol (50 mL) and add potassium carbonate (38.48 mmol) in water (10 mL). Stir the mixture at ambient temperature for 4 h. Dilute with brine, extract three times with EtOAc, dry over

anhydrous Na_2SO_4, filter through a short pad of silica gel and concentrate *in vacuo* to give the desired intermediate as a colorless oil (89%).

(*R*)-(-)-1-(2-Pyridinyl)ethanol methanesulfonate ester: To a stirred solution of (*R*)-1-(pyridin-2-yl)-ethanol (1.28 mmol) and triethylamine (2.56 mmol) in DCM (5 mL) at 0°C add methanesulfonyl chloride (1.92 mmol). Stir at 0° C for 30 min and quench the reaction mixture with saturated aqueous $NaHCO_3$ at the same temperature. Extract three times with EtOAc, dry over anhydrous Na_2SO_4, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (4:1) to give the title compound as a colorless oil (100 %). MS (APCI+) *m/z* 202 $(M+H)^+$; $[\alpha]_D^{25} = -73.5°$ (c 1, $CHCl_3$).

Preparation 205

(±)-1-(4-Fluorophenyl)ethyl bromide



Method A: Add carbon tetrabromide (646 mg, 1.95 mmol) to a solution of triphenylphosphine (511 mg, 1.95 mmol) and (±)-4-fluoro-α-methylbenzyl alcohol (260 mg, 1.86 mol) in dry DMF (20 mL) at 0°C under nitrogen. Stir the reaction for 2 h to give the title compound. No further purification required.

Method B: Add HBr (460 µL of 48% w/w in water, 4.28 mmol) to a solution of (±)-4-fluoro-α-methylbenzyl alcohol (300 mg, 2.14 mmol) in dry DCM (10 mL) at ambient temperature under an atmosphere of nitrogen. Stir for 2.5 h. Reduce volume *in vacuo* to give the title compound. Dilute with DCM (1 mL) and use without further purification.

Preparation 206

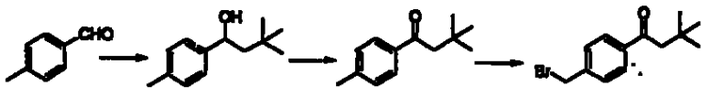
(±)-2-(1-Bromoethyl)benzonitrile



Use a method similar to the Preparation 184, using 2-ethylbenzonitrile, to give the title compound as a clear liquid.

Preparation 207

1-(4-Bromomethylphenyl)-3,3-dimethylbutan-1-one



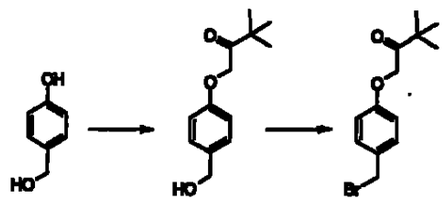
(±)-3,3-Dimethyl-1-p-tolylbutan-1-ol: To a stirred solution of 4-methylbenzaldehyde (1.51 g, 12.6 mmol) in THF (30 mL) at 0° C, add neopentyl magnesium chloride (33.0 mL, 16.34 mmol, 0.5-1M in ether) and continue stirring at 0 °C for 1 h. Dilute with saturated aqueous NH_4Cl, extract three times with EtOAc, dry over anhydrous Na_2SO_4, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (95:5) to give the desired intermediate as a colorless oil (2.15 g, 89%).

3,3-Dimethyl-1-p-tolyl-butan-1-one: To a stirred solution of (±)-3,3-dimethyl-1-*p*-tolyl-butan-1-ol (2.15 g, 11.3 mmol) in hexane (30 mL) add manganese dioxide (2.94 g, 33.8 mmol) and heat the mixture overnight at 65° C. Cool to ambient temperature, filter the manganese salts, and concentrate *in vacuo* to give the desired intermediate as a colorless oil (2.2 g, 100%).

1-(4-Bromomethylphenyl)-3,3-dimethylbutan-1-one: Use a method similar to the Preparation 184, using 3,3-dimethyl-1-*p*-tolylbutan-1-one, to give the title compound.

Preparation 208

.1-(4-Bromomethylphenoxy)-3,3-dimethylbutan-2-one



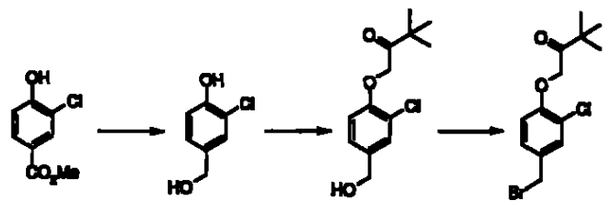
1-(4-Hydroxymethylphenoxy)-3,3-dimethylbutan-2-one: Mix potassium carbonate (2.764 g, 20 mmol), 4-hydroxy-benzyl alcohol (1.49 g, 12 mmol) in absolute ethanol (100

mL), add 1-bromopinacolone (1.791 g, 10 mmol) dropwise. Heat the mixture under reflux for 12 h. Add water to dissolve the solid, and remove most of the ethanol *in vacuo*. Extract the mixture with EtOAc three times. Combine the organic layers, wash with brine, dry over Na_2SO_4, filter and concentrate. Purify the residue by chromatography on silica gel eluting with EtOAc:hexane (1:2) to provide the desired intermediate as a colorless oil (1.08 g, 48%). MS (ES+) *m/z*: 205 $(M+H-H_2O)^+$.

1-(4-Bromomethylphenoxy)-3,3-dimethylbutan-2-one: Add phosphorous tribromide (1.45 g, 5.34 mmol) slowly to a solution of 1-(4-hydroxymethyl-phenoxy)-3,3-dimethylbutan-2-one (1.08 g, 4.85 mmol) in anhydrous THF under nitrogen at 0 °C. Stir at 0 °C for 1 h and then raise to ambient temperature. Stir overnight. Dilute with EtOAc, wash with saturated aqueous $NaHCO_3$, brine, dry over Na_2SO_4, filter and concentrate. Purify the residue by chromatography on silica gel eluting with EtOAc:hexane (1:6) to provide the title compound (1.152 g, 83%). MS (ES+) *m/z*: 205 $(M-Br)^+$.

Preparation 209

1-(4-Bromomethyl-3-chlorophenoxy)-3,3-dimethylbutan-2-one

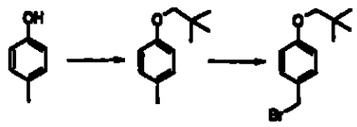


3-Chloro-4-hydroxybenzyl alcohol: Add a solution of DIBAL-H in toluene (1.0 M, 35 mL) to a solution of methyl 3-chloro-4-hydroxybenzoate (1.9 g, 10 mmol) at 0 °C under nitrogen. Stir the reaction at 0 °C and gradually warm to ambient temperature overnight. Quench the reaction with slow addition of 0.1N aqueous HCl, add more acid to break the gel-like solid to two clear layers. Separate the organic layer, and extract the aqueous layer with EtOAc three times. Combine the organic layers, wash with brine, dry over Na_2SO_4, filter and concentrate to give a white solid. MS (ES-) *m/z* 157 $(M-H)^-$.

1-(4-Bromomethyl-3-chlorophenoxy)-3,3-dimethyl-butan-2-one: Use a method similar to the Preparation 208 to convert 3-chloro-4-hydroxy-benzyl alcohol to the title compound (1.144 g, 64% two steps). MS (ES+) *m/z* 319.0 $(M+H)^+$.

Preparation 210

1-Bromomethyl-4-(2,2-dimethyl-propoxy)-benzene

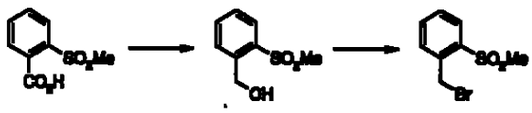


1-(2,2-Dimethyl-propoxy)-4-methyl-benzene: To a solution of *p*-cresol (526 mg, 4.87 mmol) in THF (50 mL), add with stirring diisopropyl azodicarboxylate (2.16 mL, 10.7 mmol) followed by triphenylphosphine (306 mg, 11.7 mmol) and neopentyl alcohol (5.15 g, 58.4 mmol). Heat at 60 °C for 3 h, cool to ambient temperature and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc to give the desired intermediate as a colorless oil.

1-Bromomethyl-4-(2,2-dimethyl-propoxy)-benzene: Use a method similar to the Preparation 184, using 1-(2,2-dimethyl-propoxy)-4-methylbenzene, to give the title compound.

Preparation 211

1-Bromomethyl-2-methanesulfonylbenzene

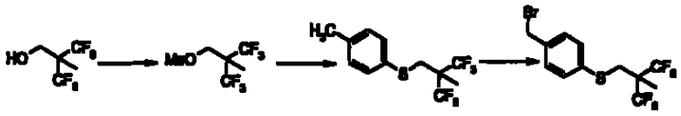


(2-Methanesulfonylphenyl)methanol: To a stirred solution of 2-methanesulfonyl-benzoic acid (2.7 g, 13.5 mmol) in dry THF (60 mL) at 0 °C, add a solution of borane in THF (27.0 mL, 0.5 M, 13.5 mmol). Allow the mixture to warm to ambient temperature and continue stirring for 2 days. Quench the excess borane by slow addition of methanol, add brine, extract three times with EtOAc, dry over anhydrous Na_2SO_4 and concentrate *in vacuo* to provide the crude desired intermediate as a clear, thick oil (2.4 g, 97 %).

1-Bromomethyl-2-methanesulfonylbenzene: To a stirred solution of (2-methanesulfonyl-phenyl)methanol (735 mg, 3.99 mmol) in dry DCM (2 mL) at 0 °C, add a solution of 1M phosphorous tribromide in DCM (6.0 mL, 6.0 mmol) and continue stirring for 1 h. Dilute with saturated aqueous $NaHCO_3$, extract three times with ethyl ether, dry over anhydrous $MgSO_4$ and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (12:1) to provide the title compound as a white solid (950 mg, 97 %).

Preparation 212

1-Bromomethyl-4-(3,3,3-trifluoro-2-methyl-2-trifluoromethylpropylthio)benzene



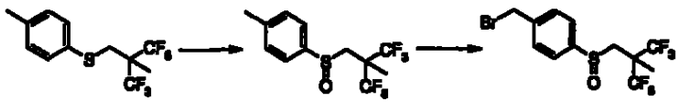
Methanesulfonic acid 3,3,3-trifluoro-2-methyl-2-trifluoromethyl-propyl ester: To 2,2-bis(trifloromethyl)propanol (4.34 g, 22.1 mmol) in DCM (100 mL) at 0 °C add with stirring triethylamine (6.2 mL, 44 mmol) followed by methanesulfonyl chloride (2.6 mL, 33 mmol). After 15 min at 0 °C dilute with water and extract three times with EtOAc. Dry over anhydrous Na_2SO_4 and concentrate *in vacuo* to give the crude desired intermediate as a yellow oil (6.16 g, 100 %).

1-Methyl-4-(3,3,3-trifluoro-2-methyl-2-trifluoromethylpropylthio)benzene: In a sealed tube dissolve 4-methylbenzenethiol (4.13 g, 33.2 mmol) in DMF (20 mL) at ambient temperature. Add portionwise with stirring sodium hydride (899 mg, 37.5 mmol) followed by tetrabutylammonium iodide (82 mg, 0.22 mmol) and a solution of methanesulfonic acid 3,3,3-trifluoro-2-methyl-2-trifluoromethylpropyl ester (6.16 g, 22.5 mmol) in DMF (10 mL). Stir at 150 °C overnight, cool the mixture to ambient temperature and dilute cautiously with water. Extract three times with EtOAc, dry over anhydrous Na_2SO_4, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane to give the desired intermediate as a yellow oil (4.5 g, 62 %).

1-Bromomethyl-4-(3,3,3-trifluoro-2-methyl-2-trifluoromethylpropylthio)benzene: Use a method similar to the Preparation 184, using 1-methyl-4-(3,3,3-trifluoro-2-methyl-2-trifluoromethylpropylthio)benzene, to give the title compound.

Preparation 213

1-Bromomethyl-4-(3,3,3-trifluoro-2-methyl-2-trifluoromethylpropane-1-sulfinyl)-benzene

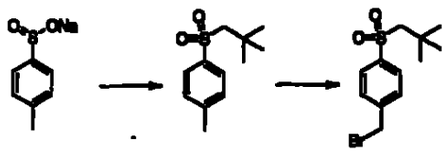


1-Methyl-4-(3,3,3-trifluoro-2-methyl-2-trifluoromethylpropane-1-sulfinyl)-benzene: To 1-methyl-4-(3,3,3-trifluoro-2-methyl-2-trifluoromethylpropylthio)benzene (4.5 g, 14.9 mmol) in acetic acid (15 mL) at ambient temperature, add with stirring aqueous hydrogen peroxide (15 mL, 30% in water) and stir for 1 h. Dilute the reaction with water, extract three times with EtOAc, dry over anhydrous Na_2SO_4, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to give the desired intermediate as a colorless oil (4.125 g, 88 %).

1-Bromomethyl-4-(3,3,3-trifluoro-2-methyl-2-trifluoromethylpropane-1-sulfinyl)-benzene: To 1-methyl-4-(3,3,3-trifluoro-2-methyl-2-trifluoromethylpropane-1-sulfinyl)-benzene (4.13 g, 13.0mmol) in carbon tetrachloride (50 mL) add NBS (2.31 g, 13.0 mmol), benzoyl peroxide (314 mg, 1.30 mmol) and stir overnight at reflux. Cool to ambient temperature, dilute with water and extract three times with EtOAc. Dry over anhydrous Na_2SO_4 and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to give the title compound as colorless oil (2.3 g, 55 %).

Preparation 214

1-Bromomethyl-4-(2,2-dimethylpropane-1-sulfonyl)benzene

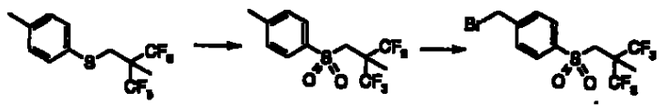


1-(2,2-Dimethyl-propane-1-sulfonyl)-4-methyl-benzene: In a sealed tube, dissolve *p*-toluenesulfinic acid sodium salt (5.71 g, 32.1 mmol) in DMF (20 mL) and water (10 mL). Add *neo*-pentyl bromide (6.3 mL, 48 mmol) and tetrabutylammonium iodide (592 mg, 1.60 mmol) and heat the mixture at 145 °C overnight. Cool the reaction to ambient temperature, dilute with water and extract 3 times with EtOAc. Dry over anhydrous Na_2SO_4 and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to give the desired intermediate as a colorless oil (3.3 g, 45 %).

1-Bromomethyl-4-(2,2-dimethylpropane-1-sulfonyl)benzene: Use a method similar to the Preparation 213 (Step 2), using 1-(2,2-dimethylpropane-1-sulfonyl)-4-methyl-benzene, to give the title compound.

Preparation 215

1-Bromomethyl-4-(3,3,3-trifluoro-2-methyl-2-trifluoromethylpropane-1-sulfonyl)-benzene

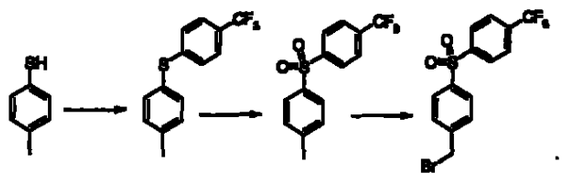


1-Methyl-4-(3,3,3-trifluoro-2-methyl-2-trifluoromethylpropane-1-sulfonyl)benzene: To 1-methyl-4-(3,3,3-trifluoro-2-methyl-2-trifluoromethylpropylthio)benzene (3.47 g, 11.49 mmol) in trifluoroacetic acid (15 mL) at ambient temperature add with stirring aqueous hydrogen peroxide (15 mL, 30% in water) and stir for 1 h. After removing trifluoroacetic acid *in vacuo*, dilute with saturated aqueous $NaHCO_3$. Extract three times with EtOAc, dry over anhydrous Na_2SO_4, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to give the desired intermediate as a colorless oil (2.8 g, 74 %).

1-Bromomethyl-4-(3,3,3-trifluoro-2-methyl-2-trifluoromethylpropane-1-sulfonyl)-benzene: Use a method similar to the Preparation 213 (Step 2), using 1-methyl-4-(3,3,3-trifluoro-2-methyl-2-trifluoromethylpropane-1-sulfonyl)benzene, to give the title compound.

Preparation 216

1-Bromomethyl-4-(4'-trifluoromethyl)-phenylsulfonylbenzene

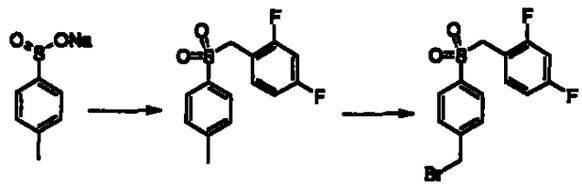


1-Methyl-4-(4-trifluoromethyl)-phenylthio-benzene: Heat a mixture of 4-methylbenzenethiol (7.67 g, 61.8 mmol), 1-bromo-4-trifluoromethyl-benzene (4.63 g, 20.6 mmol), 2,2,6,6-tetramethyl-3,5-heptanedione (379 mg, 2.06 mmol), cesium carbonate (20.1 g, 61.8 mmol) and CuCl (102 mg, 1.03 mmol) in NMP (30 mL) at 150° C for 3 h. Cool the mixture to ambient temperature, dilute with water, extract three times with EtOAc, dry the organic layer over anhydrous Na_2SO_4, and concentrate *in vacuo*. Recrystallize the residue from hexane/EtOAc to give the desired intermediate as a white solid (3.87 g, 70%).

1-Bromomethyl-4-(4-trifluoromethyl)-phenylsulfonyl-benzene: Use a method similar to the Preparation 215, using 1-methyl-4-(4-trifluoromethyl)-phenylthiobenzene, to give the title compound.

Preparation 217

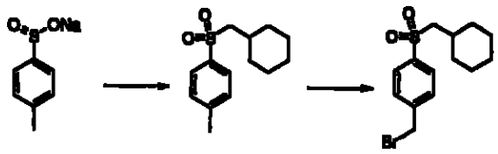
1-(4-Bromomethylbenzenesulfonylmethyl)-2,4-difluorobenzene



Use a method similar to the Preparation 214, using 2,4-difluorobenzyl bromide, to give the title compound.

Preparation 218

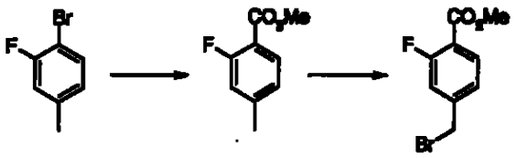
1-Bromomethyl-4-cyclohexylmethanesulfonyl-benzene



Use a method similar to the Preparation 214, using cyclohexylmethyl bromide, to give the title compound.

Preparation 219

Methyl 4-bromomethyl-2-fluorobenzoate

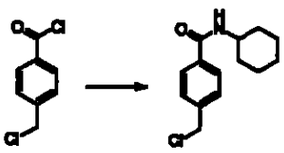


Methyl 2-fluoro-4-methyl-benzoate: Mix 1-bromo-2-fluoro-4-methylbenzene (15 g, 79.4 mmol), palladium acetate (712 mg, 3.17 mmol), 1,3-bis(diphenylphosphino)-propane (2.94 g, 7.14 mmol), triethylamine (16.1 g, 159 mmol) in methanol (150 mL) and DMF (100 mL). Degas the mixture under vacuo and pressurize to 65 psi with carbon monoxide. Stir the reaction at 110 °C for 2 days. Remove methanol *in vacuo*, dilute the mixture with water, and extract three times with EtOAc. Dry over anhydrous Na_2SO_4 and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to give the desired intermediate as a white solid (7.40 g, 55%).

Methyl 4-bromomethyl-2-fluoro-benzoate: Use a method similar to the Preparation 184, using methyl 2-fluoro-4-methylbenzoate, to give the title compound as a white solid.

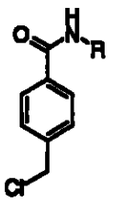
Preparation 220

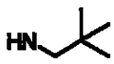
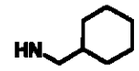
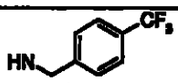
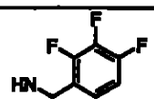
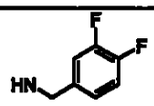
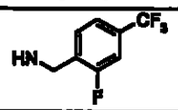
4-Chloromethyl-*N*-cyclohexylbenzamide

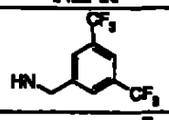
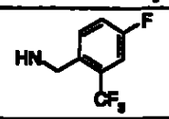
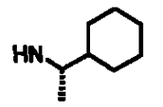
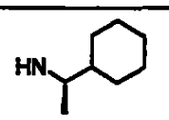
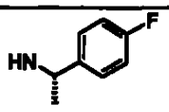
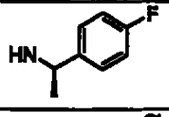
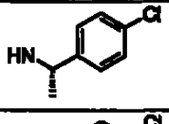
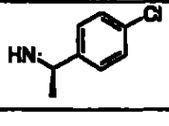


To 4-chloromethylbenzoyl chloride (1.03 g, 5.47 mmol) in DCM (20 mL) at 0 °C, add with stirring triethylamine (0.839 mL, 6.02 mmol) followed by cyclohexylamine (0.688 mL, 6.02 mmol), and continue stirring for 15 min. Dilute the reaction mixture with aqueous 1M hydrochloric acid, extract three times with EtOAc, wash with water and saturated aqueous $NaHCO_3$. Dry the combined organic extracts over anhydrous Na_2SO_4 and concentrate *in vacuo* to give the title compound as a white solid (1.31 g, 95%).

The compounds of Preparations 221-235 may be prepared essentially as described in Preparation 220by using 4-chloromethylbenzoyl chloride and the appropriate amine.

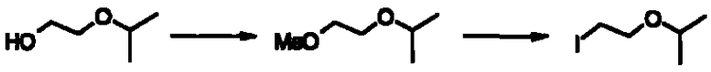


Prep.	NH-R	Compound
221		4-Chloromethyl-*N*-(2,2-dimethyl-propyl)-benzamide
222		*N-tert*-Butyl-4-chloromethyl-benzamide
223		4-Chloromethyl-*N*-cyclohexylmethyl-benzamide
224		4-Chloromethyl-*N*-(4-trifluoromethyl-benzyl)-benzamide
225		4-Chloromethyl-*N*-(2,3,4-trifluoro-benzyl)-benzamide
226		4-Chloromethyl-*N*-(3,4-difluoro-benzyl)-benzamide
227		4-Chloromethyl-*N*-(2-fluoro-4-trifluoromethyl-benzyl)-benzamide

Prep.	NH-R	Compound
228		*N*-(3,5-Bis-trifluoromethyl-benzyl)-4-chloromethyl-benzamide
229		4-Chloromethyl-*N*-(4-fluoro-2-trifluoromethyl-benzyl)-benzamide
230		(*S*)-4-Chloromethyl-*N*-(1-cyclohexyl-ethyl)-benzamide
231		(*R*)-4-Chloromethyl-*N*-(1-cyclohexyl-ethyl)-benzamide
232		(*S*)-4-Chloromethyl-*N*-[1-(4-fluoro-phenyl)-ethyl]-benzamide
233		(*R*)-4-Chloromethyl-*N*-[1-(4-fluoro-phenyl)-ethyl]-benzamide
234		(*S*)-4-Chloromethyl-*N*-[1-(4-chloro-phenyl)-ethyl]-benzamide
235		(*R*)-4-Chloromethyl-*N*-[1-(4-chlorophenyl)-ethyl]-benzamide

Preparation 236

2-(2-Iodoethoxy)propane



Methanesulfonic acid 2-isopropoxyethyl ester: To a stirred solution of 2-isopropoxyethanol (2.0 mL, 17.37 mmol) in DCM (100 mL) at ambient temperature add methanesulfonyl chloride (1.48 mL, 18.08 mmol). Add triethylamine (2.70 mL, 19.37 mmol) slowly followed by DMAP (catalytic). Continue stirring overnight and concentrate *in vacuo*. Add diethyl ether and filter. Wash the filtrate with aqueous 1N

aqueous HCl, brine, and saturated aqueous $NaHCO_3$. Dry over anhydrous $MgSO_4$ and concentrate *in vacuo* to give the desired intermediate (2.97 g, 94%).

2-(2-Iodoethoxy)propane: To a stirred solution of methanesulfonic acid 2-isopropoxy-ethyl ester (2.95 g, 16.2 mmol) in acetone (200 mL) at ambient temperature add sodium iodide (7.28 g, 19.4 mmol) and continue stirring overnight. Concentrate *in vacuo*, add diethyl ether and filter, and concentrate *in vacuo* to give the title compound as a pale yellow liquid (3.12 g, 90%).

Preparation 237

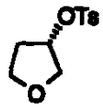
(*R*)-Toluene-4-sulfonic Acid Tetrahydrofuran-3-yl Ester



To (*R*)-tetrahydro-furan-3-ol (2.0 g, 22.7 mmol), triethylamine (3.8 mL, 27.3 mmol), DMAP (277 mg, 2.26 mmol), and silver oxide (5.26 g, 22.7 mmol) in dry DCM (30 mL) at 0 °C under nitrogen, add portion wise with stirring *p*-toluenesulfonyl chloride (4.76 g, 25.0 mmol). Warm to ambient temperature overnight, filter from silver salts, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (7:1) to give the title compound as a clear liquid (4.7 g, 85%).

Preparation 238

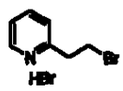
(*S*)-Toluene-4-sulfonic Acid Tetrahydrofuran-3-yl Ester



Use a method similar to the Preparation 237, using (*S*)-tetrahydro-furan-3-ol, to give the title compound as a clear liquid.

Preparation 239

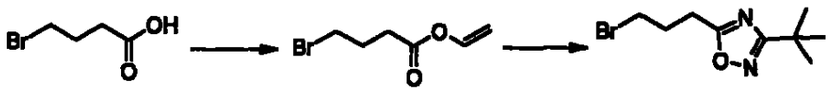
2-(2-Bromoethyl)-pyridine Hydrobromide



Use a method similar to the bromination procedure described in Preparation 186 (Step 2), using 2-pyridineethanol, to give the title compound. Recrystallize from 2-propanol to give a light brown solid.

Preparation 240

5-(3-Bromopropyl)-3-*tert*-butyl-[1,2,4]oxadiazole

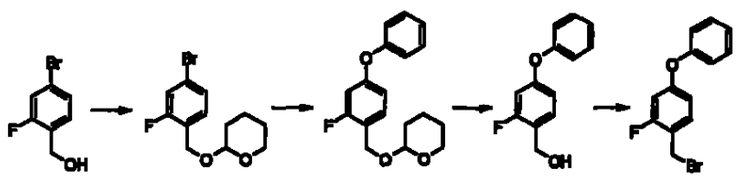


4-Bromobutyric acid vinyl ester: To 4-bromobutyric acid (1.0 g, 6.0 mmol) in vinyl acetate (54 mL) add with stirring palladium(II) acetate (188 mg, 0.84 mmol) and continue stirring overnight at ambient temperature. Filter and concentrate *in vacuo* to provide the crude desired intermediate.

5-(3-Bromopropyl)-3-*tert*-butyl-[1,2,4]oxadiazole: Use a method similar to the Preparation 178, using 4-bromobutyric acid vinyl ester, to give the title compound.

Preparation 241

1-Bromomethyl-2-fluoro-4-phenoxybenzene



2-(4-Bromo-2-fluoro-benzyloxy)-tetrahydro-pyran: Mix under nitrogen atmosphere 4-bromo-2-fluorobenzyl alcohol, (4.1 g, 20 mmol), dihydropyran (2 g, 24 mmol), *p*-toluenesulfonic acid monohydrate (100 mg, 0.52 mmol), and anhydrous DCM (70 mL). Stir for 16 h at ambient temperature. Dilute with DCM, wash sequentially with saturated aqueous $NaHCO_3$ then brine. Separate the organic layer, dry over Na_2SO_4 and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc

(1:0 and 9:1) to obtain the desired intermediate as a clear oil (4.36 g, 75%). MS (ES+) *m/z*: 312 $(M+Na)^+$.

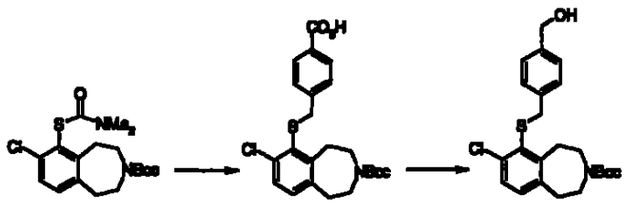
2-(2-Fluoro-4-phenoxy-benzyloxy)-tetrahydro-pyran: Mix under argon atmosphere 2-(4-bromo-2-fluorobenzyloxy)-tetrahydropyran (2.9 g, 10 mmol), phenol (1.9 g, 20 mmol), 2,2,6,6-tetramethylheptane-3,5-dione (184.3 mg, 1.0 mmol), cesium carbonate (6.5 g, 20 mmol) and anhydrous NMP (20 mL). Degas the flask and fill with argon. Add copper(I) chloride (495 mg, 5 mmol) quickly. Degas the flask three times then fill with argon. Heat at 120 °C for 3 h. Cool to ambient temperature. Dilute with EtOAc and filter. Concentrate *in vacuo* and purify by chromatography on silica gel to obtain the desired intermediate (2.05 g, 68%). MS (ES+) *m/z*: 325 $(M+Na)^+$.

(2-Fluoro-4-phenoxy-phenyl)-methanol: Mix under nitrogen atmosphere 2-(2-fluoro-4-phenoxy-benzyloxy)-tetrahydro-pyran (2.05g, 6.8 mmol), methanol (60 mL) and *p*-toluenesulfonic acid monohydrate (260 mg, 1.35 mmol). Stir at ambient temperature for 16 h. Dilute with EtOAc. Wash with saturated aqueous $NaHCO_3$. Separate the organic layer, dry over Na_2SO_4 and concentrate *in vacuo* to give the desired intermediate (1.41 g, 95%). MS (ES+) *m/z*: 201 $(M-OH)^+$.

1-Bromomethyl-2-fluoro-4-phenoxy-benzene: Dissolve under nitrogen atmosphere (2-fluoro-4-phenoxyphenyl)-methanol (1.41 g, 6.5 mmol) in anhydrous THF (60 mL). Cool to 0 °C in an ice bath. Add phosphorous tribromide (2.11 g, 7.8 mmol). Stir at cold for 1 h, then remove the ice bath and stir at ambient temperature for 16 h. Quench the reaction with saturated aqueous $NaHCO_3$. Extract aqueous phase three times with EtOAc. Combine organic fractions, wash with brine, dry over Na_2SO_4 and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1). Evaporate the solvent to obtain the title compound (1.31 g, 72%).

Preparation 242

3-*tert*-Butoxycarbonyl-7-chloro-6-(4-hydroxymethyl-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine

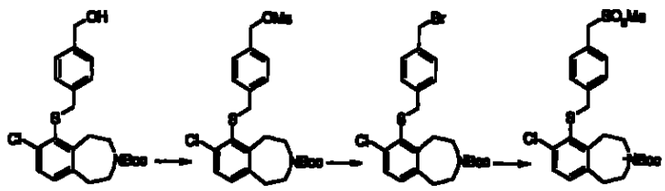


3-*tert*-Butoxycarbonyl-6-(4-carboxy-benzylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: To a solution of 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.0 g, 2.6 mmol) in methanol (15 mL) under nitrogen, add with stirring potassium hydroxide (4.5 g, 80.3 mmol) at ambient temperature. Heat at 55-60°C for 2 h, cool to ambient temperature, and add methyl 4-bromomethylbenzoate (1.2 g, 5.2 mmol). TLC after 20 min shows formation of product; however, after 4 h at ambient temperature both TLC and LC/MS indicate complete hydrolysis of the ester and the carbamate. Dilute with saturated aqueous NH_4Cl, extract three times with EtOAc, dry over anhydrous $MgSO_4$, and concentrate *in vacuo*. Dissolve the crude material in THF (10 mL), treat with di-*tert*-butyl-dicarbonate (2 equiv) and saturated aqueous $NaHCO_3$ (10 mL), and stir overnight. Extract three times with EtOAc, dry over anhydrous $MgSO_4$ and concentrate *in vacuo* to give the desired intermediate as an oil that was used without purification [2.32 g, 50% purity with $(Boc)_2O$]. MS (ES+) *m/z* 348 $(M+H\text{-}Boc)^+$.

3-*tert*-Butoxycarbonyl-7-chloro-6-(4-hydroxymethyl-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: To a solution of 3-*tert*-butoxycarbonyl-6-(4-carboxybenzylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.85 g, 50% purity, 2.06 mmol) in anhydrous THF (40 mL) under nitrogen, add with stirring 1M borane in THF (4.2 mL) at 0 °C. Warm to ambient temperature and stir 2-3 h. Quench by the careful addition of water (3 mL), dilute with saturated aqueous $NaHCO_3$, extract three times with ethyl ether, dry over anhydrous $MgSO_4$, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (5:1) to provide the title compound as a white solid (485 mg, 54 %).

Preparation 243

3-*tert*-Butoxycarbonyl-7-chloro-6-(4-methanesulfonylmethylbenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine



3-*tert*-Butoxycarbonyl-7-chloro-6-(4-methanesulfonyloxymethyl -benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: To a stirred solution of 3-*tert*-butoxycarbonyl-7-chloro-6-(4-hydroxymethyl-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (170 mg, 0.391 mmol) in anhydrous DCM under nitrogen, add methanesulfonyl chloride (33 µL, 0.426 mmol) and triethylamine (61 µL, 0.44 mmol) and continue stirring for 2 h. Dilute with water (5 mL) and extract three times with DCM. Wash the combined organic extracts with brine, dry over anhydrous Na_2SO_4, and concentrate *in vacuo* to obtain the desired intermediate that was used without purification.

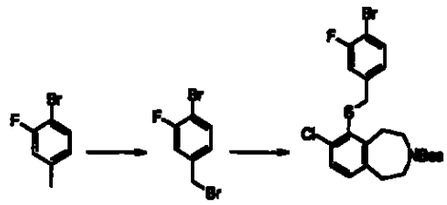
3-*tert*-Butoxycarbonyl-6-(4-bromomethyl -benzylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Dissolve the crude 3-*tert*-butoxycarbonyl-7-chloro-6-(4-methanesulfonyloxymethyl -benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine in anhydrous acetone (3 mL), treat with anhydrous lithium bromide (335 mg, 3.89 mmol) and continue stirring overnight. Add water, extract the reaction mixture three times with ethyl ether, wash with brine, dry over anhydrous $MgSO_4$, and concentrate *in vacuo* to obtain the desired intermediate that was used without purification.

3-*tert*-Butoxycarbonyl-7-chloro-6-(4-methanesulfonylmethyl -benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: To the crude 3-*tert*-butoxycarbonyl-6-(4-bromomethyl -benzylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine in anhydrous DMF (1 mL) under nitrogen, add with stirring sodium methanesulfinate (400 mg, 3.9 mmol), and continue stirring for 30 min at ambient temperature followed by 2 h at 40 °C. Add water, extract three times with EtOAc, wash with brine, dry over anhydrous $MgSO_4$, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with

hexane/EtOAc (3:1) to give a clear oil that solidifies on standing to a white solid (118 mg, 61%).

Preparation 244

6-(4-Bromo-3-fluorobenzylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[d]azepine

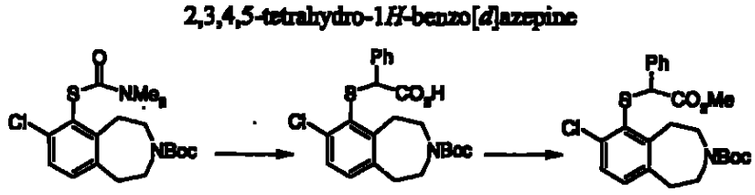


1-Bromo-4-bromomethyl-2-fluorobenzene: Use a method similar to the Preparation 184, using 4-bromo-3-fluorotoluene, to give the desired intermediate as a white solid.

6-(4-Bromo-3-fluorobenzylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[d]azepine: Use a method similar to the Preparation 177, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 1-bromo-4-bromomethyl-2-fluorobenzene, to give the title compound as a white solid.

Preparation 245

(±)-3-*tert*-Butoxycarbonyl-7-chloro-6-(1-methoxycarbonyl-1-phenyl-methylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine



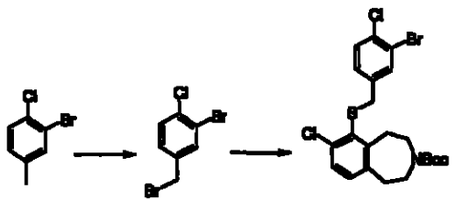
(±)-3-*tert*-Butoxycarbonyl-6-(1-carboxy-1-phenyl-methylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: To a solution of 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.23 g, 3.2 mmol) in methanol (20 mL) under nitrogen, add with stirring potassium hydroxide (5.36 g, 95.5 mmol) at ambient temperature. Heat at 55-60 °C for 2 h, cool to ambient temperature,

and add methyl α-bromophenylacetate (600 μL, 3.81 mmol). After 30 min, dilute with saturated aqueous NH_4Cl, extract three times with EtOAc, dry over anhydrous $MgSO_4$, and concentrate *in vacuo*. Dissolve the crude material in THF (10 mL), treat with di-*tert*-butyl-dicarbonate (2 equiv) and saturated aqueous $NaHCO_3$ (10 mL), and stir overnight. Extract three times with EtOAc, dry over anhydrous $MgSO_4$ and concentrate *in vacuo* to give the desired intermediate as an oil that is used without purification (1.1 g, 77%).

(±)-3-*tert*-Butoxycarbonyl-6-(1-methoxycarbonyl-1-phenyl-methylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Treat a solution of 3-*tert*-butoxycarbonyl-6-(1-carboxy-1-phenyl-methylthio)-7-chloro-2,3,4,5-tetrahydrobenzo[*d*]azepine (200 mg, 0.447 mmol) in anhydrous DMF (2 mL) with methyl iodide (317 mg, 2.237 mmol) and potassium carbonate (310 mg, 2.237 mmol) for 1.5 h at ambient temperature. Add water and extract the aqueous phase three times with EtOAc. Dry the organic phase over $MgSO_4$ and concentrate to obtain the title compound that was used without purification.

Preparation 246

6-(3-Bromo-4-chloro-benzylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine

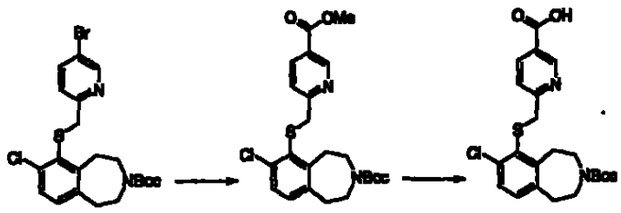


2-Bromo-4-bromomethyl-1-chloro-benzene: Use a method similar to the Preparation 184, using 3-bromo-4-chlorotoluene, to give the desired intermediate.

6-(3-Bromo-4-chloro-benzylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Use a method similar to the Preparation 177, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylsulfanyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 2-bromo-4-bromomethyl-1-chloro-benzene, to give the title compound.

Preparation 247

3-*tert*-Butoxycarbonyl-6-(5-carboxy-pyridin-2-ylmethylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine

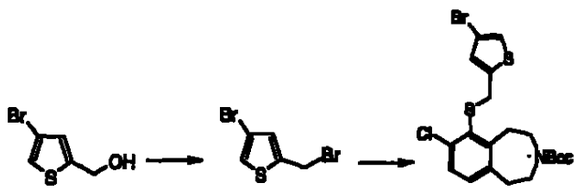


3-*tert*-Butoxycarbonyl-7-chloro-6-(5-methoxycarbonyl-pyridin-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Dissolve 3-*tert*-butoxycarbonyl-6-(5-bromopyridin-2-ylmethylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (2.13 g, 4.40 mmol), palladium acetate (35 mg, 0.156 mmol), 1,1'-bis(diphenylphosphino)ferrocene (150 mg, 0.271 mmol) and triethylamine (1.30 mL) in methanol (10 mL) and DMF (5 mL). Degas and then heat under a balloon filled with carbon monoxide at 75 ° C for 10 h. Remove methanol *in vacuo*, and dilute the mixture with water. Extract three times with EtOAc, dry over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (7:1) to give the desired intermediate as a clear oil (1.86 g, 91%). MS (APCI+) *m/z* 463 $(M+H)^+$, 363 $(M+H\text{-Boc})^+$.

3-*tert*-Butoxycarbonyl-6-(5-carboxy-pyridin-2-ylmethylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Dissolve 3-*tert*-butoxycarbonyl-7-chloro-6-(5-methoxycarbonyl-pyridin-2-ylmethylthio)-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.86 g, 4.03 mmol) in methanol (25 mL). Add 1M aqueous lithium hydroxide (12 mL) and stir at ambient temperature overnight. Remove methanol *in vacuo*, and dilute the mixture with cold 0.5M aqueous HCl to pH 4. Add brine and extract three times with EtOAc. Dry over anhydrous Na_2SO_4, and concentrate *in vacuo* to give the title compound as an off-white solid (1.78 g, 95%). MS (APCI+) *m/z* 449 $(M+H)^+$, 349 $(M+H\text{-Boc})^+$.

Preparation 248

6-(4-Bromo-thiophen-2-ylmethylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine

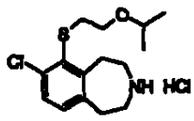


3-Bromo-5-bromomethyl-thiophene: Use the bromination procedure described in Preparation 211 (Step 2), using (3-bromothiophen-2-yl)methanol (*Synthesis* 1983, *1*, 73-75), to give the desired intermediate as a light brown liquid.

6-(4-Bromo-thiophen-2-ylmethylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Use a method similar to the Preparation 177, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 3-bromo-5-bromomethyl-thiophene, to give the title compound as a gum.

Example 315

7-Chloro-6-(2-isopropoxyethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

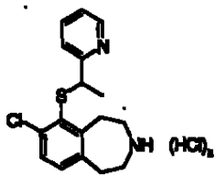


To a 4:1 mixture of 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 3-*tert*-butoxycarbonyl-7,9-dichloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (200 mg, 0.52 mmol) in methanol (5 mL) under nitrogen, add potassium hydroxide (0.9 g, 16.1 mmol) at ambient temperature. When the mixture becomes homogenous, heat at 55-60 °C for 2-3 h, until TLC shows the disappearance of starting material. Cool to ambient temperature, add aqueous saturated ammonium chloride, extract three times with diethyl ether, dry over anhydrous $MgSO_4$, and concentrate *in vacuo*. Dissolve the crude 3-*tert*-butoxycarbonyl-

7-chloro-6-mercapto-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine in anhydrous THF (5 mL) under nitrogen and add with stirring 1.0 M potassium t-butoxide in THF (1.0 mL) at ambient temperature. After 10 min, add 2-(2-iodoethoxy)propane (223 mg, 1.04 mmol), and allow the reaction to continue overnight. Dilute with aqueous saturated ammonium chloride, extract the mixture three times with diethyl ether, dry over anhydrous $MgSO_4$, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (12:1) to provide 3-*tert*-butoxycarbonyl-7-chloro-6-(2-isopropoxy-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a clear oil (127 mg, 63 %). Use a method similar to the General Procedure 1-4 to give the title compound as a white solid. MS (ES+) *m/z*: 300 $(M+H)^+$.

Example 316

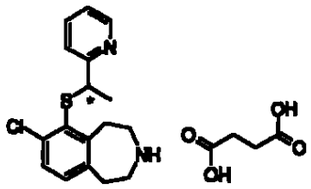
(±)-7-Chloro-6-(1-pyridin-2-yl-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the General Procedure 7, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and (±)-2-(1-bromoethyl)-pyridine to give, after deprotection by a method similar to the General Procedure 1-4, the title compound as a white solid. MS (APCI+) *m/z*: 319 $(M+H)^+$.

Example 317

(-)-7-Chloro-6-(1-pyridin-2-yl-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

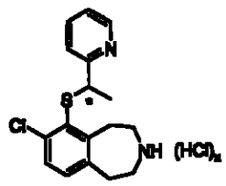


Separate the enantiomers of (±)-7-chloro-6-(1-pyridin-2-yl-ethylthio)-2,3,4,5-tetrahydro–1*H*-benzo[*d*]azepine by chiral normal phase chromatography (Chiralpak AD 8x30 cm column, eluting with 0.2% DMEA in methanol). Take the second eluting isomer and purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (100:1 to 80:20).

Use the General Procedure 2-1 to give the title compound as a white solid (4.27 g, 33%). MS (ES+) *m/z*: 319 $(M+H)^+$; ee = 99.4%; $[\alpha]^{20}_D$ -179° (c 0.5, CH_3OH).

Example 318

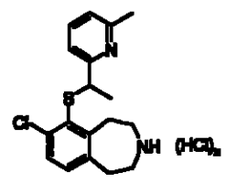
(-)-7-Chloro-6-(1-pyridin-2-yl-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the General Procedure 7, except that the alkylation is conducted at 0° C, to react 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine with (*R*)-(-)-1-(2-pyridinyl)ethanol methanesulfonate ester. Use a method similar to the General Procedure 1-4 to give the title compound as a white solid. MS (APCI+) *m/z*: 319 $(M+H)^+$; ee = 98.6% [Chiral HPLC: Chiralpak AD-H 0.46x15 cm column, eluting with 15:85 ethanol/heptane].

Example 319

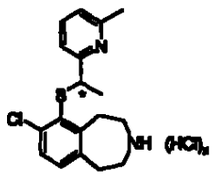
(±)-7-Chloro-6-[1-(6-methylpyridin-2-yl)-ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 315, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and (±)-2-(1-chloroethyl)-6-methylpyridine hydrochloride to give, after deprotection by a method similar to the General Procedure 1-4, the title compound as a tan solid. MS (ES+) *m/z*: 333 $(M+H)^+$.

Example 320

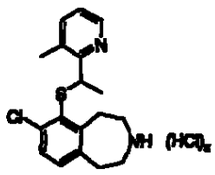
7-Chloro-6-[1-(6-methylpyridin-2-yl)-ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride, Isomer 1



Use a method similar to the Preparation 177, except that the alkylation is conducted at 0° C, to react 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine with (*R*)-methanesulfonic acid 1-(6-methyl-pyridin-2-yl)-ethyl ester. Use a method similar to the General Procedure 1-5, basic workup, and a method similar to the General Procedure 2-2 to give the title compound as a white solid. MS (APCI+) *m/z*: 333 $(M+H)^+$; ee >97%, t_R = 6.53 min. (Chiral HPLC: Chiralpak OJ 120Å 4.6x250 mm, 45 °C; eluent: 20% isopropanol with 0.05% triethylamine in SFC, flow rate 2 mL/min, UV detector at 234 nm).

Example 321

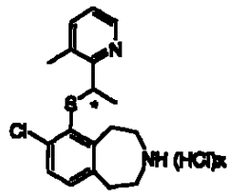
(±)-7-Chloro-6-[1-(3-methylpyridin-2-yl)-ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Preparation 177 to react 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine with (±)-2-(1-bromoethyl)-3-methyl-pyridine. Use a method similar to the General Procedure 1-5, basic workup, and a method similar to the General Procedure 2-2 to give the title compound as a white solid. MS (APCI+) *m/z*: 333 $(M+H)^+$.

Example 322

(-)-7-Chloro-6-[1-(3-methylpyridin-2-yl)-ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

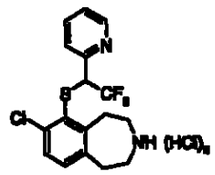


Separate the enantiomers of (±)-7-chloro-[1-(3-methyl-pyridin-2-yl)-ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine by chiral normal phase chromatography (Chiralpak AD 8x30 cm column, eluting with 85:15 heptane:0.2% DMEA in ethanol). Take the second eluting isomer and purify by SCX column chromatography.

Use the General Procedure 2-2 to give the title compound as a white solid (60 mg, 43%). MS (ES+) *m/z*: 333 $(M+H)^+$; $[\alpha]^{20}_D$ -232° (c 0.5, CH_3OH).

Example 323

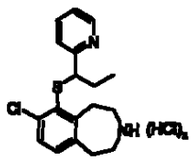
(±)-7-Chloro-6-(2,2,2-trifluoro-1-pyridin-2-yl-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Preparation 177 to react 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine with (±)-2-[1-methanesulfonyloxy-(2,2,2-trifluoroethyl)]-pyridine. Use a method similar to the General Procedure 1-5, basic workup, and a method similar to the General Procedure 2-2 to give the title compound as a white solid. MS (APCI+) *m/z*: 373 $(M+H)^+$.

Example 324

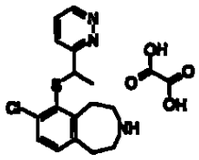
(±)-7-Chloro-6-(1-pyridin-2-yl-propylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use method similar to the Preparation 177 to react 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine with (±)-2-(1-bromopropyl)pyridine. Use a method similar to the General Procedure 1-5, basic workup, and a method similar to the General Procedure 2-2 to give the title compound as a white solid. MS (APCI+) *m/z*: 333 $(M+H)^+$.

Example 325

(±)-7-Chloro-6-[1-(pyridazin-3-yl)-ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Oxalate

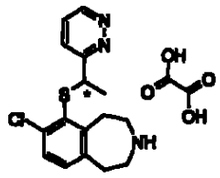


Dissolve (±)-1-pyridazin-3-yl-ethanol (38 mg, 0.31 mmol) in thionyl chloride (0.14 mL) at 0°C and stir for 1 h at ambient temperature. Evaporate the mixture, add toluene and evaporate again. Treat this residue with the thiolate prepared from 7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine-3-carboxylic acid *tert*-butyl ether (0.1 g, 0.25 mmol) according to the General Procedure 7 in the presence of potassium carbonate (0.3 g, 2.25 mmol) in DMF (3 mL) at 80°C for 16 h.

Use a method similar to the General Procedure 1-5, basic work-up, and a method similar to the General Procedure 2-5 to give the title compound (38 mg, 37%). HRMS calcd for $C_{16}H_{19}ClN_3S$ 320.0988, found 320.0970.

Example 326

(+)-7-Chloro-6-[1-(pyridazin-3-yl)-ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Oxalate

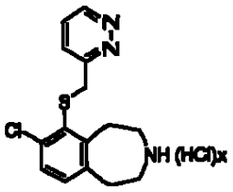


Dissolve (±)-1-pyridazin-3-yl-ethanol (0.29 g, 2.35 mmol) in thionyl chloride (1.0 mL) at 0°C and stir for 1 h at ambient temperature. Evaporate the mixture, add toluene and evaporate again. Treat this residue with the thiolate prepared from 7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine-3-carboxylic acid *tert*-butyl ether (0.72 g, 1.88 mmol) according to the General Procedure 7 in the presence of potassium carbonate (2.60 g, 18.8 mmol) and tetrabutylammonium iodide (7 mg, 0.02 mmol) in DMF (20 mL) at 80 °C for 28 h. Separate the enantiomers by preparative HPLC (Waters Symmetry C18 4.6 x 150 mm 3.5 micron column, 1 mL/min of 90:10 to 50:50:0.1% TFA in water:ACN over 25 min. Detector is at 254 nm) to obtain 3-*tert*-butoxycarbonyl-7-chloro-6-[1-(pyridazin-3-yl)-ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine, isomer 1.

Use a method similar to the General Procedure 1-5, basic work-up, and a method similar to the General Procedure 2-5 to give the title compound (56 mg, 7%). HPLC t_R = 3.0 min (Chiralpak AD-H 4.6x150 mm, 3 micron column, 1.0 mL/min of 99.8:0.2 methanol/dimethyethylamine isocratic; detector at 225 nm); HRMS calc'd for $C_{16}H_{19}ClN_3S$ 320.0988, found 320.1001. $[\alpha]^{20}_D$ +160° (c 0.5, CH_3OH).

Example 327

7-Chloro-6-(pyridazin-3-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

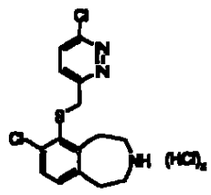


React 3-chloromethyl-pyridazine (prepared as described in WO 99/54333, WO 98/49166) (1.8 g, 11.0 mmol) with 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (2.2 g, 5.7 mmol) according to the General Procedure 7 in the presence of tetrabutylammonium iodide (0.1 g, 0.27 mmol) at ambient temperature for 3 h.

Use a method similar to the General Procedure 1-4 to give the title compound as a tan powder (1.9 g, 98 %): HRMS calcd for $C_{15}H_{16}ClN_3S$ 306.0832, found 306.0829.

Example 328

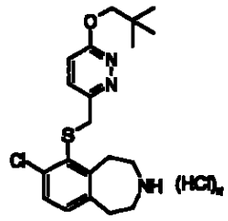
7-Chloro-6-(6-chloro-pyridazin-3-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Preparation 177, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 3-bromomethyl-6-chloropyridazine to give 3-*tert*-butoxycarbonyl-7-chloro-6-(6-chloro-pyridazin-3-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Use a method similar to the General Procedure 1-4 to give the title compound as an off-white powder. MS (APCI+) *m/z*: 340 $(M+H)^+$.

Example 329

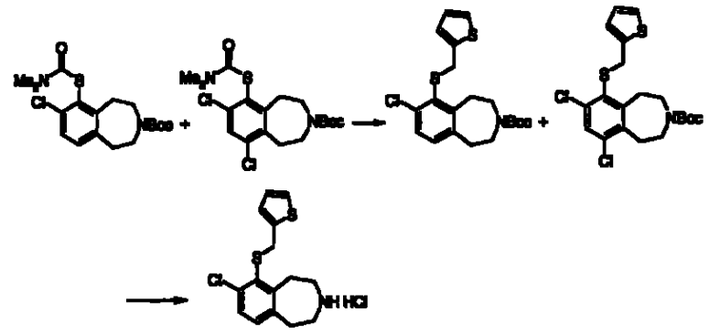
7-Chloro-6-[6-(2,2-dimethylpropoxy)-pyridazin-3-ylmethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



To a stirred solution of neopentyl alcohol (105 mg, 1.19 mmol) in THF (5 mL) at ambient temperature add sodium hydride (31 mg, 95%, 1.19 mmol) and continue stirring for 3 h at ambient temperature. Add a solution of 3-*tert*-butoxycarbonyl-7-chloro-6-(6-chloro-pyridazin-3-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (315 mg, 0.59 mmol) in THF (1 mL) and continue stirring overnight at ambient temperature and then at 60°C for 1 h. Dilute with water, extract the reaction mixture three times with EtOAc, dry over anhydrous Na_2SO_4, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (6:1) to give 3-*tert*-butoxycarbonyl-7-chloro-6-[6-(2,2-dimethyl-propoxy)-pyridazin-3-ylmethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a clear oil (81 mg, 28%). MS (APCI+) *m/z*: 492 $(M+H)^+$, 392 $(M+H\text{-Boc})^+$. Use a method similar to the General Procedure 1-4 to give the title compound as a white powder. MS (APCI+) *m/z*: 392 $(M+H)^+$, *m/z*: 322 $(M+H\text{-}C_5H_{11})^+$.

Example 330

7-Chloro-6-(thiophen-2-ylmethylthio)-2,3,4,5-tetrahydro-1H-benzo[d]azepine Hydrochloride

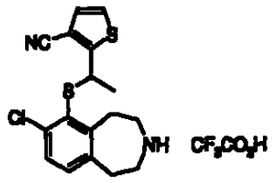


To a 4:1 mixture of 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 3-*tert*-butoxycarbonyl-7,9-dichloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-benzo[*d*]azepine (108 mg, 0.281 mmol) in methanol (3 ml), add potassium hydroxide pellets (504 mg, 9.0 mmol) and heat the mixture 2 h at 50 °C. Cool the reaction to ambient temperature, add 2-chloromethylthiophene (186 µL, 1.406 mmol), and continue stirring for 30 min. Dilute with EtOAc and water. Separate the layers and extract the aqueous layer three times with EtOAc, dry over anhydrous Na_2SO_4, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (19:1) to give 3-*tert*-butoxycarbonyl-7-chloro-6-(thiophen-2-ylmethylthio)-2,3,4,5-tetrahydro-benzo[*d*]azepine as a colorless oil (36 mg, 31%).

Use a method similar to the General Procedure 1-5, using 3-*tert*-butoxycarbonyl-7-chloro-6-(thiophen-2-ylmethylthio)-2,3,4,5-tetrahydro-benzo[*d*]azepine to give, after basic workup and a method similar to the General Procedure 2-2, the title compound as a white solid. MS (ES+) *m/z*: 310 $(M+H)^+$.

Example 331

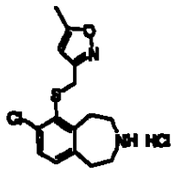
(±)-7-Chloro-6-(3-cyanothiophen-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Trifluoroacetate



Use a method similar to the Preparation 177, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and (±)-2-(1-chloroethyl)-3-cyanothiophene to give, after deprotection using a method similar to the General Procedure 1-5, the title compound as a white solid. MS (APCI+) *m/z*: 349 $(M+H)^+$.

Example 332

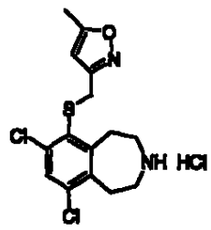
7-Chloro-6-(5-methylisoxazol-3-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



To a 4:1 mixture of 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 3-*tert*-butoxycarbonyl-7,9-dichloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (200 mg, 0.521 mmol) in methanol (3.3 mL) under nitrogen add potassium hydroxide (0.9 g, 16.1 mmol) at ambient temperature. When the mixture becomes homogenous, heat at 55-60°C for 2-3 h, until TLC shows the disappearance of starting material. Cool to ambient temperature, add 3-(chloromethyl)-5-methylisoxazole (82 mg, 0.62 mmol) and continue stirring for 30 min. Add aqueous saturated ammonium chloride, extract the mixture three times with diethyl ether, dry over anhydrous $MgSO_4$, and concentrate *in vacuo*. Treat a solution of the crude material so obtained in DCM (2 mL) with 2M hydrogen chloride in ether (excess) and continue stirring until TLC shows consumption of the starting material. Concentrate *in vacuo*, purify by preparative TLC eluting with 19:1 DCM/saturated ammonia in methanol, and convert to the hydrochloride by following a method similar to the General Procedure 2-2 to give the title compound as a white solid. MS (APCI+) *m/z*: 309 $(M+H)^+$.

Example 333

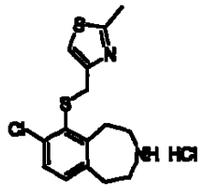
7,9-Dichloro-6-(5-methylisoxazol-3-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Obtain the free base of the title compound as a minor product from Example 332, after preparative TLC eluting with 19:1 DCM/saturated ammonia in methanol. Use a method similar to the General Procedure 2-2 to give the title compound as a white solid. MS (APCI+) *m/z*: 343 $(M+H)^+$.

Example 334

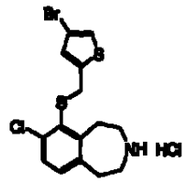
7-Chloro-6-(2-methylthiazol-4-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 332, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 4-chloromethyl-2-methylthiazole hydrochloride to give, after deprotection by the General Procedure 1-4, the title compound as a white solid. MS (APCI+) *m/z*: 325 $(M+H)^+$.

Example 335

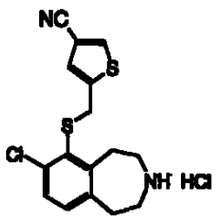
6-(4-Bromothiophen-2-ylmethylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the General Procedure 1-4, using 6-(4-bromothiophen-2-ylmethylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine to give the title compound as a white solid. MS (APCI+) *m/z*: 390 $(M+H)^+$.

Example 336

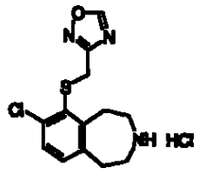
7-Chloro-6-(4-cyanothiophen-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Degas a stirred solution of 6-(4-bromothiophen-2-ylmethylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (183 mg, 0.37 mmol), zinc cyanide (50 mg, 0.42 mmol) and tetrakistriphenylphosphine palladium(0) (30 mg, 0.026 mmol) in dry DMF. Purge with dry nitrogen, and heat at 120°C for 6 h. Dilute with water, extract three times with EtOAc, dry over anhydrous $MgSO_4$ and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (10:1) to give 3-*tert*-butoxycarbonyl-7-chloro-6-(4-cyanothiophen-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (85 mg, 52%). MS (APCI+) *m/z*: 335 $(M+H-Boc)^+$. Use a method similar to the General Procedure 1-4 to give the title compound as a white solid. MS (APCI+) *m/z*: 335 $(M+H)^+$.

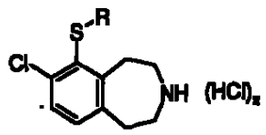
Example 337

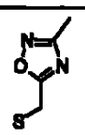
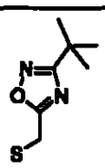
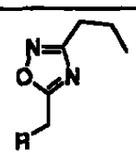
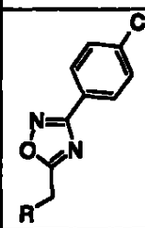
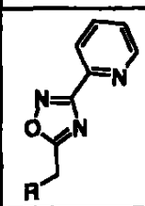
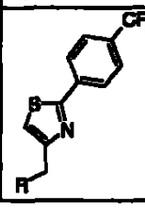
7-Chloro-6-([1,2,4]-oxadiazol-3-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Preparation 177, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 3-chloromethyl-1,2,4-oxadiazole to give, after deprotection using a method similar to the General Procedure 1-4, the title compound as a white solid. MS (ES+) *m/z* 296 $(M+H)^+$.

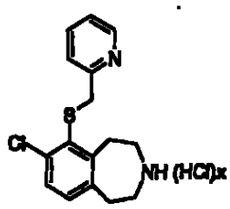
Examples 338-343 may be prepared essentially as described in Example 337 using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriately substituted 5-chloromethyl-1,2,4-oxadiazole or 4-chloromethyl-thiazole. MS (ES+) data are included in the Table below.



Ex.	SR	Compound	MS (ES+) m/z
338		7-Chloro-6-(3-methyl-[1,2,4]oxadiazol-5-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	310 $(M+H)^+$
339		6-(3-*tert*-Butyl-[1,2,4]oxadiazol-5-ylmethylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	352 $(M+H)^+$
Ex.	**SR**	**Compound**	**MS (ES+) m/z**
340		7-Chloro-6-(3-propyl-[1,2,4]oxadiazol-5-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	338 $(M+H)^+$
341		7-Chloro-6-[3-(4-chloro-phenyl)-[1,2,4]oxadiazol-5-ylmethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	406 $(M+H)^+$
342		7-Chloro-6-(3-pyridin-2-yl-[1,2,4]oxadiazol-5-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	373 $(M+H)^+$
343		7-Chloro-6-[2-(4-trifluoromethylphenyl)-thiazol-4-ylmethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	455 $(M+H)^+$

Example 344

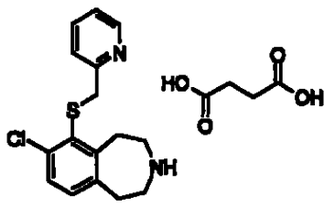
7-Chloro-6-(pyridin-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Using a method similar to the General Procedure 7, react 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylaminocarbonylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (8 g, 20.8 mmol) with 2-picolyl chloride hydrochloride (3.41 g, 20.8 mmol). Dilute the reaction mixture with diethyl ether and filter the precipitate. Concentrate the filtrate *in vacuo*, dissolve the residue in diethyl ether (100 mL) and add 1N aqueous HCl (100 mL). Stir the mixture for 16 h at ambient temperature. Separate, wash the aqueous layer with diethyl ether, adjust the pH of the aqueous layer to 12 with sodium hydroxide and extract with diethyl ether. Dry over Na_2SO_4 and concentrate *in vacuo* to give the free base of the title compound. Use the General Procedure 2-2 to give the title compound as a white solid (4.91 g, 78%). MS (ES+) *m/z*: 305 $(M+H)^+$.

Example 345

7-Chloro-6-(pyridin-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

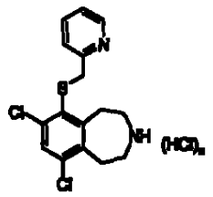


Dissolve 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1 equiv.) in methanol (0.1-0.4 M) and add potassium hydroxide (8-20 equiv.). Stir at 60°C for 4-24 h. Cool the reaction mixture in an ice bath, add picolyl chloride hydrochloride (1-3 equiv.) and stir the mixture at ambient temperature for 16-24 h. Add a volume of toluene approximately equal to the volume of

the reaction mixture and concentrate the resulting mixture to approximately ½ the resulting total volume and repeat this process once more. Add water until all solids dissolve and separate the layers. Dry the organic layer over Na_2SO_4 and filter. Heat the solution (containing about 0.25-0.40 M of free base of the title compound) to 50-75°C and then optionally seed with previously formed crystals of the title compound. Add succinic acid (1-1.3 equivalents) in isopropyl alcohol (0.25-0.40M solution) to the solution over 5-45 min. Cool the solution to 20-25°C over 1-3 h and filter, rinsing with a solution of toluene/isopropyl alcohol (1:1). Dry the resulting solid under vacuum at 50-70°C/5 Torr to give the title compound as a white solid, mp 159-160 °C. Anal. Calc'd for $C_{20}H_{23}ClN_2O_4S$: C, 56.80; H, 5.48; N, 6.62. Found: C, 56.56; H, 5.41; N, 6.57.

Example 346

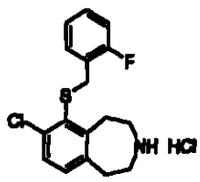
7,9-Dichloro-6-(pyridin-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Obtain as minor product from the reaction of the 4:1 mixture of 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 3-*tert*-butoxycarbonyl-7,9-dichloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-benzo[*d*]azepine with 2-bromomethylpyridine hydrobromide, using a method similar to the General Procedure 7. Treat a solution of the crude mixture in DCM with 4M hydrogen chloride in dioxane (excess) overnight. Concentrate *in vacuo* and purify by preparative TLC eluting with 19:1 DCM/saturated ammonia in methanol. Use a method similar to the General Procedure 2-2 to give the title compound as an off-white solid. MS (APCI+) *m/z*: 339 $(M+H)^+$.

Example 347

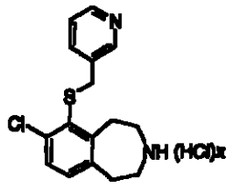
7-Chloro-6-(2-fluorobenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



To a mixture of 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 3-*tert*-butoxycarbonyl-7,9-dichloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-benzo[*d*]azepine (102 mg, 0.267 mmol) in methanol (2 ml), add potassium hydroxide pellets (450 mg, 8.02 mmol) and heat the mixture 3 h at 60 °C. Cool to ambient temperature, add aqueous saturated ammonium chloride solution, extract three times with EtOAc, dry over anhydrous Na_2SO_4, and concentrate *in vacuo*. Dissolve the crude thiophenol thus obtained in dry DCM (2 mL) under nitrogen, and add DBU (80 □L, 0.54 mmol) and 2-fluorobenzyl bromide (65 □L, 0.54 mmol) with stirring. Stir overnight at ambient temperature, dilute with water, extract three times with EtOAc, dry over anhydrous Na_2SO_4, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to give 3-*tert*-butoxycarbonyl-7-chloro-6-(2-fluorobenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow oil (31 mg, 25%). Use a method similar to the General Procedure 1-4 to give the title compound as a white solid. MS (ES+) *m/z*: 322 $(M+H)^+$.

Example 348

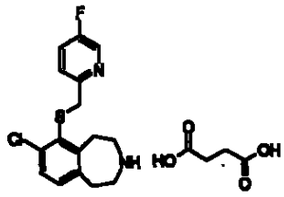
7-Chloro-6-(pyridin-3-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 347, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 3-(bromomethyl)pyridine hydrobromide to give, after deprotection by a method similar to the General Procedure 1-4, the title compound as a white solid. MS (ES+) *m/z*: 305 $(M+H)^+$.

Example 349

7-Chloro-6-(5-fluoropyridin-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

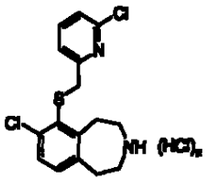


Dissolve 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (527 mg, 1.4 mmol) and potassium hydroxide (1.1 g, 20.5 mmol) in methanol (10 mL) and heat the solution to reflux for 2 h. Cool the reaction mixture to ambient temperature and remove the solvent *in vacuo*. Slurry the residue with EtOAc (50 ml), and wash the slurry with a saturated NH_4Cl. Collect and dry the organic phase over Na_2SO_4, remove the solvent under reduced pressure to obtain the intermediate thiophenol as an oil. Dissolve the oil in DMSO (10 ml), add triethylamine (1.1 ml, 8.2 mmol) and methanesulfonic acid 5-fluoro-pyridin-2-ylmethyl ester (500mg, 2.4 mmol). Heat the reaction mixture to 60 °C for 1 h. Monitor the reaction by HPLC and TLC. Cool the reaction to ambient temperature, add 1:1 hexane/EtOAc (80 ml) and wash the organic layer with a 5% NaCl (3 X 30 ml). Collect the organic layer, concentrate, and purify by chromatography on silica gel eluting with hexane/EtOAc (9:1 to 1:1) to obtain 3-*tert*-butoxycarbonyl-7-chloro-6-(5-fluoro-pyridin-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (519 mg, 89%). MS (ES+) *m/z*: 423 $(M+H)^+$.

Use the General Procedure 1-4 to deprotect 3-*tert*-butoxycarbonyl-7-chloro-6-(5-fluoro-pyridin-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (510 mg, 1.2 mmol). Purify by SCX chromatography followed by chromatography on silica gel eluting with DCM/2M ammonia in methanol (99:1 to 90:10). Use the General Procedure 2-1 to give the title compound (370 mg, 70%). MS (ES+) *m/z*: 323 $(M+H)^+$.

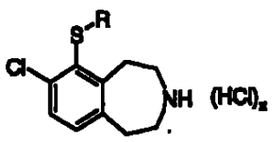
Example 350

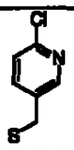
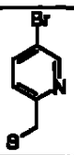
7-Chloro-6-(6-chloropyridin-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

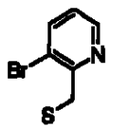
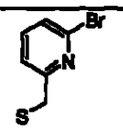
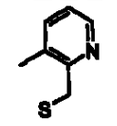
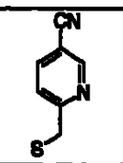
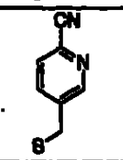
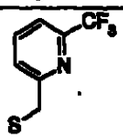
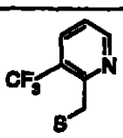
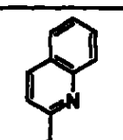


Use a method similar to the Preparation 177, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 2-bromomethyl-6-chloropyridine hydrochloride to give, after deprotection by a method similar to the General Procedure 1-4, the title compound as an off-white solid. MS (APCI+) *m/z*: 339 $(M+H)^+$.

Examples 351-360 may be prepared essentially as described in Example 350 by using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriately substituted chloromethylpyridine, bromomethylpyridine or chloromethylquinoline. MS (ES+) data are included in the Table below.

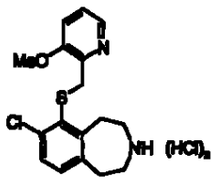


Ex.	SR	Compound	MS (ES+ or APCI+)
351		7-Chloro-6-(6-chloro-pyridin-3-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	339 $(M+H)^+$
352		6-(5-Bromo-pyridin-2-ylmethylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	385 $(M+H)^+$

Ex.	SR	Compound	MS (ES+ or APCI+)
353		6-(3-Bromo-pyridin-2-ylmethylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	385 $(M+H)^+$
354		6-(6-Bromo-pyridin-2-ylmethylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	385 $(M+H)^+$
355		7-Chloro-6-(3-methyl-pyridin-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	319 $(M+H)^+$
356		7-Chloro-6-(5-cyano-pyridin-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	330 $(M+H)^+$
357		7-Chloro-6-(6-cyano-pyridin-3-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	330 $(M+H)^+$
358		7-Chloro-6-(6-trifluoromethyl-pyridin-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	373 $(M+H)^+$
359		7-Chloro-6-(3-trifluoromethyl-pyridin-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	373 $(M+H)^+$
360		7-Chloro-6-(quinolin-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	355 $(M+H)^+$

Example 361

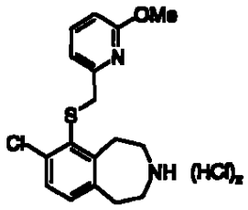
7-Chloro-6-(3-methoxypyridin-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 315, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 2-chloromethyl-3-methoxypyridine to give, after deprotection by a method similar to the General Procedure 1-4, the title compound as a white solid (71 mg). MS (APCI+) *m/z*: 335 $(M+H)^+$.

Example 362

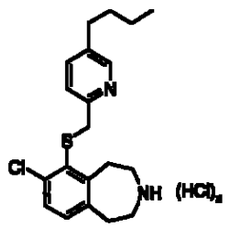
7-Chloro-6-(6-methoxypyridin-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 330, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 2-chloromethyl-6-methoxypyridine hydrochloride to give, after deprotection by a method similar to the General Procedure 1-4, the title compound as a white solid (120 mg). MS (APCI+) *m/z*: 335 $(M+H)^+$.

Example 363

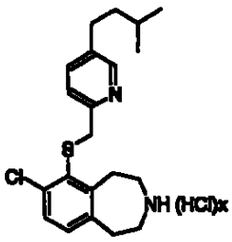
6-(5-Butylpyridin-2-ylmethylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 315, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 5-butyl-2-chloromethylpyridine hydrochloride to give the title compound as a white solid. MS (APCI$^+$) *m/z*: 330 $(M+H)^+$.

Example 364

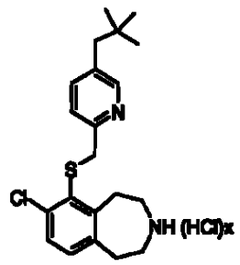
7-Chloro-6-[5-(3-methylbutyl)-pyridin-2-ylmethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



To 6-(5-bromo-pyridin-2-ylmethylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (219 mg, 0.452 mmol) and dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct (18 mg, 0.022 mmol) under dry nitrogen add with stirring a solution of 0.5M 3-methylbutylzinc bromide in THF (4.6 mL, 2.3 mmol). Degas, purge with dry nitrogen, and stir overnight at ambient temperature. Dilute with EtOAc, wash with water, dry over anhydrous $MgSO_4$ and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (5:1) to give 3-*tert*-butoxycarbonyl-7-chloro-6-[5-(3-methyl-butyl)-pyridin-2-ylmethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (160 mg, 75%). MS (APCI+) *m/z*: 475 $(M+H)^+$. Use a method similar to the General Procedure 1-4 to give the title compound as a tan solid. MS (APCI+) *m/z*: 375 $(M+H)^+$.

Example 365

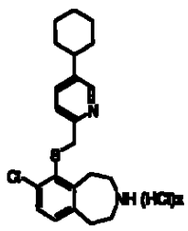
7-Chloro-6-[5-(2,2-dimethylpropyl)-pyridin-2-ylmethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



To a stirred solution of 1.0 M neopentyl magnesium chloride in diethyl ether (50 mL, 50 mmol) at –78 °C under nitrogen, add via syringe a solution of 0.5 M zinc chloride in THF (100 mL, 50 mmol). Warm gradually to ambient temperature and transfer via syringe of this solution (25 mL, ~8.33 mmol) to a stirred solution of 3-*tert*-butoxycarbonyl-6-(5-bromo-pyridin-2-ylmethylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (300 mg, 0.62 mmol) in THF (2 mL) at ambient temperature. Add dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct (50 mg, 0.061 mmol) and heat at 65°C for 6 h. Cool to ambient temperature, dilute with EtOAc, wash with water, dry over anhydrous $MgSO_4$ and concentrate *in vacuo*. Purify by chromatography onr silica gel eluting with hexane/EtOAc (6:1) to give 3-*tert*-butoxycarbonyl-7-chloro-6-[5-(2,2-dimethyl-propyl)-pyridin-2-ylmethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (69 mg, 24%). MS (APCI+) *m/z*: 501 $(M+H)^+$. Use a method similar to the General Procedure 1-4 to give the title compound as a white powder. MS (APCI+) *m/z*: 375 $(M+H)^+$.

Example 366

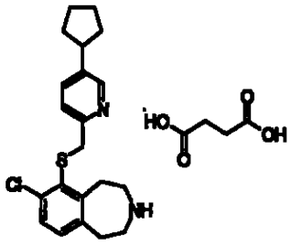
7-Chloro-6-(5-cyclohexylpyridin-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



To a mixture of 6-(5-bromopyridin-2-ylmethylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (146 mg, 0.30 mmol) and dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct (12 mg, 0.015 mmol) under dry nitrogen add with stirring a solution of 0.5 M cyclohexylzinc bromide in THF (3.0 mL, 1.5 mmol). Degas, purge with dry nitrogen, and stir overnight at 60 °C. Cool to ambient temperature, dilute with EtOAc, wash with water, dry over anhydrous $MgSO_4$ and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (5:1) to give 3-tert-butoxycarbonyl-7-chloro-6-(5-cyclohexyl-pyridin-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (46 mg, 32%). MS (APCI+) *m/z*: 487 $(M+H)^+$. Use a method similar to the General Procedure 1-4 to give the title compound as a white solid. MS (APCI+) *m/z*: 387 $(M+H)^+$.

Example 367

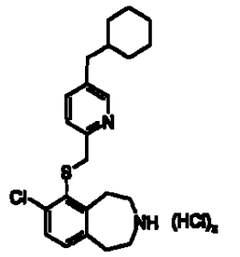
7-Chloro-6-(5-cyclopentylpyridin-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Use a method similar to the Example 366 to react 6-(5-bromo-pyridin-2-ylmethylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine with a solution of cyclopentylzinc bromide in THF. Use a method similar to the General Procedure 1-4, basic workup, and a method similar to the General Procedure 2-1 to give the title compound as a tan solid. MS (APCI+) *m/z*: 373 $(M+H)^+$.

Example 368

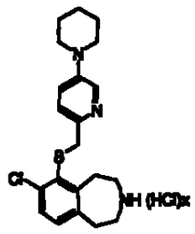
7-Chloro-6-(5-cyclohexylmethylpyridin-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 366 to react 6-(5-bromo-pyridin-2-ylmethylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine with cyclohexylmethylzinc bromide. Use a method similar to the General Procedure 1-5, basic workup, and a method similar to the General Procedure 2-2 to give the title compound as a white solid. MS (APCI+) *m/z*: 401 $(M+H)^+$.

Example 369

7-Chloro-6-(3,4,5,6-tetrahydro-2*H*-[1,3']bipyridinyl-6'-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



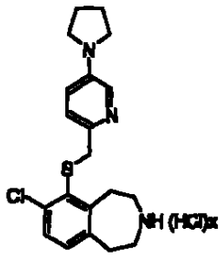
In a sealed tube, add tris(dibenzylideneacetone)dipalladium(0) (3.44 mg, 0.00376 mmol) and 2,2'-*bis*(diphenylphosphino)-1,1'-binaphthyl (4.98 mg, 0.00752 mmol) to a mixture of 6-(5-bromopyridin-2-ylmethylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (242 mg, 0.501 mmol), sodium *tert*-butoxide (96 mg, 1.0 mmol), 18-crown-6 (13 mg, 0.050 mmol) and piperidine (496 μL, 5.01 mmol) in toluene (3 mL). Flush the mixture with nitrogen and heat overnight. Cool to ambient temperature, dilute with water and extract three times with EtOAc. Dry over anhydrous

Na_2SO_4 and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to give 3-*tert*-butoxycarbonyl-7-chloro-6-(3,4,5,6-tetrahydro-2*H*-[1,3']bipyridinyl-6'-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow oil (179 mg, 73%).

Use a method similar to the General Procedure 1-5, using 3-*tert*-butoxycarbonyl-7-chloro-6-(3,4,5,6-tetrahydro-2*H*-[1,3']bipyridinyl-6'-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine to give, after basic workup and a method similar to the General Procedure 2-2, the title compound as a yellow solid. MS (ES+) *m/z*: 388 $(M+H)^+$.

Example 370

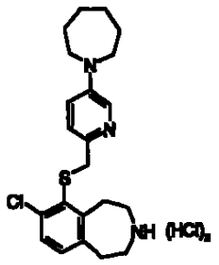
7-Chloro-6-(5-pyrrolidin-1-yl-pyridin-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 369, using 6-(5-bromopyridin-2-ylmethylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and pyrrolidine to give the title compound as a pale yellow solid. MS (ES+) *m/z*: 374 $(M+H)^+$.

Example 371

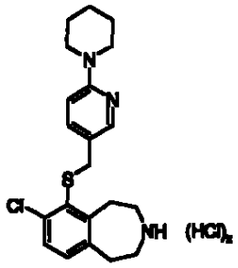
6-(5-Azepan-1-yl-pyridin-2-ylmethylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 369, using 6-(5-bromopyridin-2-ylmethylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and hornopiperidine to give the title compound as a yellow solid. MS (ES+) *m/z* 402 $(M+H)^+$.

Example 372

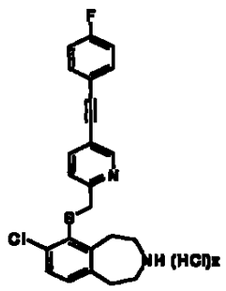
7-Chloro-6-(3,4,5,6-tetrahydro-2*H*-[1,2']bipyridinyl-5'-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 369, using 3-*tert*-butoxycarbonyl-7-chloro-6-(6-chloropyridin-3-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and piperidine, to give the title compound as a white solid. MS (ES+) *m/z*: 388 $(M+H)^+$.

Example 373

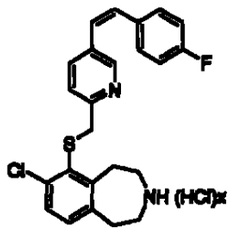
7-Chloro-6-[5-(4-fluorophenylethynyl)-pyridin-2-ylmethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Dissolve 3-*tert*-butoxycarbonyl-6-(5-bromopyridin-2-ylmethylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.0 g, 2.07 mmol), tetrakistriphenylphosphine palladium(0) (120 mg, 0.104 mmol), cuprous iodide (20 mg, 0.105 mmol), triethylamine (2.60 mL) and 1-ethynyl-4-fluorobenzene (500 mg, 4.16 mmol) in DMF (8 mL). Degas the mixture, purge with nitrogen, and heat at 65° C for 3 days. Dilute the mixture with water, extract three times with EtOAc, dry over anhydrous Na_2SO_4, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (50:1) to give 3-*tert*-butoxycarbonyl-7-chloro-6-[5-(4-fluorophenylethynyl)-pyridin-2-ylmethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a tan foam (1.02 g, 95%). MS (APCI+) *m/z*: 523 $(M+H)^+$, 423 $(M+H\text{-}Boc)^+$. Use a method similar to the General Procedure 1-4 to give the title compound as a tan powder. MS (APCI+) *m/z*: 423 $(M+H)^+$.

Example 374

(*Z*)-7-Chloro-6-{5-[2-(4-fluorophenyl)vinyl]-pyridin-2-ylmethylthio}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

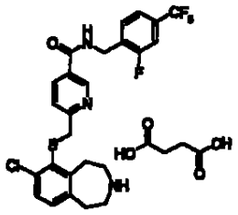


Dissolve 3-*tert*-butoxycarbonyl-7-chloro-6-[5-(4-fluorophenylethynyl)-pyridin-2-ylmethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.0 g, 1.9 mmol), Lindlar catalyst (240 mg), and quinoline (0.8 mL) in methanol (30 mL). Degas, purge with nitrogen, and stir under a balloon of hydrogen for 36 h. Filter the mixture and wash the catalyst with

additional methanol. Concentrate the filtrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (8:1) to give (*Z*)-3-*tert*-butoxycarbonyl-7-chloro-6-{5-[2-(4-fluoro-phenyl)-vinyl]-pyridin-2-ylmethylthio}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a clear oil (630 mg, 63%). MS (APCI+) *m/z*: 525 $(M+H)^+$, 425 $(M+H\text{-Boc})^+$. Use a method similar to the General Procedure 1-4 to give the title compound as a pale yellow solid. MS (APCI+) *m/z*: 425 $(M+H)^+$.

Example 375

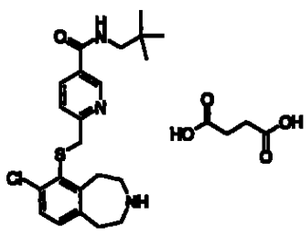
7-Chloro-6-[5-(2-fluoro-4-trifluoromethylbenzylcarbamoyl)-pyridin-2-ylmethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Dissolve 3-*tert*-butoxycarbonyl-6-(5-carboxypyridin-2-ylmethylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (300 mg, 0.67 mmol) in DMF (5.0 mL). Treat successively with HATU (305 mg, 0.802 mmol), *N,N*-diisopropylethylamine (140 µL, 0.804 mmol) and 2-fluoro-4-(trifluoromethyl)benzylamine (260 mg, 1.34 mmol). Stir overnight at 40° C. Dilute the mixture with water, extract three times with EtOAc, dry over anhydrous Na_2SO_4, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (3:1) to give 3-*tert*-butoxycarbonyl-7-chloro-6-[5-(2-fluoro-4-trifluoromethyl-benzylcarbamoyl)-pyridin-2-ylmethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a foam (409 g, 98%). Use a method similar to the General Procedure 1-4 to give, after basic work-up and a method similar to the General Procedure 2-1, the title compound as an off-white solid. MS (APCI+) *m/z*: 524 $(M+H)^+$.

Example 376

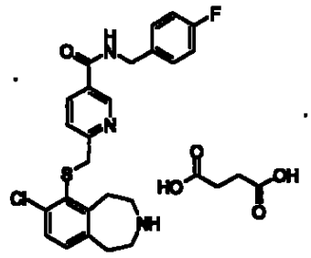
7-Chloro-6-[5-(2,2-dimethylpropylcarbamoyl)-pyridin-2-ylmethylthio]-2,3,4,5-tetrahydro-1H-benzo[*d*]azepine Succinate



Use a method similar to the Example 375, using 3-*tert*-butoxycarbonyl-6-(5-carboxy-pyridin-2-ylmethylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and neopentylamine, to give the title compound as an off-white solid. MS (APCI+) *m/z*: 418 $(M+H)^+$.

Example 377

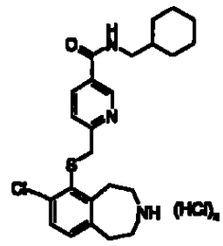
7-Chloro-6-[5-(4-fluoro-benzylcarbamoyl)-pyridin-2-ylmethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Use a method similar to the Example 375, using 3-*tert*-butoxycarbonyl-6-(5-carboxy-pyridin-2-ylmethylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 4-fluorobenzylamine, to give the title compound as an off-white solid. MS (APCI+) *m/z*: 456 $(M+H)^+$.

Example 378

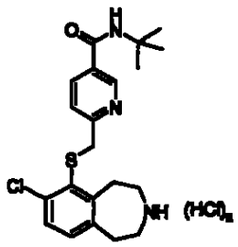
7-Chloro-6-[5-(cyclohexylmethylcarbamoyl)-pyridin-2-ylmethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 375, using 3-*tert*-butoxycarbonyl-6-(5-carboxy-pyridin-2-ylmethylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and aminomethylcyclohexane to give, after deprotection by the General Procedure 1-4, the title compound as a white solid. MS (APCI+) *m/z*: 444 $(M+H)^+$.

Example 379

6-(5-*tert*-Butylcarbamoyl-pyridin-2-ylmethylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 375, using 3-*tert*-butoxycarbonyl-6-(5-carboxy-pyridin-2-ylmethylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and *tert*-butylamine to give, after deprotection by the General Procedure 1-4, the title compound as an off-white solid. MS (APCI+) *m/z*: 404 $(M+H)^+$.

Example 380

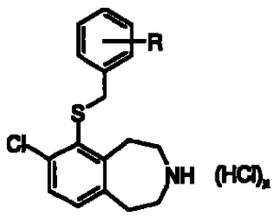
7-Chloro-6-(4-trifluoromethoxybenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



To a 4:1 mixture of 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 3-*tert*-butoxycarbonyl-7,9-dichloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (102 mg, 0.27 mmol) in methanol (1.7 mL) under nitrogen, add potassium hydroxide (0.9 g, 16.1 mmol) at ambient temperature. When the mixture becomes homogenous, heat at 55-60 °C for 2-3 h, until TLC shows the disappearance of starting material. Cool to ambient temperature, add aqueous saturated ammonium chloride solution, extract three times with diethyl ether, dry over anhydrous $MgSO_4$, and concentrate *in vacuo*. Dissolve the crude 3-*tert*-butoxycarbonyl-7-chloro-6-mercapto-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine in anhydrous DCM (2 mL) under nitrogen. Add with stirring DBU (80 µL, 0.532 mmol) and 4-(trifluoromethoxy)benzyl bromide (77 µL, 0.53 mmol) at ambient temperature and allow the reaction to continue overnight. Dilute with aqueous saturated ammonium chloride solution, extract three times with diethyl ether, dry over anhydrous $MgSO_4$, and concentrate *in vacuo*. Treat a solution of the crude 3-*tert*-butoxycarbonyl-7-chloro-6-(4-trifluoromethoxy-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine in DCM (2 mL) with 2M hydrogen chloride in ether (excess) and continue stirring until TLC shows consumption of starting material. Concentrate *in vacuo* and triturate the obtained solid with ether/pentane (10:90). Purify by preparative TLC eluting with 19:1 DCM/saturated ammonia in methanol and convert to the hydrochloride by following a method similar to the General Procedure 2-2 to give the title compound as a white solid (48 mg, 43%). MS (APCI+) *m/z*: 388 $(M+H)^+$.

Examples 381-383 may be prepared essentially as described in Example 380 by using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriately substituted benzyl bromide. Example 382 may be purified after deprotection by preparative reverse phase HPLC [Column: YMC ODS-AQ

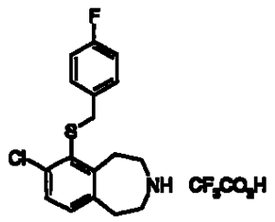
120Å 20x250mm [S10-20μm], eluent: gradient from 95:5 to 5:95 A/B, flow rate: 15 mL/min; solvent A: water, 0.1% TFA, 1% isopropanol; solvent B: acetonitrile, 0.05% TFA, 1% isopropanol]. MS (ES+) data are included in the Table below.



Ex.	R	Compound	MS (ES+) *m/z*
381	2-Cl	7-Chloro-6-(2-chloro-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	338 $(M+H)^+$
382	2-CN	7-Chloro-6-(2-cyano-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	329 $(M+H)^+$
383	4-Ph	7-Chloro-6-(4-phenyl-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	380 $(M+H)^+$

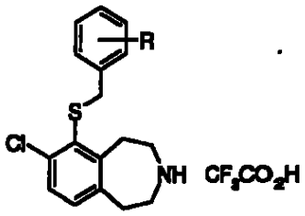
Example 384

7-Chloro-6-(4-fluoro-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Trifluoroacetate



Use a method similar to the Example 380 to react 3-*tert*-butoxylcarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]-azepine with 4-fluorobenzyl bromide. Purify by preparative reverse phase HPLC [Column: YMC ODS-AQ 120Å 20 x 250mm [S10-20μm], eluent: gradient from 95:5 to 5:95 A/B, flow rate: 15 mL/min; solvent A: water, 0.1% TFA, 1% isopropanol; solvent B: acetonitrile, 0.05% TFA, 1% isopropanol] to give the title compound as a white solid. MS (ES+) *m/z*: 322 $(M+H)^+$.

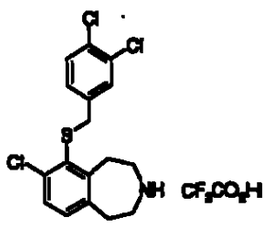
Examples 385-386 may be prepared essentially as described in Example 384 by using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriately substituted benzyl bromide. MS (ES+) data are included in the Table below.



Ex.	R	Compound	MS (ES+) *m/z*
385	4-Cl	7-Chloro-6-(4-chloro-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Trifluoroacetate	338 $(M+H)^+$
386	4-CN	7-Chloro-6-(4-cyano-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Trifluoroacetate	329 $(M+H)^+$

Example 387

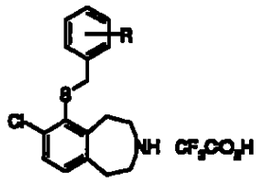
7-Chloro-6-(3,4-dichlorobenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Trifluoroacetate



To a 4:1 mixture of 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 3-*tert*-butoxycarbonyl-7,9-dichloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (200 mg, 0.521 mmol) in methanol (3.3 mL) under nitrogen add potassium hydroxide (0.9 g, 16.07 mmol) at ambient temperature. When the mixture becomes homogenous, heat at 55-60°C for 2-3 h, until TLC shows the disappearance of starting material. Cool to ambient temperature,

add aqueous saturated ammonium chloride solution, extract three times with diethyl ether, dry over anhydrous $MgSO_4$, and concentrate *in vacuo*. Dissolve the crude 3-*tert*-butoxycarbonyl-7-chloro-6-mercapto-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine in anhydrous DCM (5 mL) under nitrogen. Add PS-DIEA (Argonaut, 3.83 mmol/g, 410 mg, 1.57 mmol) and 3,4-dichlorobenzyl bromide (100 μL, 0.586 mmol) at ambient temperature and allow the reaction to continue overnight. Filter the reaction mixture from the resin and rinse with DCM (2 mL), methanol (2 mL), DCM (2 mL), and methanol (2 mL). Concentrate *in vacuo*. Treat a solution of the crude 3-*tert*-butoxycarbonyl-7-chloro-6-(3,4-dichloro-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine in DCM (2 mL) with a 2M hydrogen chloride in ether (excess) and continue stirring until TLC shows consumption of starting material. Concentrate *in vacuo* and triturate the obtained solid with ether:pentane (10:90). Purify by preparative reverse phase HPLC (Column: Xterra Prep RP18 19x250mm; Solvent A: 10 mM aqueous ammonium carbonate, Solvent B: acetonitrile; 30-100% B over 20 minutes; flow rate 25 mL/min) to give the title compound as a white solid (97 mg, 38%). MS (APCI+) *m/z*: 374 $(M+H)^+$.

Examples 388-393 may be prepared essentially as described in Example 387 by using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriately substituted benzyl bromide. MS (ES+) data are included in the Table below.

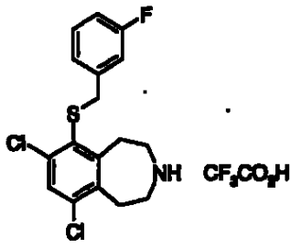


Ex.	R	Compound	MS (ES+ or APCI+)
388	3-Cl	7-Chloro-6-(3-chloro-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Trifluoroacetate	338 $(M+H)^+$
389	3-F	7-Chloro-6-(3-fluoro-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Trifluoroacetate	322 $(M+H)^+$

Ex.	R	Compound	MS (ES+ or APCI+)
390	3,4-diF	7-Chloro-6-(3,4-difluoro-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Trifluoroacetate	340 $(M+H)^+$
391	3,5-diF	7-Chloro-6-(3,5-difluoro-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Trifluoroacetate	340 $(M+H)^+$
392	3,4,5-triF	7-Chloro-6-(3,4,5-trifluoro-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Trifluoroacetate	358 $(M+H)^+$
393	3-OCF_3	7-Chloro-6-(3-trifluoromethoxybenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Trifluoroacetate	388 $(M+H)^+$

Example 394

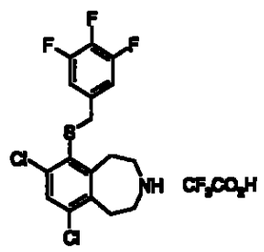
7,9-Dichloro-6-(3-fluorobenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Trifluoroacetate



Obtain as minor product from the reaction of the 4:1 mixture of 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 3-*tert*-butoxycarbonyl-7,9-dichloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-benzo[*d*]azepine with 3-fluorobenzyl bromide, using a method similar to the Example 387. Deprotect and isolate the title compound as a white solid after preparative reverse phase HPLC. MS (ES+) *m/z*: 356 $(M+H)^+$.

Example 395

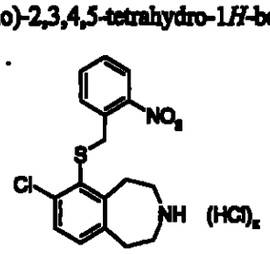
7,9-Dichloro-6-(3,4,5-trifluorobenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Trifluoroacetate



Obtain as minor product from the reaction of the 4:1 mixture of 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 3-*tert*-butoxycarbonyl-7,9-dichloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-benzo[*d*]azepine with 3,4,5-trifluorobenzyl bromide, using a method similar to the Example 387. Deprotect and isolate the title compound as a white solid after preparative reverse phase HPLC. MS (APCI+) *m/z*: 392 $(M+H)^+$.

Example 396

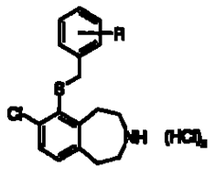
7-Chloro-6-(2-nitro-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 387, using 3-*tert*-butoxylcarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]-azepine and 2-nitrobenzyl bromide to give, after chromatography eluting with hexane/EtOAc (10:1) and deprotection by the General Procedure 1-4, the title compound as an off-white powder. MS (APCI+) *m/z*: 349 $(M+H)^+$.

Examples 397-399 may be prepared essentially as described in Example 396 by using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-

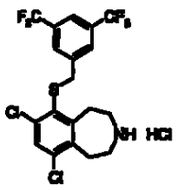
benzo[*d*]azepine and the appropriately substituted benzyl bromide. MS (ES+) data are included in the Table below.



Ex.	R	Compound	MS (ES+ or APCI+)
397	2-OCF_3	7-Chloro-6-(2-trifluoromethoxybenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	388 $(M+H)^+$
398	3-OPh	7-Chloro-6-(3-phenoxybenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	396 $(M+H)^+$
399	3,5-diCF_3	7-Chloro-6-(3,5-bistrifluoromethylbenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	440 $(M+H)^+$

Example 400

7,9-Dichloro-6-(3,5-*bis*-trifluoromethylbenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride (2148393)

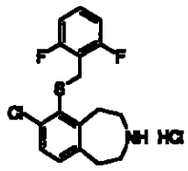


Obtain as minor product from the reaction of the 4:1 mixture of 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 3-*tert*-butoxycarbonyl-7,9-dichloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-benzo[*d*]azepine with 3,5-bis-trifluoromethylbenzyl bromide, using a method similar to the Example 396. Deprotect the crude mixture and purify by preparative reverse phase HPLC (Column: Xterra Prep RP18 19x250mm; solvent A: 10 mM aqueous ammonium carbonate; solvent B: acetonitrile; 30-100% B over 20 minutes;

flow rate 25 mL/min). Use a method similar to the General Procedure 2-2 to give the title compound as a white solid. MS (APCI+) *m/z*: 474 $(M+H)^+$.

Example 401

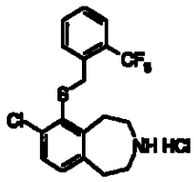
7-Chloro-6-(2,6-difluorobenzylthio-)2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 330, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 2,6-difluorobenzyl bromide to give, after deprotection by the General Procedure 1-4, the title compound.

Example 402

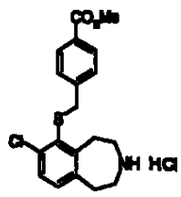
7-Chloro-6-(2-trifluoromethylbenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 347 to react 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine with 2-trifluoromethylbenzyl bromide. Use a method similar to the General Procedure 1-4 to give the title compound as a waxy tan solid. MS (APCI+) *m/z*: 372 $(M+H)^+$.

Example 403

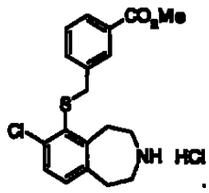
7-Chloro-6-(4-methoxycarbonylbenzylthio)-2,3,4,5-tetrahydro-benzo[*d*]azepine Hydrochloride



Use a method similar to the Preparation 177, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and methyl 4-(bromomethyl)benzoate to give, after deprotection by the General Procedure 1-4, the title compound as a white solid. MS (ES+) *m/z*: 362 $(M+H)^+$.

Example 404

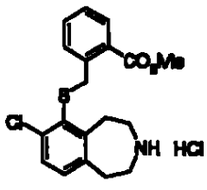
7-Chloro-6-(3-methoxycarbonylbenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 347 to react 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine with methyl 3-(bromomethyl)benzoate. Use a method similar to the General Procedure 1-5, basic workup, and a method similar to the General Procedure 2-2 to give the title compound. MS (APCI+) *m/z*: 362 $(M+H)^+$.

Example 405

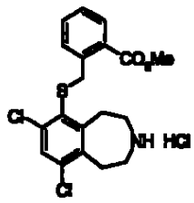
7-Chloro-6-(2-methoxycarbonylbenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 347, using the 4:1 mixture of 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 3-*tert*-butoxycarbonyl-7,9-dichloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-benzo[*d*]azepine with methyl 2-(bromomethyl)benzoate. Use a method similar to the General Procedure 1-4 and purify by preparative reverse phase HPLC (Column: Xterra Prep RP18 19x250mm; solvent A: 10 mM aqueous ammonium carbonate, solvent B: acetonitrile; 30-100% B over 20 minutes; flow rate 25 mL/min). Use a method similar to the General Procedure 2-2, to give the title compound as a white solid. MS (ES+) *m/z*: 362 $(M+H)^+$.

Example 406

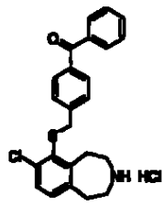
7,9-Dichloro-6-(2-methoxycarbonylbenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Obtain the free base of the title compound as a minor product from Example 405, after preparative reverse phase HPLC (Column: Xterra Prep RP18 19x250mm; solvent A: 10 mM aqueous ammonium carbonate; solvent B: acetonitrile; 30–100% B over 20 minutes; flow rate 25 mL/min). Use a method similar to the General Procedure 2-2 to give the title compound as a white solid. MS (ES+) *m/z*: 396 $(M+H)^+$.

Example 407

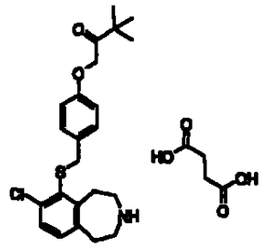
6-(4-Benzoylbenzylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 380 to react 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine with 4-(bromomethyl)benzophenone. Purify by preparative reverse phase HPLC (Column: Xterra Prep RP18 19x250mm; Solvent A: 10 mM aqueous ammonium carbonate, Solvent B: acetonitrile; 30-100% B over 20 minutes; flow rate 25 mL/min). Use a method similar to the General Procedure 2-2 to give the title compound as a white solid. MS (ES+) *m/z*: 408 $(M+H)^+$.

Example 408

7-Chloro-6-[4-(3,3-dimethyl-2-oxo-butoxy)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

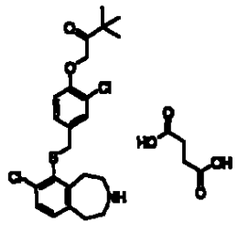


Use a method similar to the General Procedure 7, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (577 mg, 1.5 mmol) and 1-(4-bromomethylphenoxy)-3,3-dimethylbutan-2-one (556 mg, 1.95 mmol) to give, after chromatography on silica gel eluting with EtOAc/hexane (1:5), 3-*tert*-butoxycarbonyl-7-chloro-6-[4-(3,3-dimethyl-2-oxo-butoxy)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a colorless oil (669 mg, 86%). MS (ES+) *m/z*: 518 $(M+H)^+$.

Use a method similar to the General Procedure 1-5 to deprotect 3-*tert*-butoxycarbonyl-7-chloro-6-[4-(3,3-dimethyl-2-oxo-butoxy)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (669 mg, 1.29 mmol). Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (92:8) to give the free base of the title compound as a colorless oil (349 mg, 64%). MS (ES+) *m/z*: 418 $(M+H)^+$. Use a method similar to the General Procedure 2-1 to give the title compound.

Example 409

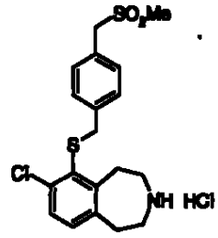
7-Chloro-6-[3-chloro-4-(3,3-dimethyl-2-oxo-butoxy)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Use a method similar to the Example 408, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 1-(4-bromomethyl-3-chlorophenoxy)-3,3-dimethylbutan-2-one to give the title compound. MS (ES+) *m/z*: 452 $(M+H)^+$.

Example 410

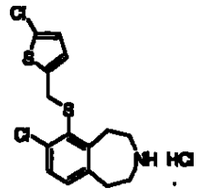
7-Chloro-6-(4-methanesulfonylmethyl-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the General Procedure 1-4, using 3-*tert*-butoxycarbonyl-7-chloro-6-(4-methanesulfonylmethyl-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine to give the title compound as a white solid. MS (ES+) *m/z*: 396 $(M+H)^+$.

Example 411

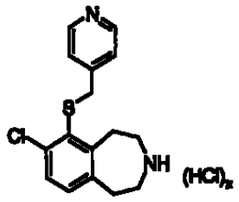
7-Chloro-6-(5-chloro-thiophen-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 387, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 2-chloro-5-(chloromethyl)thiophene to give, after hydrochloride formation by the General Procedure 2-2, the title compound as a brown solid. MS (APCI+) *m/z*: 344 $(M+H)^+$.

Example 412

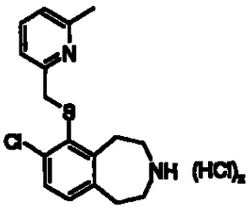
7-Chloro-6-(pyridin-4-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochlorides



Use a method similar to the Example 387, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 4-bromomethylpyridine hydrobromide to give, after hydrochloride formation by the General Procedure 2-2, the title compound as a white solid. MS (APCI+) *m/z*: 305 $(M+H)^+$.

Example 413

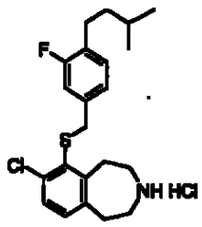
7-Chloro-6-(6-methyl-pyridin-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochlorides



Use a method similar to the Example 387, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 2-chloromethyl-6-methylpryidine to give, after chromatography on silica gel eluting with hexane/EtOAc (4:1) and deprotection by the General Procedure 1-4, the title compound as a white solid. MS (ES+) *m/z*: 319 $(M+H)^+$.

Example 414

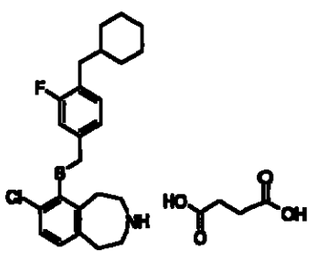
7-Chloro-6-[3-fluoro-4-(3-methylbutyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



To 6-(4-bromo-3-fluorobenzylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[d]azepine (0.210 mg, 0.42 mmol) and dichloro[1,1'-bis(diphenylphosphino)-ferrocene]palladium(II) dichloromethane adduct (17 mg, 0.021 mmol) add 0.5 M 3-methylbutylzinc bromide in THF (4.2 mL, 2.10 mmol). Degas, purge with dry nitrogen, and stir overnight at 80 °C. Cool to ambient temperature, dilute with EtOAc, wash with water, dry over anhydrous $MgSO_4$ and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to give 3-*tert*-butoxycarbonyl-7-chloro-6-[3-fluoro-4-(3-methylbutyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow oil (85 mg, 42%). Use a method similar to the General Procedure 1-4 to give the title compound as a white solid. MS (ES+) *m/z*: 392 $(M+H)^+$.

Example 415

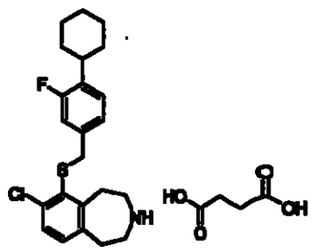
7-Chloro-6-(4-cyclohexylmethyl-3-fluorobenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Use a method similar to the Example 414 to react 6-(4-bromo-3-fluorobenzylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[d]azepine with (cyclohexyl)methylzinc bromide. Use a method similar to the General Procedure 1-4, basic work-up, and a method similar to the General Procedure 2-1, to give the title compound as a white solid. MS (ES+) *m/z*: 418 $(M+H)^+$.

Example 416

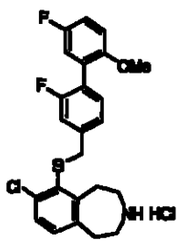
7-Chloro-6-(4-cyclohexyl-3-fluorobenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 414, using 6-(4-bromo-3-fluorobenzylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and cyclohexylzinc bromide. Use a method similar to the General Procedure 1-4, basic work-up, and a method similar to the General Procedure 2-1, to give the title compound as a white solid. MS (ES+) *m/z*: 404 $(M+H)^+$.

Example 417

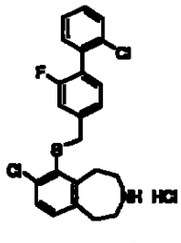
7-Chloro-6-(2,5'-difluoro-2'-methoxybiphenyl-4-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Degas a stirred mixture of 6-(4-bromo-3-fluorobenzylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (212 mg, 0.424 mmol), 5-fluoro-2-methoxybenzene boronic acid (108 mg, 0.636 mmol), potassium carbonate (292 mg, 2.12 mmol), triphenylphosphine (11 mg, 0.0424 mmol) and bis(triphenylphosphine)-palladium(II) chloride (15 mg, 0.0212 mmol) in dioxane (3 mL) and water (1 mL). Purge with dry nitrogen and heat at 100 °C for 5 h. Cool to ambient temperature, add water, extract three times with EtOAc, dry over anhydrous Na_2SO_4 and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/ EtOAc (9:1) to give 3-*tert*-butoxycarbonyl-7-chloro-6-(2,5'-difluoro-2'-methoxy-biphenyl-4-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as yellow oil (216 mg, 93%). Use a method similar to the General Procedure 1-4 to give the title compound as a yellow foam. MS (ES+) *m/z*: 446 $(M+H)^+$.

Example 418

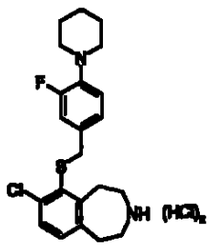
7-Chloro-6-(2'-chloro-2-fluorobiphenyl-4-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 417, using 2-chlorophenylboronic acid to give, after deprotection by the General Procedure 1-4, the title compound as a white solid. MS (ES+) *m/z*: 432 $(M+H)^+$.

Example 419

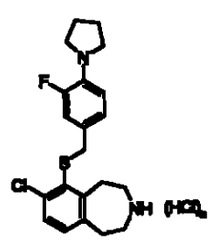
7-Chloro-6-(3-fluoro-4-piperidin-1-yl-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



In a sealed tube, add tris(dibenzylideneacetone)dipalladium (13 mg, 0.014 mmol) and 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (19 mg, 0.029 mmol) to a mixture of 6-(4-bromo-3-fluorobenzylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[d]azepine (957 mg, 1.91 mmol), sodium *tert*-butoxide (367 mg, 3.83 mmol), 18-crown-6 (50 mg, 0.191 mmol) and piperidine (944 µl, 9.57 mmol) in toluene (10 mL). Flush the mixture with nitrogen and heat overnight. Cool to ambient temperature, dilute with water and extract three times with EtOAc. Dry over anhydrous Na_2SO_4 and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to give 3-*tert*-butoxycarbonyl-7-chloro-6-(3-fluoro-4-piperidin-1-yl-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow oil (511 mg, 33%). Use a method similar to the General Procedure 1-4 to give the title compound as a white solid. MS (ES+) *m/z*: 405 $(M+H)^+$.

Example 420

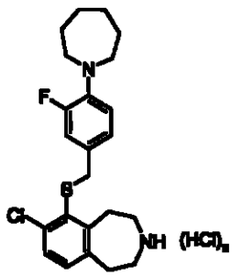
7-Chloro-6-(3-fluoro-4-pyrrolidin-1-yl-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 419 to react 6-(4-bromo-3-fluorobenzylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[d]azepine with pyrrolidine. Use a method similar to the General Procedure 1-4 to give the title compound as a white solid. MS (ES+) *m/z*: 391 $(M+H)^+$.

Example 421

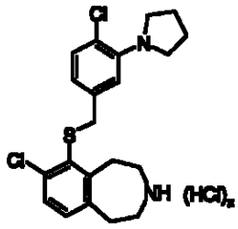
6-(4-Azepan-1-yl-3-fluorobenzylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 419 to react 6-(4-bromo-3-fluorobenzylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[d]azepine with homopiperidine. Use a method similar to the General Procedure 1-4 to give the title compound as a white solid. MS (ES+) *m/z*: 419 $(M+H)^+$.

Example 422

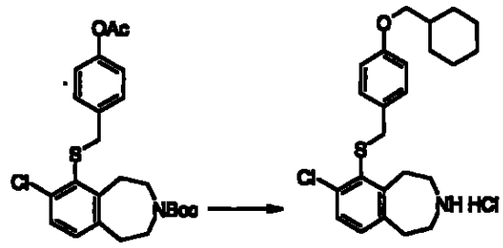
7-Chloro-6-(4-chloro-3-pyrrolidin-1-yl-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine hydrochloride



Use a method similar to the Example 419, using 6-(3-bromo-4-chloro-benzylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and pyrrolidine to give, after deprotection using a method similar to the General Procedure 1-4, the title compound as a white solid. MS (ES+) *m/z*: 407 $(M+H)^+$.

Example 423

7-Chloro-6-(4-cyclohexylmethoxybenzylthio)-3-*tert*-butoxycarbonyl- -2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

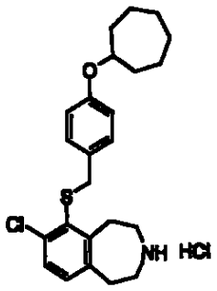


Use a method similar to the Preparation 177, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 4-(chloromethyl)phenyl acetate to give 6-(4-acetoxybenzylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a white solid.

To 6-(4-acetoxybenzylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (532 mg, 1.15 mmol) in methanol (8 mL) at ambient temperature add with stirring a solution of potassium carbonate (796 mg, 5.77 mmol) in water (4 mL) and stir the mixture for 2 h. Dilute with water, extract three times with EtOAc, dry over anhydrous Na_2SO_4, and concentrate *in vacuo*. To a portion of the crude phenol thus obtained (204 mg, 0.487 mmol) in THF (5 mL), add with stirring diisopropyl azodicarboxylate (216 µl, 1.71 mmol) followed by triphenylphosphine (306 mg, 1.17 mmol) and cyclohexylmethanol (619 mg, 5.42 mmol). Heat at 60°C for 3 h, cool to ambient temperature and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to give 3-*tert*-butoxycarbonyl-7-chloro-6-(4-cyclohexylmethoxy-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a colorless oil (176 mg, 70%). Use a method similar to the General Procedure 1-4 to give the title compound as a white solid. MS (ES+) *m/z*: 416 $(M+H)^+$.

Example 424

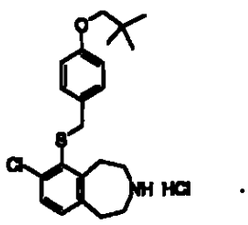
7-Chloro-6-(4-cycloheptyloxybenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 423 to react 6-(4-acetoxybenzylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine with cycloheptanol. Use a method similar to the General Procedure 1-4 to give the title compound as a white solid. MS (ES+) *m/z*: 416 $(M+H)^+$.

Example 425

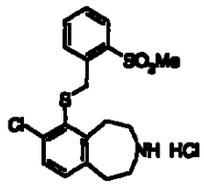
7-Chloro-6-[4-(2,2-dimethylpropoxy)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Preparation 177 to react 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 1-bromomethyl-4-(2,2-dimethylpropoxy)-benzene. Use a method similar to the General Procedure 1-4 to give the title compound as a white solid. MS (ES+) *m/z*: 390 $(M+H)^+$.

Example 426

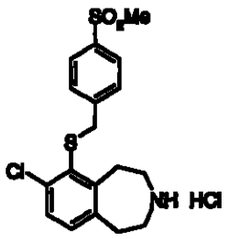
7-Chloro-6-(2-methanesulfonylbenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Preparation 177, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 1-bromomethyl-2-methanesulfonyl-benzene to give, after deprotection by the General Procedure 1-4, the title compound and as a white solid. MS (APCI+) *m/z*: 382 $(M+H)^+$.

Example 427

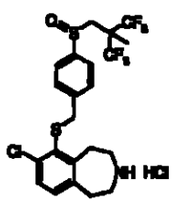
7-Chloro-6-(4-methanesulfonylbenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 380, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 4-methylsulfonylbenzyl bromide to give, after hydrochloride formation by the General Procedure 2-2, the title compound as a white solid. MS (ES+) *m/z*: 382 $(M+H)^+$.

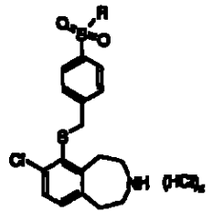
Example 428

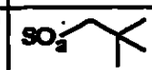
7-Chloro-6-[4-(3,3,3-trifluoro-2-methyl-2-trifluoromethylpropane-1-sulfinyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

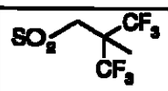
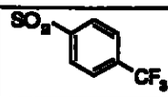
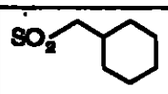


To 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (723 mg, 1.88 mmol) in methanol (10 mL) add potassium hydroxide pellets (3.34 g, 60.2 mmol) and stir mixture at 50 °C for 2 h. Cool to ambient temperature, add aqueous saturated ammonium chloride, extract three times with EtOAc, dry over anhydrous Na_2SO_4, and concentrate *in vacuo* to give the crude 3-*tert*-butoxycarbonyl-7-chloro-6-mercapto-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Dissolve the compound in DMF (5 mL), add cesium carbonate (920 mg, 2.82 mmol) and 1-bromomethyl-4-(3,3,3-trifluoro-2-methyl-2-trifluoromethyl-propane-1-sulfinyl)-benzene (824 mg, 2.071 mmol) and stir 2 h at ambient temperature. Dilute with water, extract three times with EtOAc, dry over anhydrous Na_2SO_4, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to give 3-*tert*-butoxycarbonyl-7-chloro-6-[4-(3,3,3-trifluoro-2-methyl-2-trifluoromethyl-propane-1-sulfinyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow oil (986 mg, 83%). Use a method similar to the General Procedure 1-4 to give the title compound as a white foam. MS (ES+) *m/z*: 530 $(M+H)^+$.

Examples 429-432 may be prepared essentially as described in Example 428 by using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine with the appropriately substituted benzyl bromide. MS (ES+) data are included in the Table below.

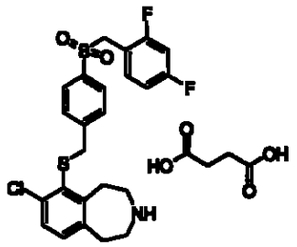


Ex.	SO_2R	Compound	MS (ES+ or APCI+)
429		7-Chloro-6-[4-(2,2-dimethyl-propane-1-sulfonyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	438 $(M+H)^+$

Ex.	SO_2R	Compound	MS (ES+ or APCI+)
430		7-Chloro-6-[4-(3,3,3-trifluoro-2-methyl-2-trifluoromethylpropane-1-sulfonyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	546 $(M+H)^+$
431		7-Chloro-6-[4-(4-trifluoromethyl-benzenesulfonyl)-benzylthio]-1,2,4,5-tetrahydro-benzo[*d*]azepine Hydrochloride	512 $(M+H)^+$
432		7-Chloro-6-(4-cyclohexylmethanesulfonyl-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	464 $(M+H)^+$

Example 433

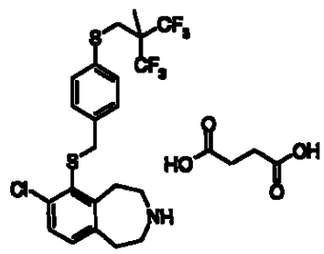
7-Chloro-6-[4-(2,4-difluoro-phenylmethanesulfonyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Use a method similar to the Example 428 to react 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine with 1-(4-bromomethyl-benzenesulfonylmethyl)-2,4-difluoro-benzene. Use a method similar to the General Procedure 1-4, basic work-up, and a method similar to the General Procedure 2-1, to give the title compound as a white solid. MS (ES+) *m/z*: 494 $(M+H)^+$.

Example 434

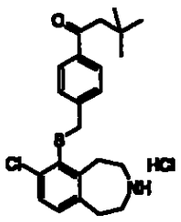
7-Chloro-6-[4-(3,3,3-trifluoro-2-methyl-2-trifluoromethylpropylthio)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Use a method similar to the Example 428 to react 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine with 1-bromomethyl-4-(3,3,3-trifluoro-2-methyl-2-trifluoromethyl-propylthio)-benzene. Use a method similar to the General Procedure 1-5, basic workup, and a method similar to the General Procedure 2-1, to give the title compound as a white solid. MS (APCI$^+$) *m/z*: 514 $(M+H)^+$.

Example 435

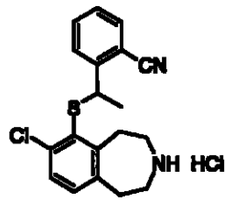
7-Chloro-6-[4-(3,3-dimethylbutyryl)-benzylthio]-1,2,4,5-tetrahydro-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 428 to react 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine with 1-(4-bromomethylphenyl)-3,3-dimethylbutan-1-one. Use a method similar to the General Procedure 1-4, basic workup, and a method similar to the General Procedure 2-2 to give the title compound as a white solid. MS (APCI$^+$) *m/z*: 402 $(M+H)^+$.

Example 436

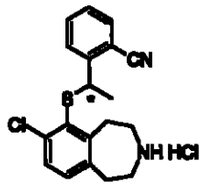
(±)-7-Chloro-6-[1-(2-cyanophenyl)-ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Preparation 177, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and (±)-2-(1-bromoethyl)benzonitrile to give, after deprotection by the General Procedure 1-4, the title compound as a white solid. MS (APCI+) *m/z*: 343 $(M+H)^+$.

Example 437

(-)-7-Chloro-6-[1-(2-cyanophenyl)-ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



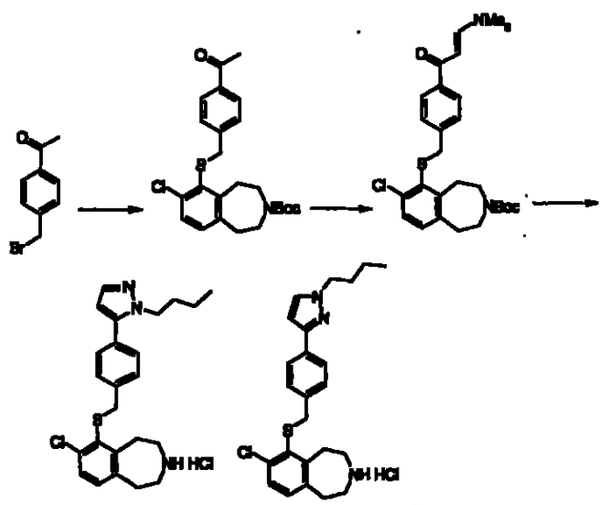
Dissolve (±)-7-chloro-6-[1-(2-cyanophenyl)-ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine succinate (326 mg, 1.0 mmol) in DCM (5 mL) and pyridine (0.4 mL, 5 mmol). Add di-*tert*-butyl-dicarbonate (270 mg, 1.2 mmol) and stir the mixture for 16 h at ambient temperature. Wash the mixture with 5N aqueous NaOH and saturated aqueous $NaHCO_3$ successively. Collect the organic layer and concentrate *in vacuo*. Purify the residue by chromatography on silica gel eluting with hexane/EtOAc (1:1) to obtain (±)-3-*tert*-butoxycarbonyl-7-chloro-6-[1-(2-cyanophenyl)-ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (393 mg, 93%). Separate the enantiomers of (±) 3-*tert*-butoxycarbonyl-7-chloro-6-[1-(2-cyanophenyl)-ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine by chiral normal phase chromatography (Chiralpak AD 8x30 cm column, eluting with heptane/isopropylamine, 95:5).

Take the second eluting isomer and deprotect using the General Procedure 1-5. Purify with SCX chromatography. Use a method similar to the General Procedure 2-2 to

obtain the title compound (125 mg, 37%). MS (ES+) *m/z*: 343 $(M+H)^+$. $[\alpha]^{20}_D$ -112° (c 0.5, CH_3OH).

Examples 438 and 439

6-[4-(2-Butyl-2*H*-pyrazol-3-yl)-benzylthio]-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride and 6-[4-(1-Butyl-1*H*-pyrazol-3-yl)-benzylthio]-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



4-Acetylbenzyl bromide: Use a method similar to the Preparation 184, using 4-methylacetophenone, to give the desired intermediate as a white solid.

6-(4-Acetylbenzylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Use a method similar to the Example 380, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 4-acetylbenzyl bromide to give, after chromatography eluting with hexane/EtOAc (15:1), the desired intermediate as a white solid. MS (APCI+) *m/z* 346 $(M+H\text{-}Boc)^+$.

3-*tert*-Butoxycarbonyl-7-chloro-6-[4-(3-dimethylaminoacryloyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Heat a solution of 6-(4-acetylbenzylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.0 g, 2.2 mmol) in

toluene (10 mL) at 110 °C overnight in the presence of *tert*-butoxy-bis(dimethylamino)-methane (1.0 mL, 4.84 mmol). Concentrate *in vacuo* to provide the desired intermediate as a dark oil (1.2 g, 100%). MS (APCI+) *m/z* 401 $(M+H\text{-}Boc)^+$.

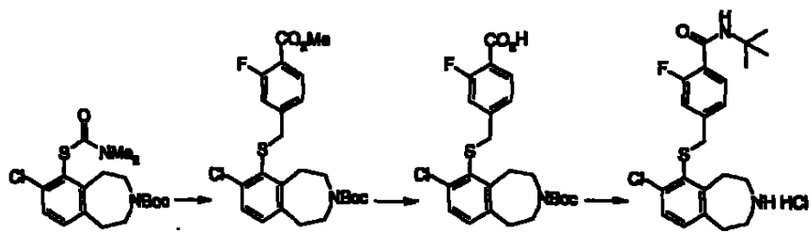
6-[4-(1-Butyl-1*H*-pyrazol-3-yl)-benzylthio]-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride: To a stirred mixture of 3-*tert*-butoxycarbonyl-7-chloro-6-[4-(3-dimethylaminoacryloyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (240 mg, 0.475 mmol), butylhydrazine oxalate (102 mg, 0.574 mmol), sodium carbonate (55 mg, 0.444 mmol) in water (8 mL) and methanol (10 mL) add acetic acid (ca. 3-6 drops) to pH 5. Heat overnight at 70 °C. Concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (10:1) to give a mixture of the desired intermediates, 3-*tert*-butoxycarbonyl-6-[4-(2-butyl-2*H*-pyrazol-3-yl)-benzylthio]-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (65 mg, 32%), MS (APCI+) *m/z*: 426 $(M+H\text{-}Boc)^+$ and 3-*tert*-butoxycarbonyl-6-[4-(1-butyl-1*H*-pyrazol-3-yl)-benzylthio]-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (100 mg, 50%), MS (APCI+) *m/z*: 426 $(M+H\text{-}Boc)^+$.

Use a method similar to the General Procedure 1-4, using 3-*tert*-butoxycarbonyl-6-[4-(2-butyl-2*H*-pyrazol-3-yl)-benzylthio]-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine, to give 6-[4-(2-butyl-2*H*-pyrazol-3-yl)-benzylthio]-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (Example 438) as a white solid. MS (APCI+) *m/z*: 426 $(M+H)^+$.

Use a method similar to the General Procedure 1-4, using 3-*tert*-butoxycarbonyl-6-[4-(1-butyl-1*H*-pyrazol-3-yl)-benzylthio]-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine, to give 6-[4-(1-butyl-1*H*-pyrazol-3-yl)-benzylthio]-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (Example 439) as a white solid. MS (APCI+) *m/z*: 426 $(M+H)^+$.

Example 440

6-(4-*tert*-Butylcarbamoyl-3-fluorobenzylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

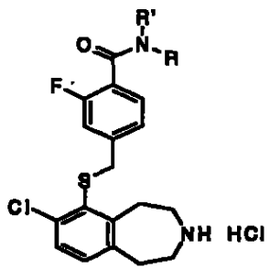


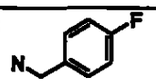
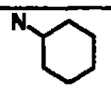
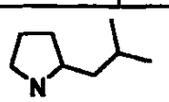
3-*tert*-Butoxycarbonyl-7-chloro-6-(3-fluoro-4-methoxycarbonylbenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Use a method similar to the Example 428, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and methyl 4-bromomethyl-2-fluorobenzoate, to give the desired intermediate as a white solid.

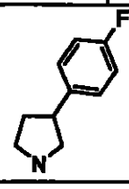
3-*tert*-Butoxycarbonyl-6-(4-carboxy-3-fluorobenzylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Heat a stirred solution of 3-*tert*-butoxycarbonyl-7-chloro-6-(3-fluoro-4-methoxycarbonylbenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (3.56 g, 7.44 mmol) in THF (50 mL) and water (40 mL) overnight at 65 °C in the presence of potassium hydroxide (8.30 g, 148.77 mmol). Cool the mixture to 0 °C, add slowly a 1N solution of hydrochloric acid until pH 5. Extract three times with EtOAc, dry over anhydrous Na_2SO_4 and concentrate *in vacuo* to provide the desired intermediate as a white solid (3.5 g, 99%).

6-(4-*tert*-Butylcarbamoyl-3-fluorobenzylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride: To a solution of 3-*tert*-butoxycarbonyl-6-(4-carboxy-3-fluoro-benzylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.1 g, 2.36 mmol) in DMF (7 mL), add *tert*-butylamine (12.05 g, 165.2 mmol), EDC (1.81 g, 9.44 mmol) and HOBt (1.44g, 10.62 mmol) and stir in a sealed tube at 70 °C overnight. Dilute with EtOAc, wash with water, dry over anhydrous $MgSO_4$ and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to give 3-*tert*-butoxycarbonyl-6-(4-*tert*-butylcarbamoyl-3-fluorobenzylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a clear oil. MS (APCI+) *m/z*: 421 $(M+H)^+$. Use a method similar to the General Procedure 1-4 to give the title compound as a white powder. MS (APCI+) *m/z*: 421 $(M+H)^+$.

Examples 441-447 may be prepared essentially as described in Example 440 by reacting 3-*tert*-butoxycarbonyl-6-(4-carboxy-3-fluorobenzylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine with the appropriate amine. MS (ES+) data are included in the Table below.

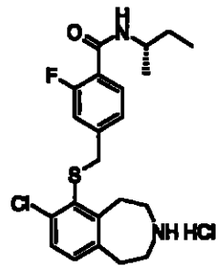


Ex.	N-R	R'	Compound	MS (ES+ or APCI+)
441	N-(*n*-Pr)	H	7-Chloro-6-(3-fluoro-4-*n*-propylcarbamoyl-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	407 $(M+H)^+$
442	N-(*i*-Bu)	H	6-(4-*iso*-Butylcarbamoyl-3-fluoro-benzylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	421 $(M+H)^+$
443	N-(*n*-Pr)	*n*-Pr	7-Chloro-6-(4-dipropylcarbamoyl-3-fluoro-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	449 $(M+H)^+$
444		H	7-Chloro-6-[3-fluoro-4-(4-fluoro-benzylcarbamoyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	473 $(M+H)^+$
445		H	7-Chloro-6-(4-cyclohexylcarbamoyl-3-fluoro-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	447 $(M+H)^+$
446			7-Chloro-6-[3-fluoro-4-(2-isobutyl-pyrrolidine-1-carbonyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	475 $(M+H)^+$

Ex.	N-R	R'	Compound	MS (ES+ or APCI+)
447			7-Chloro-6-{3-fluoro-4-[3-(4-fluoro-phenyl)-pyrrolidine-1-carbonyl]-benzylthio}-2,3,4,5-tetrahydro-1*H*-benzo[d]azepine-Hydrochloride	513 $(M+H)^+$

Example 448

(*S*)-(+)-6-(4-*sec*-Butylcarbamoyl-3-fluorobenzylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

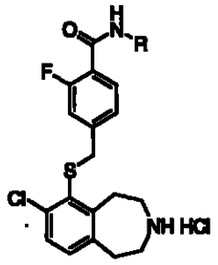


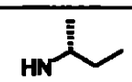
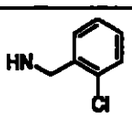
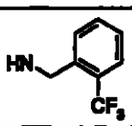
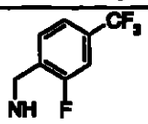
3-*tert*-Butoxycarbonyl-7-chloro-6-(4-chlorocarbonyl-3-fluorobenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: To a solution of 3-*tert*-butoxycarbonyl-6-(4-carboxy-3-fluoro-benzylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.95 g, 4.21 mmol) in DCM (20 mL) at 0 °C under nitrogen, add three drops of DMF and oxalyl chloride (1.06 g, 8.41 mmol). Stir for 2 h and concentrate *in vacuo* to afford the desired intermediate as a yellow oil (1.93 g, 95%).

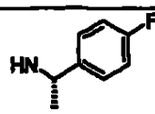
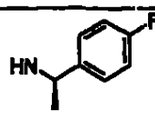
(*S*)-3-*tert*-Butoxycarbonyl-6-(4-sec-butylcarbamoyl-3-fluorobenzylthio)-7-chloro-2,3,4,5-tetrahydro-1H-benzo[*d*]azepine: To a solution of 3-*tert*-butoxycarbonyl-7-chloro-6-(4-chlorocarbonyl-3-fluoro-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (415 mg, 0.860 mmol) in DCM (10 mL), add (*S*)-(+)-*sec*-butylamine (1.0 g, 13.7 mmol) and stir at ambient temperature for 30 min. Concentrate *in vacuo* and purify by chromatography on silica gel eluting with hexane/EtOAc (4:1) to give the desired intermediate as a pale oil (352 mg, 79%). MS (APCI+) *m/z*: 421 $(M+H\text{-Boc})^+$.

(*S*)- (+)-6-(4-*sec*-Butylcarbamoyl-3-fluorobenzylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride: Use a method similar to the General Procedure 1-4, using (+)-3-*tert*-butoxycarbonyl-6-(4-*sec*-butylcarbamoyl-3-fluoro-benzylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine, to give the title compound as a pale solid. MS (APCI+) *m/z*: 421 $(M+H)^+$. $[\alpha]^{20}_D$ +8.7° (c 0.5, CH_3OH).

Examples 449-454 may be prepared essentially as described in Example 448 by reacting 3-*tert*-butoxycarbonyl-6-(4-carboxy-3-fluoro-benzylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine with the appropriate amine. Optical rotation and MS (ES+) data are included in the Table below.

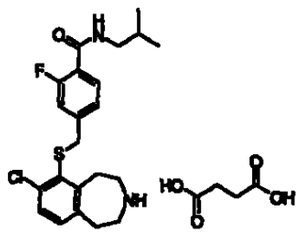


Ex.	NH-R	Compound	$[\alpha]^{20}_D$ (c, solvent	MS (ES+) *m/z*
449		(*R*)-(-)-6-(4-*sec*-Butylcarbamoyl-3-fluoro-benzylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	-7.0° (c 0.5, CH_3OH).	421 $(M+H)^+$
450		7-Chloro-6-[4-(2-chloro-benzylcarbamoyl)-3-fluoro-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	-	489 $(M+H)^+$
451		7-Chloro-6-[3-fluoro-4-(2-trifluoromethyl-benzylcarbamoyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine-3-Hydrochloride	-	523 $(M+H)^+$
452		7-Chloro-6-[3-fluoro-4-(2-fluoro-4-trifluoromethyl-benzyl-carbamoyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]aze-pine Hydrochloride	-	541 $(M+H)^+$

Ex.	NH-R	Compound	$[\alpha]^{20}_D$ (c, solvent	MS (ES+) *m/z*
453		(*S*)-(-)-7-Chloro-6-{3-fluoro-4-[1-(4-fluoro-phenyl)-ethyl-carbamoyl]-benzylthio}-2,3,4,5-tetrahydro-1*H*-benzo-[*d*]azepine Hydrochloride	-25.8° (c 0.5, CH_3OH)	487 $(M+H)^+$
454		(*R*)-(+)-7-Chloro-6-{3-fluoro-4-[1-(4-fluoro-phenyl)-ethyl-carbamoyl]-benzylthio}-2,3,4,5-tetrahydro-1*H*-benzo-[*d*]azepine Hydrochloride	+24.9° (c 0.5, CH_3OH)	487 $(M+H)^+$

Example 455

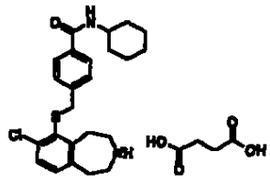
7-Chloro-6-(3-fluoro-4-isobutylcarbamoyl-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Use a method similar to the Example 448 to react 3-*tert*-butoxycarbonyl-6-(4-carboxy-3-fluoro-benzylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine with isobutylamine. Use a method similar to the General Procedure 1-4, basic work-up, and a method similar to the General Procedure 2-1 to give the title compound as a white solid. MS (ES+) *m/z*: 403 $(M+H)^+$.

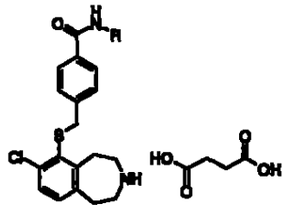
Example 456

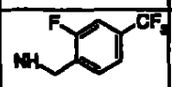
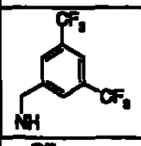
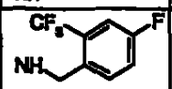
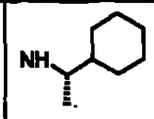
7-Chloro-6-(4-cyclohexylcarbamoylbenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

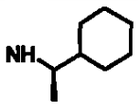
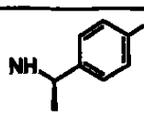
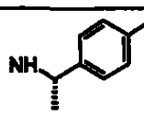
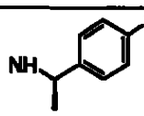
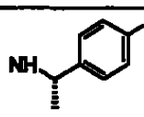


Use a method similar to the Preparation 177 to react 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine with 4-chloromethyl-*N*-cyclohexylbenzamide. Use a method similar to the General Procedure 1-5, basic workup, and a method similar to the General Procedure 2-1 to give the title compound as a white solid. MS (ES+) *m/z*: 429 $(M+H)^+$.

Examples 457-465 may be prepared essentially as described in Example 456 by using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriately substituted benzyl chloride. Optical rotation and MS (ES+) data are included in the Table below.

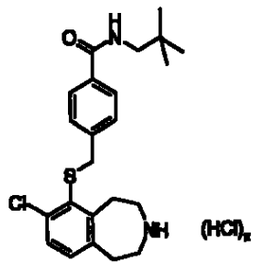


Ex.	NH-R	Compound	$[\alpha]^{25}_D$ (c, solvent)	MS (ES+ or APCI+)
457		7-Chloro-6-[4-(2-fluoro-4-trifluoromethyl-benzylcarbamoyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	-	523 $(M+H)^+$
458		[4-(3,5-Bis-trifluoromethyl-benzylcarbamoyl)-benzylthio]-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	-	573 $(M+H)^+$
459		7-Chloro-6-[4-(4-fluoro-2-trifluoromethyl-benzylcarbamoyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	-	523 $(M+H)^+$
460		(*S*)-(+)-7-Chloro-6-[4-(1-cyclohexyl-ethylcarbamoyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	+11.2° (c 0.5, CH_3OH)	457 $(M+H)^+$

Ex.	NH-R	Compound	$[\alpha]^{20}_D$ (c, solvent)	MS (ES+ or APCI+)
461		(*R*)-(-)-7-Chloro-6-[4-(1-cyclohexyl-ethylcarbamoyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	-11.3° (c 0.5, CH_3OH)	457 $(M+H)^+$
462		(*R*)-(+)-7-Chloro-6-{4-[1-(4-fluoro-phenyl)-ethylcarbamoyl]-benzylthio}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	+2.2° (c 0.5, CH_3OH)	469 $(M+H)^+$
463		(*S*)-(-)-7-Chloro-6-{4-[1-(4-fluoro-phenyl)-ethylcarbamoyl]-benzylthio}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	-1.6° (c 0.5, CH_3OH)	469 $(M+H)^+$
464		(*R*)-(-)-7-Chloro-6-{4-[1-(4-chloro-phenyl)-ethylcarbamoyl]-benzylthio}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	-5.8° (c 0.5, CH_3OH)	485 $(M+H)^+$
465		(*S*)-(+)-7-Chloro-6-{4-[1-(4-chloro-phenyl)-ethylcarbamoyl]-benzylthio}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	+5.5° (c 0.5, CH_3OH)	485 $(M+H)^+$

Example 466

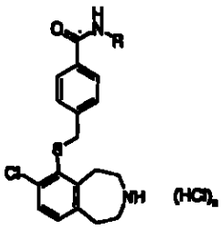
7-Chloro-6-[4-(2,2-dimethyl-propylcarbamoyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

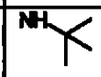
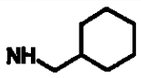
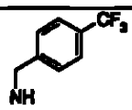
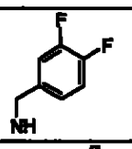
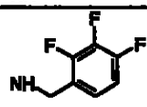


Use a method similar to the Example 456, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 4-chloromethyl-*N*-

(2,2-dimethyl-propyl)-benzamide to give, after deprotection by a method similar to the General Procedure 1-4, the title compound as a white solid. MS (ES+) *m/z*: 417 $(M+H)^+$.

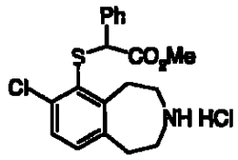
Examples 467-471 may be prepared essentially as described in Example 466 by using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriately substituted benzyl chloride. MS (ES+) data are included in the Table below.



Ex.	NH-R	Compound	MS (ES+) *m/z*
467		6-(4-*tert*-Butylcarbamoyl-benzylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	403 $(M+H)^+$
468		7-Chloro-6-[4-(cyclohexylmethyl-carbamoyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	443 $(M+H)^+$
469		7-Chloro-6-[4-(4-trifluoromethyl-benzylcarbamoyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	505 $(M+H)^+$
470		7-Chloro-6-[4-(3,4-difluoro-benzylcarbamoyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	473 $(M+H)^+$
471		7-Chloro-6-[4-(2,3,4-trifluoro-benzylcarbamoyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	491 $(M+H)^+$

Example 472

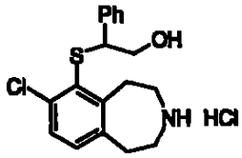
(±)-7-Chloro-6-(1-methoxycarbonyl-1-phenyl-methylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the General Procedure 1-4, using (±)-3-*tert*-butoxycarbonyl-7-chloro-6-(1-methoxycarbonyl-1-phenyl-methylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine, to give the title compound as a white solid. MS (ES+) *m/z* 362 $(M+H)^+$.

Example 473

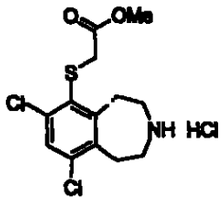
(±)-7-Chloro-6-(2-hydroxy-1-phenyl-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



To a stirred solution of (±)-3-*tert*-butoxycarbonyl-6-(1-carboxy-1-phenyl-methylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (220 mg, 0.447 mmol) in THF (10 mL) at 0° C, add a solution of 1M borane in THF (1.4 mL, 1.4 mmol). Continue stirring for 2 h at 0° C and then overnight at ambient temperature. Quench by slow addition of methanol, stir 1 h at ambient temperature and concentrate *in vacuo*. Add aqueous saturated ammonium chloride, extract three times with EtOAc, dry over anhydrous $MgSO_4$, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with 19:1 DCM/saturated ammonia in methanol. Use a method similar to the General Procedure 1-4 to give the title compound as a white solid. MS (ES+) *m/z*: 334 $(M+H)^+$.

Example 474

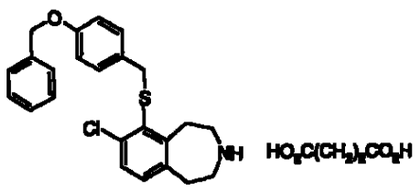
7,9-Dichloro-6-methoxycarbonylmethylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Obtain as minor product from the reaction of the 4:1 mixture of 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 3-*tert*-butoxycarbonyl-7,9-dichloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-benzo[*d*]azepine with methyl bromoacetate, using a method similar to the Example 347. Use a method similar to the General Procedure 1-4 to give the title compound as a white solid. MS (ES+) *m/z*: 320 $(M+H)^+$.

Example 475

6-(4-Benzyloxybenzylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



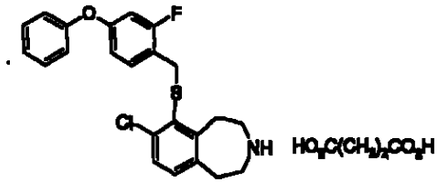
Dissolve 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (706 mg, 1.84 mmol) in methanol (20 mL). Add potassium hydroxide (3.5 g, 55 mmol) and heat the mixture at reflux for 3h. Cool to ambient temperature. Pour reaction in saturated aqueous NH_4Cl solution. Extract three times with EtOAc. Combine organic extracts, dry over Na_2SO_4 and concentrate *in vacuo* to obtain crude 3-*tert*-butoxycarbonyl-7-chloro-6-mercapto-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (602 mg, 100%). Dissolve 3-*tert*-butoxycarbonyl-7-chloro-6-mercapto-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (282 mg, 0.9 mmol) in acetone (30 mL). Add 4-benzyloxybenzyl chloride (251 mg, 1.08 mmol), potassium carbonate (powder) (373 mg, 2.7 mmol) and potassium iodide (powder) (15 mg, 0.1 mmol) and reflux for 16 h. Cool the reaction to ambient temperature, dilute with acetone, filter and concentrate *in vacuo*.

Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0 and 17:3) to give 6-(4-benzyloxybenzylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (309 mg, 67%). MS (ES+) *m/z*: 510 $(M+H)^+$.

Use a method similar to the General Procedure 1-4 and purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (95:5) to obtain the free base of the title compound (230 mg, 92%). MS (ES+) *m/z*: 410 (M+H)+. Use a method similar to the General Procedure 2-1 to obtain the title compound.

Example 476

7-Chloro-6-[(2-fluoro-4-phenoxy)benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

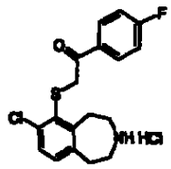


Use a method similar to the Example 475, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 1-bromomethyl-2-fluoro-4-phenoxybenzene to provide, after chromatography on silica gel eluting with hexane/EtOAc (85:15), 3-*tert*-butoxycarbonyl-7-chloro-6-[(2-fluoro-4-phenoxy)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (384 mg, 83%). MS (ES+) *m/z*: 414 $(M\text{-}Boc+2H)^+$.

Use a method similar to the General Procedure 1-4 and purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (95:5) to obtain the free base of the title compound (203 mg, 65%). MS (ES+) *m/z*: 414 $(M+H)^+$. Use a method similar to the General Procedure 2-1 to obtain the title compound.

Example 477

7-Chloro-6-[2-(4-fluorophenyl)-2-oxo-ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

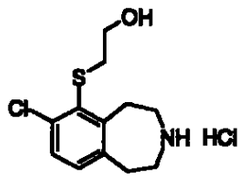


Use a method similar to the Example 475, using crude 3-*tert*-butoxycarbonyl-7-chloro-6-mercapto-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 2-bromo-4'-fluoroacetophenone (239 mg, 1.1 mmol) to provide, after stirring at ambient temperature for 16 h and purification by chromatography on silica gel eluting with hexane/EtOAc (4:1), 3-*tert*-butoxycarbonyl-7-chloro-6-[2-(4-fluorophenyl)-2-oxo-ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (38 mg, 9%).

Use a method similar to the General Procedure 1-5 and purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (95:5) to obtain the free base of the title compound (23 mg, 78%). MS (ES+) *m/z*: 350 $(M+H)^+$. Use a method similar to the General Procedure 2-2 to obtain the title compound.

Example 478

7-Chloro-6-(2-hydroxyethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 347, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and methyl bromoacetate to give 3-*tert*-butoxycarbonyl-7-chloro-6-methoxycarbonylmethylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine.

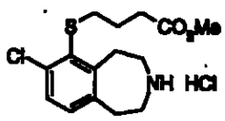
To a solution of 3-*tert*-butoxycarbonyl-7-chloro-6-methoxycarbonylmethylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (750 mg, 1.94 mmol) in THF (25 mL) at –78 °C under nitrogen, add 1M DIBAL in toluene (5.0 mL, 5.0 mmol) dropwise with stirring. Warm to –30°C over 1 h and quench carefully with water. Extract with EtOAc, dry over

anhydrous $MgSO_4$, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (4:1) to give 3-*tert*-butoxycarbonyl-7-chloro-6-(2-hydroxy-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (651 mg, 94%).

Use a method similar to the General Procedure 1-4, using 3-*tert*-butoxycarbonyl-7-chloro-6-(2-hydroxyethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (190 mg, 0.531 mmol) to give the title compound as a white solid (105 mg, 67%). MS (ES+) *m/z*: 258 $(M+H)^+$.

Example 479

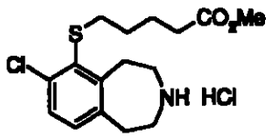
7-Chloro-6-(3-methoxycarbonylpropylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 347, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and methyl 4-bromobutyrate to give, after deprotection by the General Procedure 1-4, the title compound as a white solid. MS (ES+) *m/z*: 314 $(M+H)^+$.

Example 480

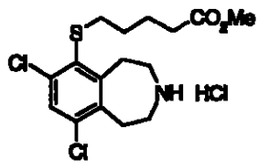
7-Chloro-6-(4-methoxycarbonyl -butylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 387 to react 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine with methyl-5-bromovalerate. Purify by preparative TLC eluting with 19:1 DCM/saturated ammonia in methanol. Use a method similar to the General Procedure 2-2 to give the title compound as a white solid. MS (APCI+) *m/z*: 328 $(M+H)^+$.

Example 481

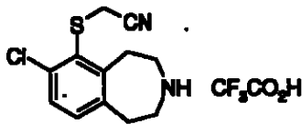
7,9-Dichloro-6-(4-methoxycarbonylbutylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Obtain the free base of the title compound as a minor product from Example 480, after preparative TLC eluting with 19:1 DCM/saturated ammonia in methanol. Use a method similar to the General Procedure 2-2 to obtain the title compound as a pale yellow solid. MS (APCI+) *m/z*: 362 $(M+H)^+$.

Example 482

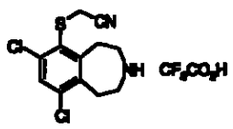
7-Chloro-6-cyanomethylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Trifluoroacetate



Use a method similar to the Example 387 to react 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine with bromoacetonitrile. Purify by preparative reverse phase HPLC (Column: Xterra Prep RP18 19x250mm; Solvent A: 10 mM aqueous ammonium carbonate, Solvent B: acetonitrile; 30-100% B over 20 minutes; flow rate 25 mL/min) to give the title compound as a white solid. MS (APCI+) *m/z*: 253 $(M+H)^+$.

Example 483

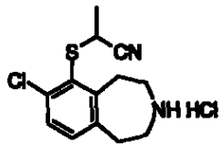
6-Cyanomethylthio-7,9-dichloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Trifluoroacetate



Obtain the title compound as a minor product from Example 482, after preparative reverse phase HPLC (Column: Xterra Prep RP18 19x250mm; solvent A: 10 mM aqueous ammonium carbonate, solvent B: acetonitrile; 30-100% B over 20 minutes; flow rate 25 mL/min). MS (APCI+) *m/z*: 287 $(M+H)^+$.

Example 484

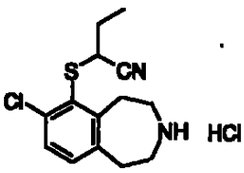
(±)-7-Chloro-6-(1-cyanoethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Preparation 177, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 2-bromopropionitrile to give, after deprotection using a method similar to the General Procedure 1-4, the title compound as a white solid. MS (ES+) *m/z*: 267 $(M+H)^+$.

Example 485

(±)-7-Chloro-6-(1-cyanopropylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

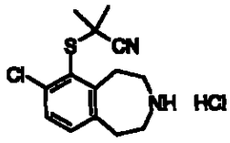


To a stirred solution of 1.5M lithium diisopropylamide in cyclohexane (1.37 mL, 2.05 mmol) in dry THF (5 mL) at –78 °C under dry nitrogen, add a solution of 3-*tert*-butoxycarbonyl-7-chloro-6-cyanomethylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]-azepine (600 mg, 1.70 mmol) in THF (5 mL) and continue stirring for 2 h. Rapidly transfer the above solution via cannula to a solution of ethyl iodide (13.2 g, 84.9 mmol) in THF (5 mL) and continue stirring for 1 h. Quench with aqueous saturated ammonium chloride solution, extract three times with EtOAc, dry over anhydrous Na_2SO_4, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to give

(±)-3-*tert*-butoxycarbonyl-7-chloro-6-(1-cyanopropylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a pale oil (350 mg, 68%). Use a method similar to the General Procedure 1-4 to give the title compound as an off-white solid. MS (ES+) *m/z*: 281 $(M+H)^+$.

Example 486

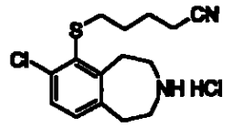
7-chloro-6-(1-cyano-1-methylethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



To a stirred solution of 3-*tert*-butoxycarbonyl-7-chloro-6-cyanomethylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]-azepine (300 mg, 0.85 mmol) in THF (5 mL) at 0°C, add potassium *tert*-butoxide (480 mg, 4.26 mmol) at ambient temperature. After 15 min, add methyl iodide (3.02 g, 21.31 mmol) and continue stirring overnight at ambient temperature. Concentrate *in vacuo* and purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to give 3-*tert*-butoxycarbonyl-7-chloro-6-(1-cyano-1-methyl-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (177 mg, 55%). MS (ES+) *m/z*: 282 $(M+H\text{-Boc})^+$. Use a method similar to the General Procedure 1-4 to give the title compound as an off-white solid. MS (ES+) *m/z*: 282 $(M+H)^+$.

Example 487

7-Chloro-6-(4-cyanobutylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

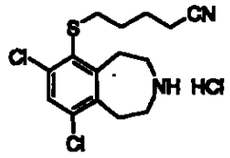


Use a method similar to the Example 387 to react 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine with 5-bromovaleronitrile. Purify by preparative reverse phase HPLC (Column: Xterra Prep RP18 19x250mm; Solvent A: 10 mM aqueous ammonium carbonate, Solvent B: acetonitrile; 30-100% B over 20 minutes; flow rate 25 mL/min). Use a method similar to

the General Procedure 2-2 to give the title compound as an off-white solid. MS (APCI+) *m/z*: 295 $(M+H)^+$.

Example 488

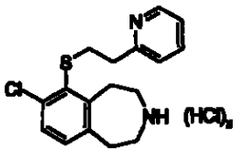
7,9-Dichloro-6-(4-cyanobutylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Obtain the free base of the title compound as a minor product from Example 487, after preparative reverse phase HPLC (Column: Xterra Prep RP18 19x250mm; Solvent A: 10 mM aqueous ammonium carbonate, Solvent B: acetonitrile; 30-100% B over 20 minutes; flow rate 25 mL/min). Use a method similar to the General Procedure 2-2 to obtain the title compound as a tan solid. MS (ES+) *m/z*: 329 $(M+H)^+$.

Example 489

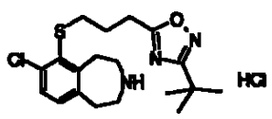
7-Chloro-6-(2-pyridin-2-yl-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Preparation 177, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 2-(2-bromoethyl)-pyridine hydrobromide to give, after deprotection using a method similar to the General Procedure 1-4, the title compound. MS (ES+) *m/z* 319 $(M+H)^+$.

Example 490

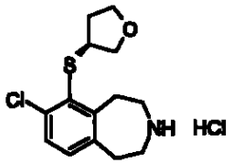
6-[3-(3-*tert*-Butyl-[1,2,4]oxadiazol-5-yl)-propylthio]-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 387, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 5-(3-bromopropyl)-3-*tert*-butyl-[1,2,4]oxadiazole to give, after deprotection using a method similar to the General Procedure 1-4, the title compound as a white solid. MS (APCI+) *m/z* 380 $(M+H)^+$.

Example 491

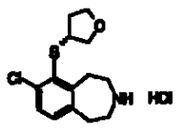
(-)-7-Chloro-6-(tetrahydrofuran-3-ylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 332, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and (*S*)-toluene-4-sulfonic acid tetrahydrofuran-3-yl ester to give, after deprotection using a method similar to the General Procedure 1-4, the title compound as an off-white solid. MS (APCI+) *m/z*: 284 $(M+H)^+$; $[\alpha]^{20}_D$ -28.0° (c 0.5, CH_3OH). ee = 97.8% [Chiral HPLC: Column: YMC ODS-AQ 120Å 4.6x50 mm [S-3μm]; eluent: gradient from 95:5 to 5:95 A/B; solvent A: water, 0.01% HFBA, 1% isopropanol; solvent B: acetonitrile, 0.01% HFBA, 1% isopropanol; flow rate 2 mL/min].

Example 492

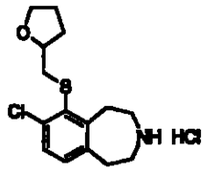
(+)-7-Chloro-6-(tetrahydrofuran-3-ylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 332, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and (*R*)-toluene-4-sulfonic acid tetrahydro-furan-3-yl ester to give, after deprotection using a method similar to the General Procedure 1-4, the title compound as an off-white solid. MS (APCI+) *m/z*: 284 (M+H); $[\alpha]^{20}_{D}$ +32.5° (c 0.5, CH_3OH); ee = 95.7% [Chiral HPLC: Column: YMC ODS-AQ 120Å 4.6x50 mm [S-3μm]; eluent: gradient from 95:5 to 5:95 A/B; solvent A: water, 0.01% HFBA, 1% isopropanol; solvent B: acetonitrile, 0.01% HFBA, 1% isopropanol; flow rate 2 mL/min].

Example 493

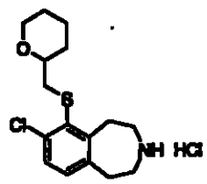
(±)-7-Chloro-6-(tetrahydrofuran-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 330, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 2-(bromomethyl)tetrahydrofuran to give, after deprotection by the General Procedure 1-4, the title compound as white crystals. MS (APCI+) *m/z*: 298 $(M+H)^+$.

Example 494

(±)-7-Chloro-6-(tetrahydropyran-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

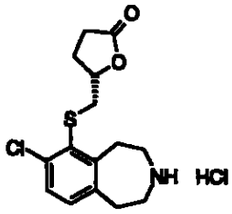


Use a method similar to the Example 330, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 2-

(bromomethyl)tetrahydropyran to give, after deprotection by the General Procedure 1-4, the title compound as a white solid. MS (APCI+) *m/z*: 312 $(M+H)^+$.

Example 495

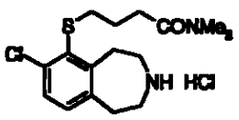
(S)-(+)-7-Chloro-6-(5-oxo-tetrahydrofuran-2-ylmethylthio)-2,3,4,5-tetrahydro-1H-benzo[d]azepine Hydrochloride



Use a method similar to the General Procedure 1-4, using (*S*)-3-*tert*-butoxycarbonyl-7-chloro-6-(5-oxo-tetrahydrofuran-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine to give the title compound as a white solid. MS (ES+) *m/z*: 312 $(M+H)^+$. $[\alpha]^{20}_D$ +78° (c 0.5, CH_3OH).

Example 496

7-Chloro-6-(3-dimethylcarbamoylpropylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



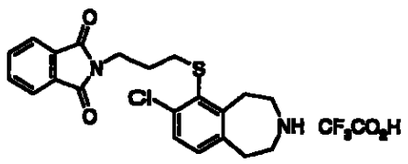
Treat a solution of 3-*tert*-butoxycarbonyl-7-chloro-6-(3-methoxycarbonyl-propylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (385 mg, 0.90 mmol) in dioxane/water (1:1, 3.5 mL) with lithium hydroxide (43.0 mg, 1.01 mmol) at 80 °C for 1.5 h. Cool to ambient temperature, add aqueous saturated ammonium chloride and brine, extract three times with ethyl ether, dry over anhydrous $MgSO_4$, and concentrate *in vacuo*. Dissolve the residue in DCM (3.5 mL) and add EDC (162 mg, 0.84 mmol), 1-hydroxybenzotriazole (91.0 mg, 0.67 mmol), triethylamine (0.20 mL, 1.35 mmol), and dimethylamine (0.700 mL, 1.35 mmol). Stir overnight at ambient temperature. Dilute with water, extract with ethyl ether, dry over anhydrous $MgSO_4$, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc/methanol

60:40:1 to give 3-*tert*-butoxycarbonyl-7-chloro-6-(3-dimethylcarbamoyl-propylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine.

Dissolve 3-*tert*-butoxycarbonyl-7-chloro-6-(3-dimethylcarbamoyl-propylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine in DCM (1 mL) at ambient temperature and add 4M hydrogen chloride in dioxane (200 μL, 0.8 mmol). Continue stirring until TLC shows consumption of starting material. Concentrate *in vacuo*, triturate the obtained solid with dry diethyl ether and dry at 50° C under high vacuum overnight to give the title compound as a hygroscopic white solid (45.0 mg, 57%). MS (ES+) *m/z*: 327 $(M+H)^+$.

Example 497

7-Chloro-6-[3-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-propylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Trifluoroacetate

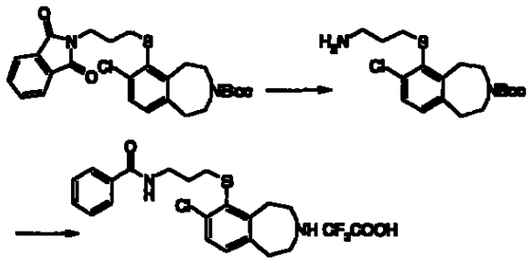


Dissolve 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (2.0 g, 5.20 mmol) in methanol (58 mL) and add potassium hydroxide (9.36 g, 167 mmol). Heat at 50 °C for 2 h. Cool to ambient temperature, add aqueous saturated ammonium chloride and water, extract three times with EtOAc, dry over anhydrous Na_2SO_4, and concentrate *in vacuo* to give 3-*tert*-butoxycarbonyl-7-chloro-6-mercapto-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.62 g, 5.20 mmol). Dissolve the crude 3-*tert*-butoxycarbonyl-7-chloro-6-mercapto-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.40 g, 4.46 mmol) in dry DMF (49.8 mL) and add DBU (0.80 mL, 5.35 mmol) and 3-bromopropyl phthalimide (1.55 g, 5.80 mmol). Stir at ambient temperature for 3 h. Add aqueous saturated ammonium chloride and water. Extract twice with EtOAc, dry over anhydrous Na_2SO_4, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (6:1) to give the free base of title compound (1.64 g, 74%).

Use a method similar to the General Procedure 1-5, to deprotect 3-*tert*-butoxycarbonyl-7-chloro-6-[3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and purify by preparative reverse phase HPLC to give the title compound. MS (APCI+) *m/z* 401 $(M+H)^+$.

Example 498

6-(3-Benzoylaminopropylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Trifluoroacetate

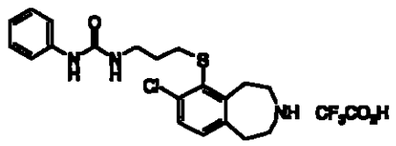


Suspend 3-*tert*-butoxycarbonyl-7-chloro-6-[3-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-propylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.20 g, 2.39 mmol) in ethanol (53.2 mL), add hydrazine (0.150 mL, 4.78 mmol) and heat at 65 °C for 2 h. Cool to ambient temperature, filter from precipitate, and concentrate *in vacuo* to provide the 6-(3-aminopropylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (861 mg, 97%). MS (APCI+) *m/z*: 371 $(M+H)^+$.

To a solution of 6-(3-aminopropylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (46.7 mg, 0.126 mmol) in dry DCM (0.5 mL) at ambient temperature under nitrogen, add triethylamine (19.3 µL, 0.139 mmol) and benzoyl chloride (16.1 µL, 0.139 mmol). Stir at ambient temperature for 2.5 h. Add aqueous saturated ammonium chloride and water, extract three times with EtOAc, dry over anhydrous Na_2SO_4, and concentrate *in vacuo*. Dissolve the residue in DCM (0.16 mL), add trifluoroacetic acid (44.6 µL, 0.58 mmol) and stir for 18 h at ambient temperature. Concentrate *in vacuo* and purify by preparative HPLC [Column: YMC ODS-AQ 120Å 20x250mm [S10-20µm]; eluent: 95:5 to 5:95 A/B; solvent A: water, 0.1% TFA, 1% isopropanol; solvent B: acetonitrile, 0.05% TFA, 1% isopropanol; flow rate 20 mL/min] to give the title compound (7.0 mg, 12%). MS (APCI+) *m/z* 375 $(M+H)^+$.

Example 499

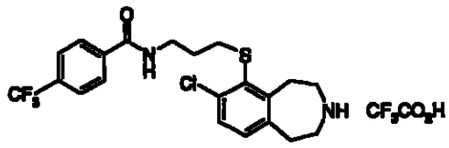
6-[3-(3-Phenylureido)-propylthio]-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Trifluoroacetate



Use a method similar to the Example 498, using phenyl isocyanate, to give the title compound. MS (APCI+) *m/z* 390 $(M+H)^+$.

Example 500

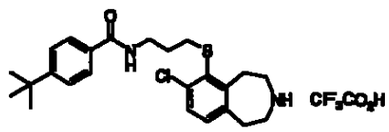
7-Chloro-6-[3-(4-trifluoromethylbenzoylamino)-propylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Trifluoroacetate



To a stirred solution of 4-trifluoromethylbenzoic acid (60.0 mg, 0.316 mmol) in anhydrous DMF (1.2 mL) at ambient temperature under nitrogen, add EDC (63.6 mg, 0.332 mmol), 1-hydroxybenzotriazole (44.8 mg, 0.332 mmol), 4-dimethylaminopyridine (40.5 mg, 0.332 mmol) and a solution of 6-(3-aminopropylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (123 mg, 0.332 mmol) in DCM (2 mL). Stir for 18 h at ambient temperature. Add water, extract twice with EtOAc, dry over anhydrous Na_2SO_4, and concentrate *in vacuo*. Treat the residue with trifluoroacetic acid (0.272 mL, 0.640 mmol) in DCM (0.451 mL) at ambient temperature for 18 h. Concentrate *in vacuo* and purify by preparative reverse phase HPLC [Column: YMC ODS-AQ 120Å 20x250mm [S10-20μm]; eluent: 95:5 to 5:95 A/B; solvent A: water, 0.1% TFA, 1% isopropanol; solvent B: acetonitrile, 0.05% TFA, 1% isopropanol; flow rate 20 mL/min] to give the title compound as a white solid (31.0 mg, 18%). MS (APCI+) *m/z* 443 $(M+H)^+$.

Example 501

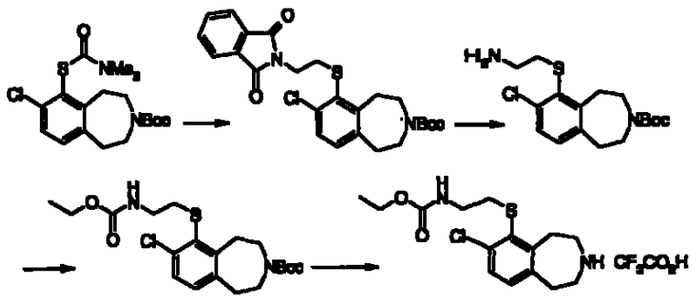
7-Chloro-6-[3-(4-*tert*-butylbenzoylamino)-propylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Trifluoroacetate



Use a method similar to the Example 500, using 6-(3-aminopropylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 4-*tert*-butyl benzoic acid to give the title compound as a white solid. MS (APCI+) *m/z* 431 $(M+H)^+$.

Example 502

7-Chloro-6-(2-ethoxycarbonylamino-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Trifluoroacetate

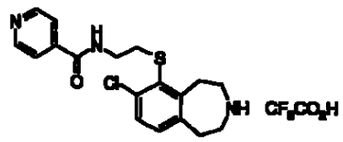


Use a method similar to the Example 497, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*- benzo[*d*]azepine and 3-bromoethyl phthalimide to give 6-(3-aminoethylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. MS (ES+) *m/z* 357 $(M+H)^+$.

Use a method similar to the Example 498, using 6-(3-aminoethylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and ethyl chloroformate to give, after deprotection using a method similar to the General Procedure 1-5, the title compound as a white solid. MS (APCI+) *m/z*: 329 $(M+H)^+$.

Example 503

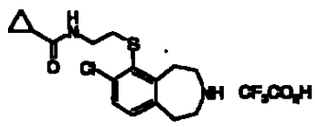
7-Chloro-6-{2-[(pyridine-4-carbonyl)amino]-ethylthio}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Trifluoroacetate



Use a method similar to the Example 500, using 6-(3-aminoethylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and isonicotinic acid to give the title compound. MS (ES+) *m/z*: 362 $(M+H)^+$.

Example 504

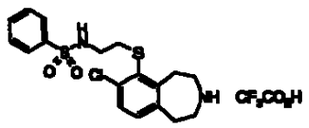
7-Chloro-6-[2-(cyclopropanecarbonylamino)-ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Trifluoroacetate



Use a method similar to the Example 498, using 6-(3-aminoethylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and cyclopropanecarbonyl chloride to give, after deprotection using a method similar to the General Procedure 1-5, the title compound. MS (ES+) *m/z*: 325 $(M+H)^+$.

Example 505

6-(2-Benzenesulfonylamino-ethylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Trifluoroacetate

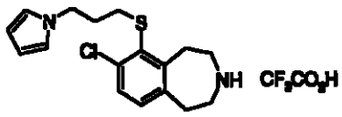


Use a method similar to the Example 498, using 6-(3-amino-ethylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and benzenesulfonyl

chloride to give, after de protection using a method similar to the General Procedure 1-5, the title compound as a white solid. MS (APCI+) *m/z*: 397 $(M+H)^+$.

Example 506

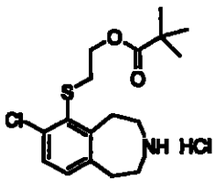
7-Chloro-6-(3-pyrrol-1-yl-propylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Trifluoroacetate



Use a method similar to the Example 497, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and *N*-(3-bromopropyl)pyrrole to give, after deprotection using a method similar to the General Procedure 1-5, the title compound as a white solid. MS (ES+) *m/z*: 321 $(M+H)^+$.

Example 507

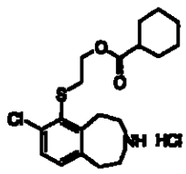
7-Chloro-6-[2-(2,2-dimethylpropionyloxy)-ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



To a stirred solution of 3-*tert*-butoxycarbonyl-7-chloro-6-(2-hydroxyethylthio)-2,3,4,5-tetrahydrobenzo[d]azepine (85 mg, 0.238 mmol) in DCM (3 ml) at 0°C, add triethylamine (331 µl, 2.381 mmol) followed by trimethylacetyl chloride (147 µl, 1.190 mmol). Continue stirring for 15 min, dilute with water, extract three times with EtOAc, dry over anhydrous Na_2SO_4, and concentrate *in vacuo*. Deprotection by the General Procedure 1-5, basic workup, and by the General Procedure 2-2 give the title compound. MS (ES+) *m/z* 342 (M+H).

Example 508

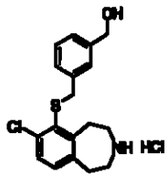
7-Chloro-6-(2-cyclohexanecarbonyloxy-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 507, using cyclohexanecarbonyl chloride, to give the title compound. MS (ES+) *m/z* 368 (M+H).

Example 509

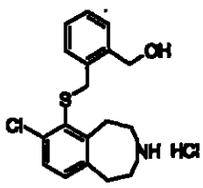
7-Chloro-6-(3-hydroxymethylbenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Preparation 242, using 3-*tert*-butoxycarbonyl-7-chloro-6-(3-hydroxymethylbenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine to give, after deprotection by the General Procedure 1-4, the title compound as a white solid. MS (ES+) *m/z*: 334 $(M+H)^+$.

Example 510

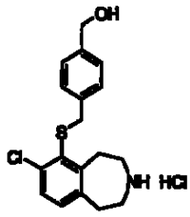
7-Chloro-6-(2-hydroxymethylbenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Preparation 242, using 3-*tert*-butoxycarbonyl-7-chloro-6-(2-hydroxymethylbenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine to give, after deprotection by the General Procedure 1-4, the title compound as a white solid. MS (ES+) *m/z*: 334 $(M+H)^+$.

Example 511

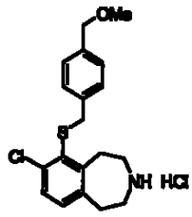
7-Chloro-6-(4-hydroxymethylbenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the General Procedure 1-4, using 3-*tert*-butoxycarbonyl-7-chloro-6-(4-hydroxymethylbenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine, to give the title compound as a white solid. MS (ES+) *m/z*: 334 $(M+H)^+$.

Example 512

7-Chloro-6-(4-methoxymethylbenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

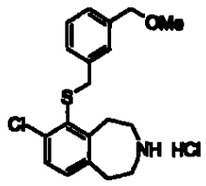


To a stirred solution of 3-*tert*-butoxycarbonyl-7-chloro-6-(4-hydroxymethyl-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (133 mg, 0.306 mmol) in anhydrous DMF (2 mL) under nitrogen, add sodium hydride (60% dispersion, 13-15 mg, 0.375 mmol) at ambient temperature and continue stirring for 30 min. Add methyl iodide (80 □L, 1.28 mmol). After 15 min, dilute with water, extract three times with EtOAc, dry over anhydrous $MgSO_4$ and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (15:1) to give 3-*tert*-butoxycarbonyl-7-chloro-6-(4-

methoxymethyl-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a clear oil, which crystallizes on standing to a white solid (87 mg, 63%), along with recovered starting material (22 mg, 17%). Use a method similar to the General Procedure 1-4 to give the title compound as a white solid. MS (ES+) *m/z*: 348 $(M+H\text{-Boc})^+$.

Example 513

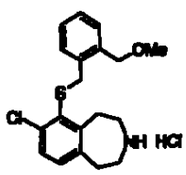
7-Chloro-6-(3-methoxymethylbenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 512, using 3-*tert*-butoxycarbonyl-7-chloro-6-(3-hydroxymethylbenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine to give the title compound as a white solid. MS (ES+) *m/z*: 348 (M+H).

Example 514

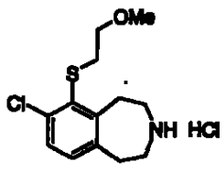
7-Chloro-6-(2-methoxymethylbenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 512, using 3-*tert*-butoxycarbonyl-7-chloro-6-(2-hydroxymethylbenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine to give the title compound as a white solid. MS (ES+) *m/z*: 348 (M+H).

Example 515

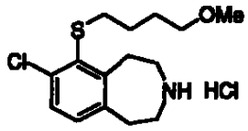
7-Chloro-6-(2-methoxyethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine hydrochloride



Use a method similar to the Example 512, using 3-*tert*-butoxycarbonyl-7-chloro-6-(2-hydroxy-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine, to give the title compound as a white solid. MS (ES+) *m/z*: 272 (M+H).

Example 516

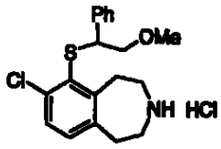
7-Chloro-6-(4-methoxybutylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine hydrochloride



Use a method similar to the Example 478, using 3-*tert*-butoxycarbonyl-7-chloro-6-(3-methoxycarbonyl-propylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine to give 3-*tert*-butoxycarbonyl-7-chloro-6-(4-hydroxybutylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Use a method similar to the Example 512, using 3-*tert*-butoxycarbonyl-7-chloro-6-(4-hydroxybutylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine to give the title compound as a white solid. MS (ES+) *m/z*: 300 $(M+H)^+$.

Example 517

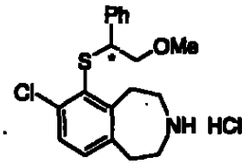
(±)-7-Chloro-6-(2-methoxy-1-phenylethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 512, using (±)-3-*tert*-butoxycarbonyl-7-chloro-6-(2-hydroxy-1-phenylethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine to give, after deprotection by a method similar to the General Procedure 1-4, the title compound as an off-white solid. MS (ES+) *m/z*: 348 $(M+H)^+$.

Example 518

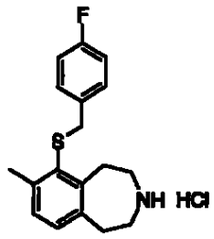
(-)-7-Chloro-6-(2-methoxy-1-phenylethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Separate the enantiomers of (±)-7-chloro-6-(2-methoxy-1-phenyl-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine by chiral normal phase chromatography (Chiralcel OJ 8x33 cm column, eluting with 0.2% DMEA in ethanol/heptane, 40:60). Collect the second eluting isomer and use the General Procedure 2-2 to give the title compound as a white solid (76 mg, 29%). MS (ES+) *m/z*: 349 $(M+H)^+$. $[\alpha]^{20}_D$ -176° (c 0.5, CH_3OH).

Example 519

6-(4-Fluorobenzylthio)-7-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

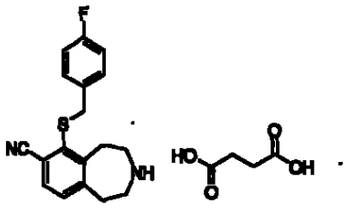


Use a method similar to the General Procedure 7, using 3-*tert*-butoxycarbonyl-6-dimethylcarbamoylthio-7-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (75 mg, 0.206 mmol) and 4-fluorobenzyl bromide (195 mg, 1.03 mmol) to give, after chromatography on silica gel eluting with hexane/EtOAc (1:0, 9:1 and 4:1), 3-*tert*-butoxycarbonyl-6-(4-fluorobenzylthio)-7-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (59 mg, 71%). MS (ES+) *m/z*: 302 $(M+H\text{-Boc})^+$.

Use a method similar to the General Procedure 1-4, using 3-*tert*-butoxycarbonyl-6-(4-fluoro-benzylthio)-7-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (55 mg, 0.137 mmol) to give the title compound as a white solid (42 mg, 91%). MS (ES+) *m/z*: 285 $(M+H)^+$.

Example 520

7-Cyano-6-(4-fluorobenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



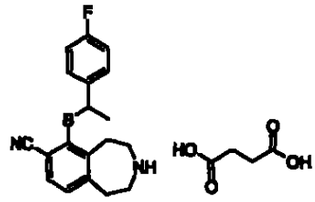
Use a method similar to the General Procedure 7, using 3-*tert*-butoxycarbonyl-7-cyano-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (123 mg, 0.33 mmol) and 4-fluorobenzyl bromide (204 mg, 1.64 mmol), to give 3-*tert*-butoxycarbonyl-7-cyano-6-(4-fluoro-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a colorless oil (118 mg, 87%).

Use a method similar to the General Procedure 1-4, using 3-*tert*-butoxycarbonyl-7-cyano-6-(4-fluoro-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (118 mg, 0.286

mmol) to give, after basic work-up, the free base of the title compound (89 mg, 100%). MS (ES+) *m/z* 313 $(M+H)^+$. Use a method similar to the General Procedure 2-1 to give the title compound (123 mg, 100%). MS (ES+) *m/z* 313 $(M+H)^+$.

Example 521

(±)-7-Cyano-6-[1-(4-fluorophenyl)ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

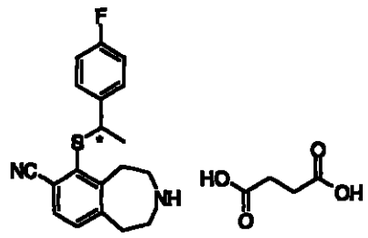


Use a method similar to the General Procedure 7, using 3-*tert*-butoxycarbonyl-7-cyano-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (171 mg, 0.46 mmol) and (±)-1-(4-fluorophenyl)ethyl bromide (377 mg, 1.85 mmol) to give, after purification by chromatography on silica gel, (±)-3-*tert*-butoxycarbonyl-7-cyano-6-[1-(4-fluorophenyl)-ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a colorless oil (10.3 mg, 5.3%). MS (ES+) *m/z* 449 $(M+Na)^+$, 465 $(M+K)^+$.

Use a method similar to the General Procedure 1-5, using (±)-3-*tert*-butoxycarbonyl-7-cyano-6-[1-(4-fluorophenyl)ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (10.3 mg, 0.024 mmol) to give, after basic work-up, the free base of the title compound (6.8 mg, 87%). MS (ES+) *m/z* 327 $(M+H)^+$. Use a method similar to the General Procedure 2-1 to give the title compound as a white solid (9.3 mg, 87%). MS (ES+) *m/z* 327 $(M+H)^+$.

Example 522

7-Cyano-6-[1-(4-fluorophenyl)ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate, Isomer 1

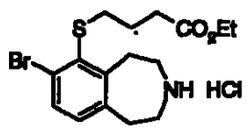


Separate the two enantiomers of (±)-7-cyano-6-[1-(4-fluorophenyl)ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine by chiral HPLC (Chiralpak AD-H 15cm x 4.6mm column with a 5 μm packing size. Elute with heptane/ethanol (95:5) containing 0.2% DEA at 0.5 mL/min with an injection volume of 10.00 μL).

Subject the first eluting isomer (t_R = 17.2 min, ee > 99%) to the General Procedure 2-1 to afford the title compound as a white solid. MS (ES+) *m/z* 327 $(M+H)^+$.

Example 523

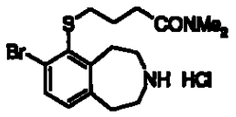
7-Bromo-6-(3-ethoxycarbonylpropylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Preparation 177, using 3-*tert*-butoxycarbonyl-7-bromo-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and ethyl 4-bromobutyrate to give, after deprotection by a method similar to the General Procedure 1-4, the title compound. MS (ES+) *m/z*: 374 $(M+H)^+$.

Example 524

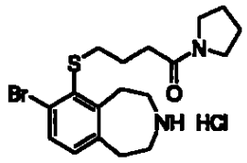
7-Bromo-6-(3-dimethylcarbamoylpropylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 523, using 7-bromo-3-*tert*-butoxycarbonyl-6-(3-ethoxycarbonylpropylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine, to give the title compound as a white solid. MS (ES+) *m/z*: 373 $(M+H)^+$.

Example 525

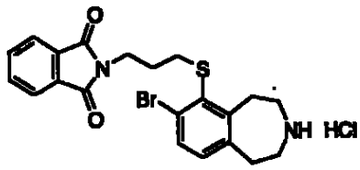
7-Bromo-6-(4-oxo-4-pyrrolidin-1-yl-butylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 523, using 7-bromo-3-*tert*-butoxycarbonyl-6-(3-ethoxycarbonylpropylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and pyrrolidine to give the title compound. MS (ES+) *m/z*: 397 $(M+H)^+$.

Example 526

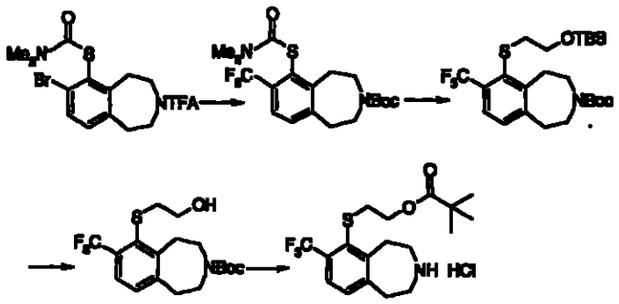
7-Bromo-6-[3-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-propylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 497 to react 7-bromo-3-*tert*-butoxycarbonyl-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine with 3-bromopropyl phthalimide. Use a method similar to the General Procedure 1-4 to give the title compound as a white solid. MS (ES+) *m/z* 445 $(M+H)^+$.

Example 527

6-[2-(2,2-Dimethylpropionyloxy)-ethylthio]-7-trifluoromethyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



3-*tert*-Butoxycarbonyl-6-dimethylcarbamoylthio-7-trifluoromethyl-2,3,4,5-tetrahydro-benzo[*d*]azepine: To a stirred solution of 7-bromo-6-dimethylcarbamoylthio-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.383 g, 3.254 mmol), in NMP (40 ml) add sodium trifluoromethyl acetate (3.54 g, 26.03 mmol), copper(I) iodide (2.47 g, 13.0 mmol) and heat the mixture at 180 °C for 4 h. Cool to ambient temperature. Dilute with EtOAc, water and remove the copper solid residue by filtration. Separate the layers of filtrate and extract the aqueous layer three times with EtOAc. Dry over anhydrous Na_2SO_4, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (6:1) to give the desired intermediate as a yellow oil (882 mg, 74%).

3-*tert*-Butoxycarbonyl-6-[2-(*tert*-butyl-dimethylsilanyloxy)ethylthio]-7-trifluoromethyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Use a method similar to the Preparation 177, using 3-*tert*-butoxycarbonyl-6-dimethylcarbamoylthio-7-trifluoromethyl-2,3,4,5-tetrahydro-benzo[*d*]azepine and (2-bromoethoxy)-*tert*-butyldimethylsilane to give the desired intermediate.

3-*tert*-Butoxycarbonyl-6-(2-hydroxyethylthio)-7-trifluoromethyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Dissolve 6-[2-(*tert*-butyl-dimethyl-silanyloxy)-ethylthio]-7-trifluoromethyl-2,3,4,5-tetrahydro-1*H* -benzo[*d*]azepine (153 mg, 0.303 mmol) in THF (3 mL). Add 1.0 M tetrabutylammonium fluoride in THF (600 µL, 0.606 mmol,) and stir

overnight. Dilute with water, extract three times with EtOAc, dry over anhydrous Na_2SO_4, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (85:15) to give the desired intermediate.

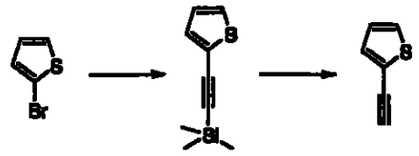
6-[2-(2,2-Dimethylpropionyloxy)-ethylthio]-7-trifluoromethyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine hydrochloride: Use a method similar to the Example 507, using 3-*tert*-butoxycarbonyl-6-(2-hydroxyethylthio)-7-trifluoromethyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine to give, after deprotection using a method similar to the General Procedure 1-4, the title compound as a white solid. MS (ES+) *m/z*: 376 $(M+H)^+$.

General Procedure 8

Dissolve the appropriate bromide (2 equiv.) in isopropylamine (300-400 equiv.) at room temperature, under nitrogen, then add palladium(II) bis(benzonitrile) dichloride (0.2 equiv.), triphenylphoshine (0.4 equiv.) and copper(I) iodide (0.2 equiv.). Degas the solution and purge with nitrogen, then add the appropriate alkyne (1.0 equiv.). Seal the reaction vessel, stir at room temperature for 30 min, then at 75 °C for 3-4 h. Remove most of the solvent *in vacuo*, add diethyl ether and 2M aqueous HCl. Dry the organic layer over $MgSO_4$, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with isohexane/EtOAc or hexane/EtOAc mixtures.

Preparation 249

2-Ethynyl-thiophene

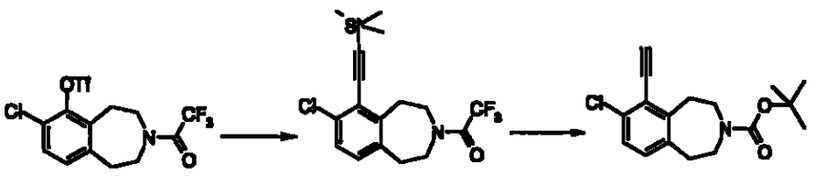


Trimethyl-thiophen-2-ylethynyl-silane: Use a method similar to the General Procedure 8 to couple 2-bromo-thiophene (0.97 mL, 10 mmol) with ethynyl-trimethylsilane (2.82 mL, 20 mmol). Purify by chromatography on silica gel eluting with isohexane to give the desired intermediate (1.46 g, 81%). GC-MS *m/z* 180 (M^+).

2-Ethynyl-thiophene: Add a saturated solution of potassium carbonate in methanol (7.5 mL) to trimethyl-thiophen-2-ylethynyl-silane (540 mg, 3 mmol) in deoxygenated methanol (100 mL) at room temperature under nitrogen. Stir the reaction for 3.5 h, then dilute with dichloromethane (100 mL) and wash with water (3 x 100 mL). Remove the organic layer, dry using an ISCO® phase separator and then concentrate *in vacuo* to give the title compound (302 mg, 93%).

Preparation 250

3-*tert*-Butoxycarbonyl-7-chloro-6-ethynyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine



7-Chloro-3-(2,2,2-trifluoroacetyl)-6-trimethylsilanylethynyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Use a method similar to the General Procedure 3 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (425 mg, 1 mmol) with 2-trimethylsilylacetylene (0.28 mL, 2 mmol). Purify by chromatography on silica gel eluting with isohexane/EtOAc (100:0 to 85:15 gradient over 40 min) to give the desired intermediate (247 mg, 81%). MS (ES+) *m/z*: 306 $(M+H)^+$.

3-*tert*-Butoxycarbonyl-7-chloro-6-ethynyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Add a solution of potassium carbonate (999 mg, 7.2 mmol) in water (5 mL) to 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trimethylsilanylethynyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (180 mg, 0.48 mmol) in methanol (10 mL) and stir at room temperature, under nitrogen for 1.5 h. Add di-*tert*-butyl-dicarbonate (115 mg, 0.53 mmol) in dichloromethane (8 mL) and stir for 3 days. Add another solution of di-*tert*-butyl-dicarbonate (115 mg, 0.53 mmol) in dichloromethane (5 mL) and stir for 2 h. Add water (10 mL) and dichloromethane (10 mL) and separate the organic layer. Extract the aqueous layer with dichloromethane (3 x 10 mL) and combine the organic layers. Dry using an ISCO® phase separator and concentrate. Purify by chromatography on silica gel eluting with

isohexane/EtOAc (1:0 to 4:1 gradient over 30 min) to give the title compound as a solid (150 mg, 100%). MS (ES+) *m/z*: 328 $(M+Na)^+$.

Preparation 251

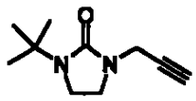
2-Chloro-pyridazine



Add 3(2*H*)-pyridazinone (2 g, 22 mmol) to neat phosphorus oxycloride (4 mL) in a sealed tube and heat the mixture at 80 °C with stirring for 2 h. Add caustiously water (10 mL), saturated aqueous $NaHCO_3$ (50 mL) and solid Na_2CO_3 until pH= 9. Extract the mixture with dichloromethane (4 x 50 mL). Dry the organic layer over Na_2SO_4, filtrate and concentrate *in vacuo* to give the title compound as brown oil (2 g, 84%).

Preparation 252

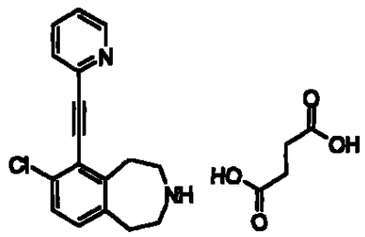
1-*tert*-Butyl-3-prop-2-ynyl-imidazolidin-2-one



Dissolve 1-*tert*-butyl-imidazolidin-2-one (2 g, 14 mmol) in anhydrous THF (60 mL) and cool at –78 °C. Slowly add *n*-butyllithium (6.8 mL, 17 mmol, 2.5 M solution in hexanes). Stir the solution for 30 min. Rapidly add propargyl bromide (3.2 mL, 28.2 mmol, 80% solution in toluene). Warm the solution to room temperature while stirring overnight. Concentrate the reaction mixture *in vacuo* and filter the residue on a short pad of silica gel eluting with dichloromethane/diethyl ether (1:1) to give the title compound as a yellow oil that solidifies on standing (1.77 g, 70%). GC-MS *m/z* (%) 180 (M^+, 7), 165 (100), 123 (12), 84 (17).

Example 528

7-Chloro-6-pyridin-2-ylethynyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

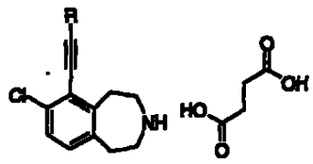


Use a method similar to the General Procedure 3 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (425 mg, 1 mmol) with 2-ethynyl-pyridine (0.20 mL, 2 mmol). Purify by chromatography on silica gel eluting with isohexane/EtOAc (1:0 to 1:1 gradient over 40 min) to give 7-chloro-6-pyridin-2-ylethynyl-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (342 mg, 90%). MS (ES+) *m/z*: 379 $(M+H)^+$.

Use a method similar to the General Procedure 1-2 to deprotect 7-chloro-6-pyridin-2-ylethynyl-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (60 mg, 0.159 mmol). Purify by SCX chromatography to give the free base of the title compound (33 mg, 73%). MS (ES+) *m/z*: 283 $(M+H)^+$. Use a method similar to the General Procedure 2-1 to give the title compound as a light brown solid (45 mg, 95%). MS (ES+) *m/z*: 283 $(M+H)^+$.

Examples 529-531

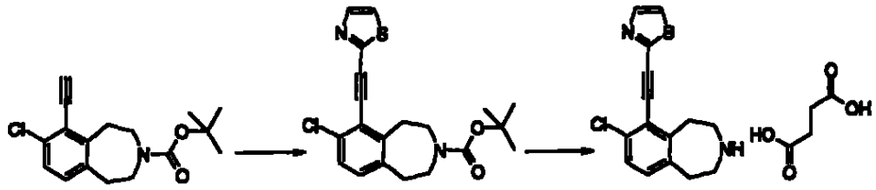
Examples 529-531 may be prepared essentially as described in Example 528 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate alkyne. Overall yields and MS (ES+) data are shown in the Table below.



Ex.	R	Compound	Yield (%)	MS (ES+) *m/z*	
529	3-Pyridyl	7-Chloro-6-pyridin-3-ylethynyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	78	283 $(M+H)^+$	
530	4-Pyridyl	7-Chloro-6-pyridin-4-ylethynyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	84	283 $(M+H)^+$	
531	2-Thiophenyl	7-Chloro-6-thiophen-2-ylethynyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	95	288 $(M+H)^+$	

Example 532

7-Chloro-6-thiazol-2-ylethynyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

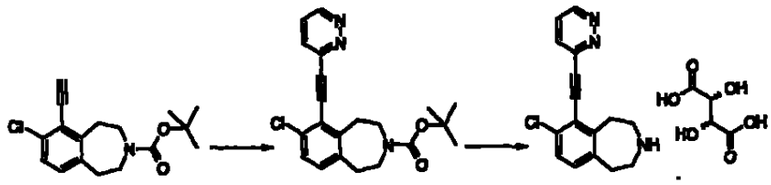


3-*tert*-Butoxycarbonyl-7-chloro-6-(thiazol-2-ylethynyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Use a method similar to the General Procedure 8 to couple 2-bromo-thiazole (0.09 mL, 0.96 mmol) with 3-*tert*-butoxycarbonyl-7-chloro-6-ethynyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (148mg, 0.48mmol). Purify by chromatography on silica gel eluting with isohexane/EtOAc (1:0 to 4:1 gradient over 30 min) to give the desired intermediate (165 mg, 89%). MS (ES+) *m/z*: 389 $(M+H)^+$.

7-Chloro-6-(thiazol-2-ylethynyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate: Use a method similar to the General Procedure 1-5 to deprotect 3-*tert*-butoxycarbonyl-7-chloro-6-(thiazol-2-ylethynyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (140 mg, 0.36 mmol). Elute through SCX column to give the free base of the title compound (89 mg, 86%). MS (ES+) *m/z*: 289 $(M+H)^+$. Use a method similar to the General Procedure 2-1 to give the title compound as a light yellow solid (125 mg, 86%). MS (ES+) *m/z*: 289 $(M+H)^+$.

Example 533

7-Chloro-6-pyridazin-3-ylethynyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate

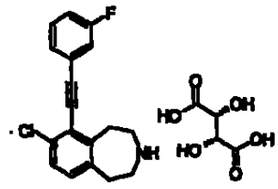


3-*tert*-Butoxycarbonyl-7-chloro-6-pyridazin-3-ylethynyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Use a method similar to the General Procedure 8 to couple 2-chloro-pyridazine (98 mg, 0.86 mmol) with 3-*tert*-butoxycarbonyl-7-chloro-6-ethynyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (104 mg, 0.34 mmol). Purify by chromatography on silica gel eluting with isohexane/EtOAc (1:0 to 4:1 gradient over 30 min) to give 3-*tert*-butoxycarbonyl-7-chloro-6-pyridazin-2-ylethynyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (26 mg, 10 %). MS (ES+) *m/z*: 384 $(M+H)^+$.

7-Chloro-6-pyridazin-3-ylethynyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-tartrate: Use a method similar to the General Procedure 1-5 to deprotect 3-*tert*-butoxycarbonyl-7-chloro-6-pyridazin-2-ylethynyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Use a method similar to the General Procedure 2-6 to give the title compound as a solid (15 mg, 51%). MS (ES+) *m/z*: 284 $(M+H)^+$.

Example 534

7-Chloro-6-(3-fluoro-phenylethynyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate



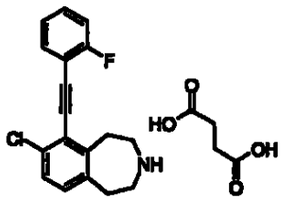
Use a method similar to the General Procedure 3 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (425 mg, 1 mmol) with (3-fluorophenyl)-ethyne (241 mg, 2 mmol). Purify by chromatography on silica gel eluting with isohexane/EtOAc (1:0 to 1:1 gradient over 40

min) to give 7-chloro-6-(3-fluoro-phenylethynyl)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (247 mg, 64%). MS (ES+) *m/z*: 396 $(M+H)^+$.

Use a method similar to the General Procedure 1-1 to deprotect 7-chloro-6-(3-fluoro-phenylethynyl)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (68 mg, 0.18 mmol). Purify by SCX chromatography to give the free base of the title compound (46 mg, 85%). MS (ES+) *m/z*: 300 $(M+H)^+$. Use a method similar to the General Procedure 2-6 to give the title compound as a white solid (61 mg, 94%). MS (ES+) *m/z*: 300 $(M+H)^+$.

Example 535

7-Chloro-6-(2-fluoro–phenylethynyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

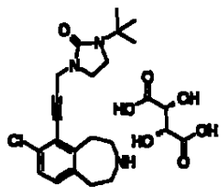


Use a method similar to the General Procedure 3 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (425 mg, 1 mmol) with (2-fluorophenyl)-ethyne (241 mg, 2 mmol). Purify by chromatography on silica gel eluting with isohexane/EtOAc (1:0 to 1:1 gradient over 40 min) to give 7-chloro-6-(2-fluoro-phenylethynyl)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (262 mg, 68%). MS (ES+) *m/z*: 396 $(M+H)^+$.

Use methods similar to the General Procedures 1-1 and 2-1 to give the title compound as a white solid (93%). MS (ES+) *m/z*: 300 $(M+H)^+$.

Example 536

6-[3-(3-*tert*-Butyl-2-oxo-imidazolidin-1-yl)-prop-1-ynyl]-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate

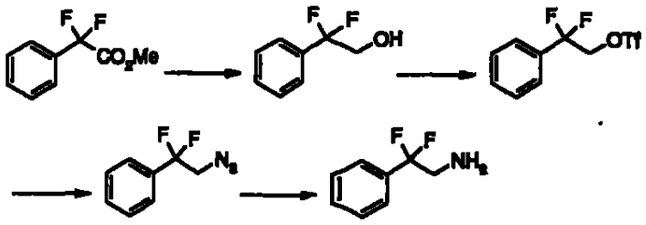


Use a method similar to the General Procedure 3 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (425 mg, 1 mmol) with 1-*tert*-butyl-3-prop-2-ynyl-imidazolidin-2-one (360 mg, 2 mmol). Purify by chromatography on silica gel eluting with isohexane/EtOAc (19:1 to 3:2 gradient) to give 6-[3-(3-*tert*-butyl-2-oxo-imidazolidin-1-yl)-prop-1-ynyl]-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (380 mg, 83%) as a yellow oil. LC-MS (ES+) *m/z*: 478 $(M+Na)^+$, 456 $(M+H)^+$, t_R = 4.43 min.

Use a method similar to the General Procedure 1-1, but adding water (10 mL) to the ammonia/methanol solution (20 mL, 7N solution), to deprotect 6-[3-(3-*tert*-butyl-2-oxo-imidazolidin-1-yl)-prop-1-ynyl]-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (329 mg, 0.72 mmol) and give the free base of the title compound (217 mg, 84%). Use a method similar to the General Procedure 2-6 to give the title compound as a solid (211 mg, 58% overall yield). LC-MS (ES+) *m/z*: 360 $(M+H)^+$, t_R = 4.54 min.

Preparation 253

2,2-Difluoro-2-phenyl-ethylamine



2,2-Difluoro-2-phenyl-ethanol: Add lithium aluminum hydride (5.18 mL, 5.18 mmol, 1M solution in THF) to a solution of methyl difluorophenylethanoate (0.964 g, 5.18 mmol, prepared by following the procedure described in *J. Org. Chem.* 1995, *60*, 5174-5179) in anhydrous THF (10 mL) at 0 °C. Stir the mixture at room temperature for 45 min. Cool to 0 °C and quench with EtOAc and then water. Separate the organic phase and extract twice the aqueous phase with EtOAc. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo* to provide the desired intermediate (0.8 g, 98%) that was used without any further purification.

2,2-Difluoro-2-phenyl-ethyl trifluoromethanesulfonate: Add triflic anhydride (1.28 mL, 2.14 g) dropwise to a stirred solution of 2,2-difluoro-2-phenyl-ethanol (0.8 g, 5.06 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (1.556 g, 7.59 mmol) in anhydrous dichloromethane (25 mL) at -78 °C. Stir the reaction overnight while the temperature warms up. Dilute the mixture with pentane and filter the precipitate over Celite®. Concentrate the filtrate *in vacuo* and purify the crude mixture by chromatography on silica gel eluting with hexane and hexane/EtOAc (95:5) to provide the title compound (946 mg, 64%).

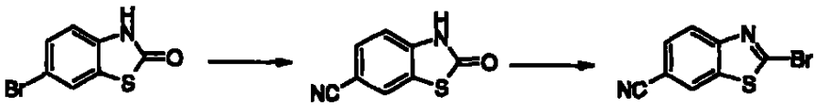
(2-Azido-1,1-difluoro-ethyl)-benzene: Heat at 60 °C a solution of 2,2-difluoro-2-phenyl-ethyl trifluoromethanesulfonate (759 mg, 2.617 mmol) and sodium azide (357 mg, 5.496 mmol) in anhydrous DMF (10 mL) under nitrogen for 3 h. Cool the reaction mixture to room temperature. Dilute with water and extract the aqueous phase twice with

diethyl ether. Wash the combined organic extracts twice with ice-cold water, dry over Na_2SO_4, filter and concentrate *in vacuo* to provide the desired intermediate as an oil (475 mg, 99%) that was used without any further purification.

2,2-Difluoro-2-phenyl-ethylamine: Dissolve (2-azido-1,1-difluoro-ethyl)-benzene (475 mg, 2.59 mmol) in EtOAc (30 mL). Add 10% Pd/C and submit the mixture to hydrogenation under atmospheric pressure (balloon) for 1 h. Filter the catalyst through Celite® and concentrate the filtrate *in vacuo* to provide the title compound as an oil (400 mg, 98%) that was used without any further purification.

Preparation 254

2-Bromo-benzothiazole-6-carbonitrile

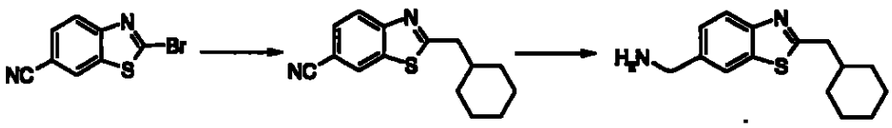


2-Oxo-2,3-dihydro-benzothiazole-6-carbonitrile: Combine 6-bromobenzothiazolinone (2 g, 8.69 mmol), copper cyanide (1.3 g, 1.48 mmol), anhydrous DMF (5 mL) and heat at reflux for 15 h. Add water (20 mL) and sodium cyanide (1.4 g, 27.7 mmol) at 100 °C. Cool the reaction mixture to room temperature and stir for 2 h. Extract the reaction mixture with EtOAc (5 x 30 mL) at 70 °C. Combine the organic layers, wash with water (3 x 40 mL) and dry over anhydrous Na_2SO_4. Concentrate *in vacuo* to obtain the desired intermediate as a yellow solid (2 g, 87%). GC-MS *m/z*: 176 (M^+).

2-Bromo-benzothiazole-6-carbonitrile: Combine 2-oxo-2,3-dihydro-benzothiazole-6-carbonitrile (1.1 g, 6.24 mmol), tetrabutylammonium bromide (3 g, 9.36 mmol), phosphorus pentoxide (2.7 g, 18.7 mmol), anhydrous toluene (40 mL) and heat at reflux for 2.5 h. Cool the reaction mixture to room temperature. Decant the toluene layer and wash with saturated aqueous $NaHCO_3$ (3 x 10 mL). Concentrate the organic phase *in vacuo* and purify the residue by chromatography on silica gel eluting with hexane/EtOAc (1:0 to 4:1 gradient) to obtain the title compound as a colorless oil (0.9 g, 61%). GC-MS *m/z*: 239 (M^+).

Preparation 255

6-Aminomethyl-2-cyclohexylmethyl-benzothiazole

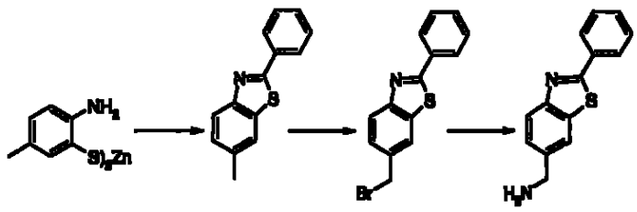


2-Cyclohexylmethyl-benzothiazole-6-carbonitrile: Place 2-bromo-benzothiazole-6-carbonitrile (0.2 g, 0.96 mmol), anhydrous THF (3 mL), 1-methyl-2-pyrrolidinone (3 mL), tetrabutylammonium iodide (1.1 g, 2.89 mmol), tris(dibenzylideneacetone)dipalladium(0) (18 mg, 0.09 mmol) and [1,1'-bis(diphenylphosphino)ferrocine]dichloropalladium (II) (11 mg, 0.09 mmol) in a flask. Add 0.5M cyclohexylmethylzinc bromide in THF (3.8 mL, 1.92 mmol) to the mixture, degas 3 times by partially evacuating the atmosphere and flushing with nitrogen and stir the reaction mixture at 80 °C for 2 h. Cool the reaction mixture to room temperature, dilute with EtOAc (10 mL) and wash with brine (10 mL). Dry the organic layer over anhydrous Na_2SO_4, filter and concentrate *in vacuo*. Purify the residue by chromatography on silica gel eluting sequentially with hexane/EtOAc (1:0 to 4:1 gradient) to obtain the desired intermediate as a yellow solid (140 mg, 57%). GC-MS *m/z*: 256 (M^+).

6-Aminomethyl-2-cyclohexylmethyl-benzothiazole: Dissolve 2-cyclohexylmethyl-benzothiazole-6-carbonitrile (0.2 g, 0.55 mmol) in anhydrous THF (2 mL) and add slowly 1M lithium aluminum hydride in THF (0.82 mL, 0.82 mmol) at room temperature. Stir the reaction mixture at room temperature for 0.5 h. Quench the reaction mixture with water until a granular precipitate starts to form and filter through a pad of Celite®. Evaporate the solvent and purify the residue by SCX chromatography to obtain the title compound as a yellow oil (0.1 g, 92%). MS (ES+) *m/z*: 260 $(M+H)^+$.

Preparation 256

6-Aminomethyl-2-phenyl-benzothiazole



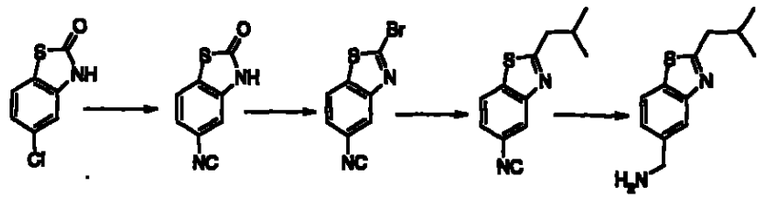
6-Methyl-2-phenyl-benzothiazole: Heat at reflux a mixture of 2-amino-5-methyl-benzenethiol zinc salt (13.5 g, 24.9 mmol, prepared by following the procedure described in *Helv. Chim. Acta* 1974, *57*, 2664) and ethyl benzimidate hydrochloride (9.23 g, 49.7 mmol) in methanol (240 mL) for 9 h. Filter the mixture, evaporate the filtrate and purify the residue by chromatography on silica gel eluting with hexane/EtOAc (100:0 to 85:15 gradient) to obtain the desired intermediate (5.7 g, 51%). MS (EI) *m/z*: 225 (M^+).

6-Bromomethyl-2-phenyl-benzothiazole: Heat 5-methyl-2-phenyl-benzothiazole (5.7 g, 25.3 mmol) and NBS (4.73 g, 26.6 mmol) in carbon tetrachloride (140 mL) at 80 °C for 3 h. Cool the mixture, double the volume with dichloromethane, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane/EtOAc (1:0 to 7:3 gradient) to obtain the desired intermediate (3.1 g, 40%). MS (EI) *m/z*: 303, 305 (M^+).

6-Aminomethyl-2-phenyl-benzothiazole: Add 6-bromomethyl-2-phenyl-benzothiazole (2 g, 6.57 mmol) as a suspension in methanol (100 mL) to 7M ammonia in methanol (400 mL) at 0 °C over 10 min and then stir for 3 h at room temperature. Concentrate *in vacuo* and purify the crude mixture by chromatography on silica gel eluting with dichloromethane/methanol (1:0 to 3:1) to obtain the title compound (1.2 g, 76%). MS (ES+) *m/z*: 241 ($M+H^+$).

Preparation 257

5-Aminomethyl-2-isobutyl-benzothiazole



2-Oxo-2,3-dihydro-benzothiazole-5-carbonitrile: Heat a mixture of 5-chloro-3*H*-benzothiazol-2-one (9.3 g, 50 mmol), nickel(II) bromide (10.9 g, 50 mmol) and sodium cyanide (4.91 g, 100 mmol) in 1-methyl-pyrrolidinone (100 mL) in a microwave reactor to 200 °C over 15 min and hold 1 h. Filter the cooled mixture through a glass frit, add diethyl ether and brine and filter again. Wash the organic phase with brine three times and concentrate *in vacuo*. Pass the residue through a plug of silica gel eluting with hexane/EtOAc (2:1) and then dichloromethane/methanol (9:1) to obtain the desired intermediate (3.2 g, 36%). MS (ES+) *m/z*: 177 $(M+H)^+$.

2-Bromo-benzothiazole-5-carbonitrile: Heat 2-oxo-2,3-dihydro-benzothiazole-5-carbonitrile (3.2 g, 18.2 mmol) in toluene (120 mL) with tetrabutylammonium bromide (8.78 g, 27.2 mmol) and phosphorus pentoxide (7.73 g, 54.5 mmol) for 3 h at reflux. Cool the mixture, decant the solution from the reaction residue and partition between diethyl ether and brine. Add water and dichloromethane to the reaction residue and reflux for 20 min. Wash the dichloromethane layer with saturated aqueous $NaHCO_3$ and brine, and combine with the ether washing. Dry the organic mixture over Na_2SO_4 and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane/EtOAc (1:0 to 3:7 gradient) to give the desired intermediate (0.85 g, 20%). MS (EI) *m/z*: 238, 240 (M^+).

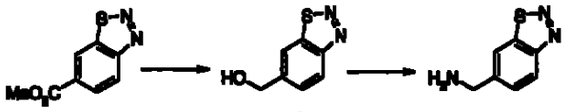
2-Isobutyl-benzothiazole-5-carbonitrile: Heat 2-bromo-benzothiazole-5-carbonitrile (0.3 g, 1.26 mmol) in 1-methyl-pyrrolidinone (4.2 mL) with 2-methylpropylzinc bromide (5 mL, 2.5 mmol, 0.5M solution in THF), N-methylimidazole (0.15 g, 1.88 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (1:1) (20.5 mg, 0.025 mmol) at 80 °C for 3 h. Cool the mixture and partition between diethyl ether and brine. Dry the organic layer over Na_2SO_4 and

concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane/EtOAc (1:0 to 1:1 gradient) to give the desired intermediate (113 mg, 42%). MS (EI) *m/z*: 216 (M^+).

5-Aminomethyl-2-isobutyl-benzothiazole: Add lithium aluminum hydride (0.78 mL, 0.78 mmol, 1M solution in THF) to 2-isobuty-benzothiazole-5-carbonitrile (113 mg, 0.52 mmol) in THF (5 mL) and stir for 4 h at room temperature. Add water (0.27 mL), 2N sodium hydroxide (0.27 mL) and water (0.37 mL). Filter the precipitate and wash the filtrate with brine. Dry over Na_2SO_4 and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane/EtOAc (1:1) and then 1*M* ammonia in methanol/dichloromethane (1:9). Purify the polar fraction by SCX chromatography to give the title compound (63 mg, 55%). MS (ES+) *m/z*: 221 ($M+H^+$).

Preparation 258

6-Aminomethyl-benzo[1,2,3]thiadiazole

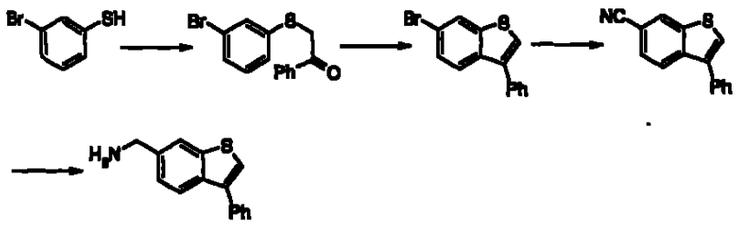


6-Hydroxymethyl-benzo[1,2,3]thiadiazole: Add sodium borohydride (1.35 g, 36 mmol) in five portions over 4 h to a solution of benzo[1,2,3]thiadiazole-6-carboxylic acid methyl ester (0.35 g, 1.8 mmol, prepared by following the procedure described in *J. Heterocyclic Chem.* 1972, 1149) in methanol (18 mL) at 0 °C. Add acetone to quench and evaporate the mixture onto silica gel. Purify the residue by chromatography on silica gel eluting with hexane/EtOAc (1:0 to 2:3 gradient) to give the desired intermediate (133 mg, 45%). MS (GCMS) *m/z*: 166 M^+.

6-Aminomethyl-benzo[1,2,3]thiadiazole: Stir 6-hydroxymethyl-benzo[1,2,3]thiadiazole (133 mg, 0.8 mmol) in thionylchloride (5 mL) for 3 h at room temperature. Evaporate the mixture then add 7M ammonia in methanol (10 mL) and stir at room temperature in a sealed tube for 48 h. Evaporate the mixture and purify the residue by SCX chromatography to give the title compound (115 mg, 87%). MS (ES+) *m/z*: 166 $(M+H)^+$.

Preparation 259

6-Aminomethyl-3-phenyl-benzothiophene



2-(3-Bromo-phenylthio)-1-phenyl-ethanone: Add potassium hydroxide (4.89 g, 87.3 mmol) and 2-bromoacetophenone (15.8 g, 79.3 mmol) to a solution of 3-bromobenzenethiol (15 g, 79.3 mmol) in ethanol (200 mL, 70% in water) at 0 °C. After stirring 16 h, add water to precipitate a yellow solid. Filter to obtain the desired intermediate (24.6 g, 100%).

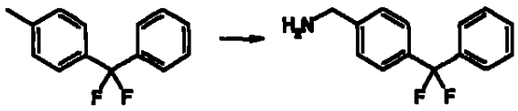
6-Bromo-3-phenylbenzothiophene: Heat 2-(3-bromo-phenylthio)-1-phenyl-ethanone (4 g, 13 mmol) in polyphosphoric acid (4 g) at 80 °C for 4 h. Add EtOAc and water to the mixture and wash with saturated aqueous $NaHCO_3$ and brine. Dry the organic layer over Na_2SO_4, filter and concentrate *in vacuo*. Slurry the residue in hexane and purify by chromatography on silica gel eluting with hexane to give the desired intermediate that is used without further purification (2.7 g, 72%). MS (GCMS) *m/z*: 289 M^+.

6-Cyano-3-phenylbenzothiophene: Combine 6-bromo-3-phenylbenzothiophene (0.5 g, 1.73 mmol) and copper cyanide (0.56 g, 6.23 mmol) and reflux 3 h in 1-methyl-2-pyrrolidinone (1.73 mL). Add ferric chloride (2.11 g, 7.79 mmol) in concentrated HCl (1.73 mL) and stir 1.5 h. Cool the mixture and partition between diethyl ether and brine. Dry the organic layer over Na_2SO_4, filter and evaporate onto silica gel. Purify the residue by chromatography on silica gel eluting with hexane/EtOAc (1:0 to 3:2 gradient) to give the desired intermediate that is used without further purification (0.27 g, 67%). MS (GCMS) *m/z*: 235 M^+.

6-Aminomethyl-3-phenyl-benzothiophene: Dissolve 6-cyano-3-phenylbenzothiophene (0.27 g, 1.16 mmol) in anhydrous THF (6 mL) and add lithium aluminum hydride (3.45 mL, 1M solution in THF) at 0 °C. After 2 h, add water (0.86 mL), 2N aqueous NaOH (0.86 mL) and water (1.24 mL). Filter off the solids and evaporate the residue. Purify by prep HPLC (Zorbax SB-Phenyl column 21.2 x 250 mm, 5% to 50% acetonitrile in 0.1% TFA-water solution) and obtain the free base by SCX chromatography to give the title compound that is used without further purification (187 mg, 68%). MS (ES+) *m/z*: 223 $(M-NH_2)^+$.

Preparation 260

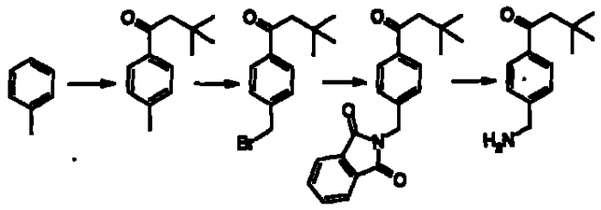
4-(Difluoro-phenyl-methyl)-benzylamine



Combine 4-(difluoro-phenyl-methyl)-toluene (0.29 g, 1.35 mmol, prepared by following the procedure described in *Tetrahedron* 1996, *52*, 9), NBS (0.26 g, 1.48 mmol), and AIBN (6 mg, 0.03 mmol) in carbon tetrachloride (8 mL) and heat at 80 °C for 16 h. Evaporate the mixture and pass the residue through a pad of silica gel washing with hexane and evaporate the filtrate. Dissolve the residue in methanol and add dropwise to 7M ammonia in methanol (100 mL) at 0 °C. After 4.5 h, evaporate the mixture and isolate the amine by SCX chromatography (0.1 g, 32%). MS (ES+) *m/z*: 234 $(M+H)^+$.

Preparation 261

4-(3,3-Dimethyl-butyryl)-benzylamine



3,3,4'-Trimethylbutyrophenone: Add slowly *tert*-butylacetyl chloride (2 g, 14.858 mmol) to an ice-cold stirred solution of aluminum trichloride (2.972 g, 22.28 mmol) in

anhydrous toluene (40 mL). Stir the reaction mixture at ambient temperature overnight. Add slowly ice-cold water and extract the mixture twice with EtOAc. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo* to give the desired intermediate (2.82 g, 100%) that was used without any further purification. GC-MS *m/z*: 190 (M^+).

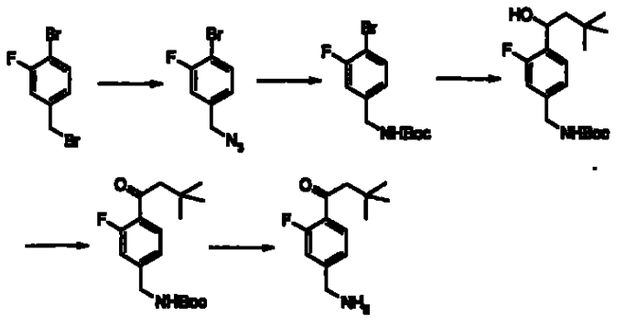
4-(3,3-Dimethyl-butyryl)-benzyl bromide: Heat a mixture of 3,3,4'-trimethylbutyrophenone (2 g, 10.52 mmol), NBS (2.061 g, 11.57 mmol), and AIBN (43 mg, 0.263 mmol) in carbon tetrachloride (60 mL) for 14 h at reflux. Cool the reaction mixture to ambient temperature and wash sequentially with water, 1M aqueous HCl, 5% aqueous $NaHCO_3$ and brine. Concentrate the organic layer *in vacuo* to provide the desired intermediate as oil (2.54 g, 90%) that was used without any further purification.

2-[4-(3,3-Dimethyl-butyryl)-benzyl]-isoindole-1,3-dione: Add 4-(3,3-dimethyl-butyryl)-benzyl bromide (1 g, 3.731 mmol) to a stirred suspension of potassium phthalimide (0.705 g, 3.805 mmol) in anhydrous DMF (20 mL). Stir the mixture overnight at room temperature. Dilute with EtOAc and wash twice with ice-cold water. Dry the organic layer over Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting sequentially with hexane and hexane/EtOAc (19:1, 4:1) to provide the desired intermediate as oil (1.24 g, 100%).

4-(3,3-Dimethyl-butyryl)-benzylamine: Add hydrazine hydrate (0.189 mL, 3.913 mmol) to a stirred suspension of 2-[4-(3,3-dmethyl-butyryl)-benzyl]-isoindole-1,3-dione (875 mg, 2.609 mmol) in methanol (15 mL). Heat the mixture to reflux overnight. Cool the mixture to room temperature and concentrate *in vacuo*. Partition the residue between EtOAc and 5N aqueous HCl and wash the acidic aqueous phase again with 5N aqueous HCl. Basify with 5N aqueous NaOH to pH 12. Extract the basic aqueous solution three times with chloroform. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo* to give the title compound as a yellow oil (411 mg, 77%) that was used without any further purification.

Preparation 262

4-(3,3-Dimethyl-butyryl)-3-fluoro-benzylamine



4-Azidomethyl-1-bromo-2-fluoro-benzene: Add sodium azide (2.912 g, 44.8 mmol) to a solution of 4-bromo-3-fluorobenzyl bromide (6 g, 22.4 mmol) in anhydrous DMF (127 mL) at room temperature under nitrogen. Heat the mixture at 90 °C for 1 h. Concentrate *in vacuo* and partition the residue between water and EtOAc. Extract the aqueous phase twice with EtOAc. Wash the combined organics extracts with iced-water. Dry the organic layer over Na_2SO_4, filter and concentrate *in vacuo* to obtain the desired intermediate as a solid (4.92 g, 96%).

4-Bromo-*N*-(*tert*-butoxycarbonyl)-3-fluoro-benzylamine: Add 10% Pd/C (492 mg) and di-*tert*-butyl-dicarbonate (4.668 g, 21.4 mmol) to a solution of 4-azidomethyl-1-bromo-2-fluoro-benzene (4.92 g, 21.4 mmol) in ethanol (90 mL) and submit the mixture to hydrogenation at atmospheric pressure overnight. Filter the reaction mixture over Celite® and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (85:15) to obtain the desired intermediate as a solid (1.55 g, 25%).

N-(*tert*-Butoxycarbonyl)-3-fluoro-4-(1-hydroxy-3,3-dimethyl-butyl)-benzylamine: Add butyllithium (7.3 mL, 11.7 mmol) to a solution of 4-bromo-*N*-(*tert*-butoxycarbonyl)-3-fluoro-benzylamine (1.55 g, 5.1 mmol) in diethyl ether (54 mL) at –78 °C under nitrogen and stir for 30 min. Add 3,3-dimethylbutyraldehyde (562 mg, 0.7 mL, 5.6 mmol), stir for 30 min at –78 °C and then warm to room temperature. Add water and extract twice the aqueous phase with EtOAc. Dry the combined organic extracts over

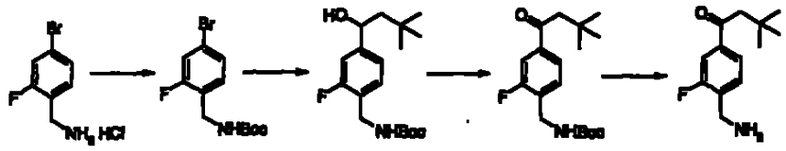
Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (85:15) to obtain the desired intermediate as a yellow oil (394 mg, 24%).

N-(*tert*-Butoxycarbonyl)-4-(3,3-dimethyl-butyryl)-3-fluoro-benzylamine: Add manganese dioxide (1.132 g, 13 mmol) to a solution of *N*-(*tert*-butoxycarbonyl)-3-fluoro-4-(1-hydroxy-3,3-dimethyl-butyl)-benzylamine (283 mg, 0.87 mmol) in anhydrous 1,4-dioxane (11.5 mL) at room temperature. Heat the reaction mixture at 70 °C overnight. Filter the reaction mixture over Celite® and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (4:1) to obtain the desired intermediate as an oil (216 mg, 77%).

4-(3,3-Dimethyl-butyryl)-3-fluoro-benzylamine: Add 4N hydrogen chloride in dioxane (2.7 mL, 10.8 mmol) to a solution of *N*-(*tert*-butoxycarbonyl)-4-(3,3-dimethyl-butyryl)-3-fluoro-benzylamine (296 mg, 0.92 mmol) in dichloromethane (11 mL) and stir for 4 h. Concentrate *in vacuo* and wash the solid obtained with diethyl ether. Suspend the solid in saturated aqueous $NaHCO_3$ and stir for 30 min. Extract twice with dichloromethane. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo* to obtain the title compound as an oil (175 mg, 82%).

Preparation 263

4-(3,3-Dimethyl-butyryl)-2-fluoro-benzylamine



4-Bromo-*N*-(*tert*-butoxycarbonyl)-2-fluoro-benzylamine: Add triethylamine (6.334 g, 8.8 mL, 52.6 mmol) and di-*tert*-butyl-dicarbonate (4.54 g, 20.8 mmol) to a solution of 4-bromo-2-fluoro-benzylamine hydrochloride (5 g, 20.8 mmol) in dichloromethane (254 mL) and stir overnight. Wash the organic layer with water and then extract back the aqueous phase with dichloromethane. Dry the combined organic extracts over Na_2SO_4,

filter and concentrate *in vacuo* to obtain the desired intermediate as a white solid (6.11 g, 97%).

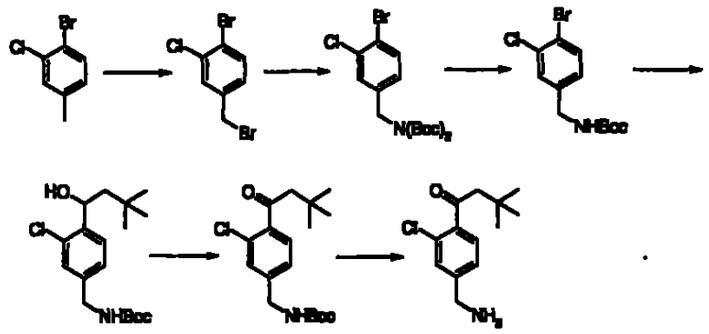
N-(*tert*-Butoxycarbonyl)-2-fluoro-4-(1-hydroxy-3,3-dimethyl-butyl)-benzylamine: Add butyllithium (14.2 mL, 22.7 mmol) to a solution of 4-bromo-*N*-(*tert*-butoxycarbonyl)-2-fluoro-benzylamine (3 g, 9.9 mmol) in diethyl ether (105 mL) at –78 °C under nitrogen and stir for 30 min. Add 3,3-dimethylbutyraldehyde (1.086 g, 1.4 mL, 10.8 mmol), stir for 30 min at –78 °C and then warm to room temperature. Add water and extract twice the aqueous phase with EtOAc. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (85:15) to obtain the desired intermediate as a yellow oil (1.179 g, 37%).

N-(*tert*-Butoxycarbonyl)-4-(3,3-dimethyl-butyryl)-2-fluoro-benzylamine: Add manganese dioxide (4.4 g, 50.6 mmol) to a solution of *N*-(*tert*-butoxycarbonyl)-2-fluoro-4-(1-hydroxy-3,3-dimethyl-butyl)-benzylamine (1.1 g, 3.38 mmol) in anhydrous 1,4-dioxane (45 mL) at room temperature. Heat the reaction mixture at 70 °C overnight. Filter the reaction mixture over Celite® and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to obtain the desired intermediate as an oil (980 mg, 90%).

4-(3,3-Dimethyl-butyryl)-2-fluoro-benzylamine: Add 4N hydrogen chloride in dioxane (5.5 mL, 22 mmol) to a solution of *N*-(*tert*-butoxycarbonyl)-4-(3,3-dimethyl-butyryl)-2-fluoro-benzylamine (600 mg, 1.85 mmol) in dichloromethane (22 mL) and stir for 6.5 h. Concentrate *in vacuo* and wash the solid obtained with diethyl ether. Suspend the solid into saturated aqueous $NaHCO_3$ and stir for 30 min. Extract the aqueous phase twice with EtOAc. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo* to obtain the title compound as an oil (420 mg, 99%).

Preparation 264

3-Chloro-4-(3,3-dimethyl-butyryl)-benzylamine



4-Bromo-3-chloro-benzyl bromide: Add NBS (5.266 g, 23.9 mmol) and benzoyl peroxide (49 mg, 0.2 mmol) to a solution of 4-bromo-3-chlorotoluene (4.925 g, 23.9 mmol) in carbon tetrachloride (49 mL) and heat overnight at 90 °C. Cool to 0 °C and filter the mixture. Concentrate the filtrate *in vacuo* to obtain the desired intermediate as a yellow oil (5.807 g, 85%).

4-Bromo-3-chloro-*N*-(di-*tert*-butoxycarbonyl)-benzylamine: Add sodium hydride (382 mg, 15.9 mmol) to a solution of di-*tert*-butyl-iminodicarboxylate (2.533 g, 11.7 mmol) in anhydrous DMF (15 mL) at room temperature under nitrogen and stir for 15 min. Then add a solution of 4-bromo-3-chloro-benzyl bromide (3 g, 10.6 mmol) in anhydrous DMF (5 mL) and stir for 1 h. Add water and extract the aqueous phase twice with EtOAc. Wash the combined organic extracts with iced-water. Dry the organic layer over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (4:1) to obtain the desired intermediate (2.783 g, 62%).

4-Bromo-3-chloro-*N*-(*tert*-butoxycarbonyl)-benzylamine: Add a solution of sodium hydroxide (264 mg, 6.6 mmol) in methanol (23.5 mL) to a solution of 4-bromo-3-chloro-*N*-(di-*tert*-butoxycarbonyl)-benzylamine (2.783 g, 6.6 mmol) in THF (11.7 mL) and stir overnight. Concentrate *in vacuo*. Add water and filter the precipitate formed to obtain the desired intermediate as a white solid (1.823 g, 86%).

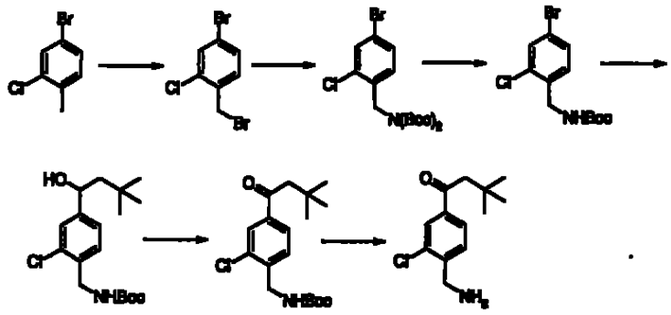
N-(*tert*-Butoxycarbonyl)-3-chloro-4-(1-hydroxy-3,3-dimethyl-butyl)-benzylamine: Add butyllithium (8.2 mL, 13.1 mmol) to a solution of 4-bromo-3-chloro-*N*-(*tert*-butoxycarbonyl)-benzylamine (1.823 g, 5.7 mmol) in diethyl ether (46 mL) at –78 °C under nitrogen and stir for 30 min. Add 3,3-dimethylbutyraldehyde (1.427 g, 1.7 mL, 14.3 mmol), stir for 30 min at –78 °C and then warm to room temperature. Add water and extract twice the aqueous phase with EtOAc. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (4:1) to obtain the desired intermediate as a yellow oil (274 mg, 14%).

N-(*tert*-Butoxycarbonyl)-3-chloro-4-(3,3-dimethyl-butyryl)-benzylamine: Add manganese dioxide (1.096 g, 12.6 mmol) to a solution of *N*-(*tert*-butoxycarbonyl)-3-chloro-4-(1-hydroxy-3,3-dimethyl-butyl)-benzylamine (274 mg, 0.8 mmol) in anhydrous 1,4-dioxane (11.5 mL) at room temperature. Heat the mixture at 70 °C overnight. Filter the reaction mixture over Celite® and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (4:1) to obtain the desired intermediate as a yellow oil (175 mg, 64%).

3-Chloro-4-(3,3-dimethyl-butyryl)-benzylamine: Add 4N hydrogen chloride in dioxane (0.9 mL, 3.6 mmol) to a solution of *N*-(*tert*-butoxycarbonyl)-3-chloro-4-(3,3-dimethyl-butyryl)-benzylamine (100 mg, 0.3 mmol) in dichloromethane (6 mL) and stir overnight. Concentrate *in vacuo* and wash the solid obtained with diethyl ether. Suspend the solid into saturated aqueous $NaHCO_3$ and stir for 30 min. Extract twice with dichoromethane. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo* to obtain the title compound as a yellow oil (66 mg, 92%).

Preparation 265

2-Chloro-4-(3,3-dimethyl-butyryl)-benzylamine



4-Bromo-2-chloro-benzyl bromide: Add NBS (13.171 g, 74 mmol) and benzoyl peroxide (152 mg, 0.63 mmol) to a solution of 4-bromo-2-chlorotoluene (15.2 g, 74 mmol) in carbon tetrachloride (152 mL) and stir for 6 days at 90 °C. Cool to 0 °C, filter the mixture and concentrate the filtrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (99:1) to obtain the desired intermediate as a yellow oil (12.7 g, 61%).

4-Bromo-2-chloro-*N*-di-(*tert*-butoxycarbonyl)-benzylamine: Add sodium hydride (382 mg, 15.9 mmol) to a solution of di-*tert*-butyl-iminodicarboxylate (2.533 g, 11.7 mmol) in anhydrous DMF (15 mL) at room temperature under nitrogen and stir for 15 min. Then add a solution of 4-bromo-2-chloro-benzyl bromide (3 g, 10.6 mmol) in anhydrous DMF (5 mL) and stir for 1 h. Add water and extract the aqueous phase twice with EtOAc. Wash the combined organic extracts with iced-water. Dry the organic layer over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting sequentially with hexane and hexane/EtOAc (4:1) to obtain the desired intermediate (4.2 g, 94%).

4-Bromo-*N*-(*tert*-butoxycarbonyl)-2-chloro-benzylamine: Add a solution of sodium hydroxide (399 mg, 9.98 mmol) in methanol (35.5 mL) to a solution of 4-bromo-2-chloro-*N*-di-(*tert*-butoxycarbonyl)-benzylamine (4.2 g, 9.98 mmol) in THF (17.7 mL) and stir overnight. Concentrate *in vacuo* and partition the residue between water and EtOAc. Extract the aqueous phase twice with EtOAc. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in* vacuo. Purify by chromatography on silica gel eluting with hexane/EtOAc (4:1) to obtain the desired intermediate (2.625 g, 82%).

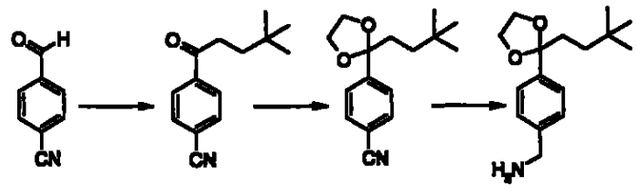
N-(*tert*-Butoxycarbonyl)-2-chloro-4-(1-hydroxy-3,3-dimethyl-butyl)-benzylamine: Add butyllithium (11.7 mL, 18.65 mmol) to a solution of 4-bromo-*N*-(*tert*-butoxycarbonyl)-2-chloro-benzylamine (2.601 g, 8.11 mmol) in diethyl ether (86 mL) at –78 °C under nitrogen and stir for 2 h. Add 3,3-dimethylbutyraldehyde (1.868 g, 2.3 mL, 18.65 mmol), stir for 30 min at –78 °C and then warm to room temperature. Add water and extract twice the aqueous phase with EtOAc. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting hexane/EtOAc (85:15) to obtain the desired intermediate as a yellow oil (1.825 mg, 66%).

N-(*tert*-Butoxycarbonyl)-2-chloro-4-(3,3-dimethyl-butyryl)-benzylamine: Add manganese dioxide (7.276 g, 83.7 mmol) to a solution of *N*-(*tert*-butoxycarbonyl)-2-chloro-4-(1-hydroxy-3,3-dimethyl-butyl)-benzylamine (1.819 g, 5.3 mmol) in anhydrous 1,4-dioxane (75 mL) at room temperature. Heat the mixture at 70 °C overnight. Filter the reaction mixture over Celite® and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (85:15) to obtain the desired intermediate as a yellow oil (1.362 g, 76%).

2-Chloro-4-(3,3-dimethyl-butyryl)-benzylamine: Add 4N hydrogen chloride in dioxane (6 mL, 24 mmol) to a solution of *N*-(*tert*-butoxycarbonyl)-2-chloro-4-(3,3-dimethyl-butyryl)-benzylamine (700 mg, 2.06 mmol) in dichloromethane (25 mL) and stir overnight. Concentrate *in vacuo* and wash the solid obtained with diethyl ether. Suspend the solid into saturated aqueous $NaHCO_3$ and stir for 30 min. Extract twice with dichoromethane. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo* to obtain the title compound as a yellow oil (477 mg, 97%).

Preparation 266

4-[2-(3,3-Dimethyl-butyl)-[1,3]dioxolan-2-yl]-benzylamine



4-(4,4-Dimethyl-pentanoyl)-benzonitrile: Keep Mg turnings (402 mg, 15.251 mmol) *in vacuo* in a two-neck round bottom flask for 2 h. Purge the flask with nitrogen/vacuo several times. Add a couple crystals of iodine, anhydrous THF (60 mL) and 3,3-dimethyl-bromobutane (0.8 mL, 5.59 mmol) slowly (exothermic reaction observed). Add dropwise the remaining 3,3-dimethyl-bromobutane (1.6 mL, 11.18 mmol) and reflux the mixture overnight. Add some additional 3,3-dimethyl-bromobutane (0.24 mL, 1.67 mmol) and reflux for 30 min. Cool the mixture to –10 °C and add a solution of 4-cyanobenzaldehyde (4 g, 30.502 mmol) in anhydrous THF (40 mL). Warm the flask gradually to room temperature overnight. Quench the mixture with 0.1M aqueous HCl (100 mL) and extract twice with EtOAc. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane/EtOAc (19:1) to give the desired intermediate as an oil (0.752 g, 23%).

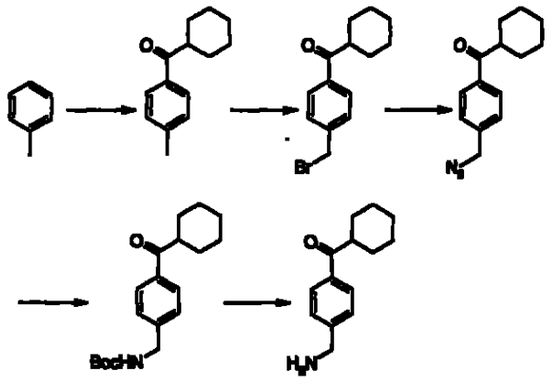
4-[2-(3,3-Dimethyl-butyl)-[1,3]dioxolan-2-yl]-benzonitrile: Dissolve 4-(4,4-dimethyl-pentanoyl)-benzonitrile (275 mg, 1.28 mmol) in toluene (10 mL). Add ethylene glycol (0.35 mL, 6.4 mmol) and p-toluenesulfonic acid monohydrate (24 mg, 0.128 mmol). Heat the mixture at 135 °C in a Dean-Stark for 2 h and then at 120 °C overnight. Cool the mixture to room temperature, dilute with EtOAc ans wash with saturated aqueous $NaHCO_3$. Dry the organic phase over $MgSO_4$, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on basic alumina eluting with hexane and hexane/EtOAc (19:1) to give the desired intermediate as an oil (0.272 g, 82%).

4-[2-(3,3-Dimethyl-butyl)-[1,3]dioxolan-2-yl]-benzylamine: Dissolve 4-[2-(3,3-dimethyl-butyl)-[1,3]dioxolan-2-yl]-benzonitrile (271 mg, 1.046 mmol) in anhydrous THF (10 mL). Add under nitrogen 1M lithium aluminum hydride in THF (2.1 mL, 2.1

mmol) at 0 °C and stir the mixture at room temperature for 2 h. Cool to 0 °C, add water and extract the aqueous phase twice with EtOAc. Dry the combined organic extracts over $MgSO_4$, filter and concentrate *in vacuo* to obtain the desired intermediate as an oil (0.263 mg) that was used without any further purification.

Preparation 267

4-Cyclohexanecarbonyl-benzylamine



Cyclohexyl-*p*-tolyl-methanone: Dissolve cyclohexanecarbonyl chloride (2 g, 13.6 mmol) in anhydrous toluene (30 mL). Cool the solution to 0 °C, add aluminum trichloride (2.72 g, 20.46 mmol) in three portions and stir the reaction mixture at ambient temperature overnight. Cool to 0 °C, add slowly water and extract the mixture with EtOAc. Dry the organic layer over Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane and hexane/EtOAc (19:1) to give the desired intermediate (2.75 g, 100%).

4-(Cyclohexanecarbonyl)-benzyl bromide: Heat a mixture of cyclohexyl-*p*-tolyl-methanone (1 g, 4.943 mmol), NBS (1.232 g, 6.92 mmol), and AIBN (41 mg, 0.247 mmol) in carbon tetrachloride (80 mL) for 14 h at reflux. Add additional NBS (264 mg) and AIBN (19 mg) and reflux the mixture for 4 h. Cool the reaction mixture to ambient temperature and filter. Concentrate the filtrate *in vacuo* to provide the desired intermediate as oil (1.132 g, 81%) that was used without any further purification.

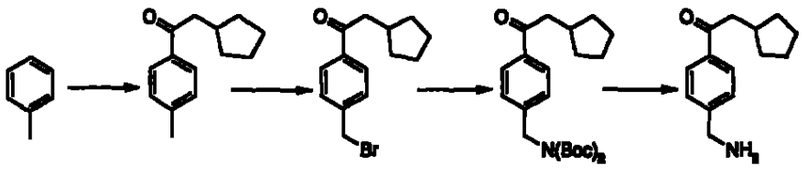
(4-Azidomethyl-phenyl)-cyclohexyl-methanone: Add sodium azide (441 mg, 6.785 mmol) to a stirred solution of 4-(cyclohexanecarbonyl)-benzyl bromide (954 mg, 3.393 mmol) in anhydrous DMF (20 mL) and heat the mixture to 90 °C for 2 h. Cool the mixture to room temperature, add water and extract the aqueous solution with diethyl ether. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane and hexane/EtOAc (19:1) to give the desired intermediate as oil (310 mg, 38%).

N-(*tert*-Butoxycarbonyl)-4-cyclohexanecarbonyl-benzylamine: Add 10% Pd/C (100 mg) to a solution of (4-azidomethyl-phenyl)-cyclohexyl-methanone (310 mg, 1,274 mmol) and di-*tert*-butyl-dicarbonate (278 mg, 1274 mmol) in ethanol (5 mL). Submit the mixture to hydrogenation under atmospheric pressure (balloon) for 1 h. Filter the catalyst through Celite® and concentrate the filtrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane and hexane/EtOAc (92:8) to provide the desired intermediate as a white solid (197 mg, 49%).

4-Cyclohexanecarbonyl-benzylamine: Add 4N hydrogen chloride in dioxane (1 mL) to a stirred solution of *N*-(*tert*-butoxycarbonyl)-4-cyclohexanecarbonyl-benzylamine (197 mg, 0.621 mmol) in anhydrous dichloromethane (4 mL) and stir the mixture at ambient temperature for 16 h. Concentrate *in vacuo* and partition the residue between dichloromethane and saturated aqueous $NaHCO_3$. Extract the aqueous phase twice with dichloromethane. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo* to give the title compound (125 mg, 93%) that was used without any further purification. MS (ES+) *m/z*: 218 $(M+H)^+$.

Preparation 268

4-(2-Cyclopentyl-acetyl)-benzylamine



2-Cyclopentyl-1-*p*-tolyl-ethanone: Add aluminum trichloride (2.719 g, 20.4 mmol) in three portions to a solution of cyclopentylacetyl chloride (2 g, 13.6 mmol) in anhydrous toluene (30 mL) at 0 °C. Stir the solution at room temperature overnight. Cool to 0 °C, add water and extract the aqueous phase with EtOAc. Dry the organic phase over $MgSO_4$, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane and hexane/EtOAc (19:1) to give the desired intermediate as an oil (2.5 g, 91%).

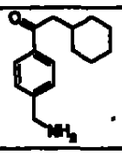
1-(4-Bromomethyl-phenyl)-2-cyclopentyl-ethanone: Add NBS (523 mg, 2.94 mmol) and AIBN (44 mg, 0.267 mmol) to a solution of 2-cyclopentyl-1-*p*-tolyl-ethanone (540 mg, 2.67 mmol) in carbon tetrachloride (80 mL) and heat overnight at 85 °C. Add water and extract the aqueous phase with dichloromethane. Dry the organic phase over $MgSO_4$, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane and hexane/EtOAc (98:2, 95:5) to obtain the desired intermediate as an oil (479 mg, 64%).

N-Di-(*tert*-butoxycarbonyl)-4-(2-cyclopentyl-acetyl)-benzylamine: Add sodium hydride (42 mg, 1.65 mmol) to a solution of di-*tert*-butyl-iminodicarboxylate (262 mg, 1.21 mmol) in anhydrous DMF (5 mL) at room temperature under nitrogen and stir for 5 min. Then add a solution of 1-(4-bromomethyl-phenyl)-2-cyclopentyl-ethanone (310 mg, 1.1 mmol) in anhydrous DMF (15 mL) and stir for 1 h. Add water and extract the aqueous phase twice with EtOAc. Wash the combined organic extracts with iced-water. Dry the organic layer over $MgSO_4$, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (19:1) to obtain the desired intermediate (360 mg, 78%).

4-(2-Cyclopentyl-acetyl)-benzylamine: Add 4N hydrogen chloride in dioxane (15 mL) to a solution of *N*-di-(*tert*-butoxycarbonyl)-4-(2-cyclopentyl-acetyl)-benzylamine (300 mg, 0.72 mmol) in EtOAc (20 mL) and stir overnight. Concentrate *in vacuo*, suspend the solid obtained in diethyl ether and add hexane. Filter and wash the solid with hexane. Suspend the solid into dichloromethane, add saturated aqueous $NaHCO_3$ and stir until both phases are clear (15 min). Extract the aqueous phase with dichoromethane and EtOAc. Dry the combined organic extracts over $MgSO_4$, filter and concentrate *in vacuo* to obtain the title compound as an oil that was used without any further purification.

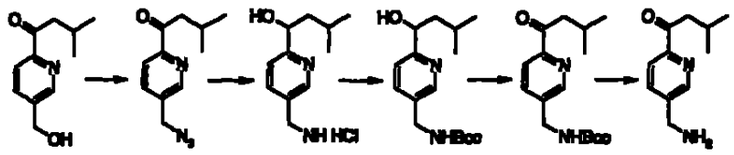
Preparation 268

The compound of Preparation 269 may be prepared essentially as described in Preparation 268 by using cyclohexylacetyl chloride. Overall yield and MS (ES+) data are shown in the Table below.

Prep.	NH-R	Compound	Yield (%)	MS (ES+) *m/z*
269		4-(2-Cyclohexyl-acetyl)-benzylamine	40	232 $(M+H)^+$

Preparation 270

5-Aminomethyl-2-(3-methyl-butyryl)-pyridine



5-Azidomethyl-2-(3-methyl-butyryl)-pyridine: Add DBU (240 mg, 1.55 mmol) to a solution of 5-hydroxymethyl-2-(3-methyl-butyryl)-pyridine (250 mg, 1.29 mmol) and diphenylphosphorylazide (430 mg, 1.55 mmol) in anhydrous toluene (10 mL) at 0 °C. Stir at 0 °C for 30 min, warm to room temperature and stir for 4 h. Dilute with EtOAc and water. Extract the aqueous phase twice with EtOAc. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by

chromatography on silica gel eluting with hexane and hexane/EtOAc (9:1) to provide the desired intermediate (300 mg, 99%). MS (ES+) *m/z*: 219 $(M+H)^+$.

5-Aminomethyl-2-(1-hydroxy-3-methyl-butyl)-pyridine hydrochloride: Add 10% Pd/C (20 mg) to a solution of 5-azidomethyl-2-(3-methyl-butyryl)-pyridine (80 mg, 0.367 mmol) in ethanol (10 mL) containing concentrated HCl (1 mL). Submit the mixture to hydrogenation at atmospheric pressure for 2 h. Filter the reaction mixture over Celite® and concentrate *in vacuo* to afford the desired intermediate (95 mg, 98%). MS (ES+) *m/z*: 195 $(M+H)^+$.

5-*tert*-Butoxycarbonylaminomethyl-2-(1-hydroxy-3-methyl-butyl)-pyridine: Add di-*tert*-butyl-dicarbonate (78 mg, 0.356 mmol) and triethylamine (0.149 mL, 1.068 mmol) to a solution of 5-aminomethyl-2-(1-hydroxy-3-methyl-butyl)-pyridine hydrochloride (95 mg, 0.356 mmol) in anhydrous dichloromethane (5 mL). Stir the solution at room temperature for 3 h. Dilute the reaction mixture with dichloromethane and wash with water. Extract the aqueous phase with dichloromethane. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane/EtOAc (4:1) to afford the desired intermediate (60 mg, 59%).

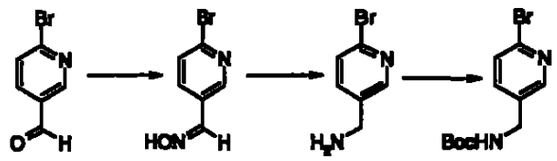
5-*tert*-Butoxycarbonylaminomethyl-2-(3-methyl-butyryl)-pyridine: Add manganese dioxide (240 mg) to a solution of 5-*tert*-butoxycarbonylaminomethyl-2-(1-hydroxy-3-methyl-butyl)-pyridine (60 mg, 0.2 mmol) in anhydrous 1,4-dioxane (1 mL) at room temperature. Heat the reaction mixture at 70 °C for 2 h. Filter the reaction mixture over Celite® and concentrate *in vacuo* to afford the desired intermediate (60 mg, 99%).

5-Aminomethyl-2-(3-methyl-butyryl)-pyridine: Add 4N hydrogen chloride in dioxane (0.5 mL) to a solution of 5-*tert*-butoxycarbonylaminomethyl-2-(3-methyl-butyryl)-pyridine (60 mg, 0.2 mmol) in anhydrous dichloromethane (2 mL) and stir the solution overnight. Concentrate *in vacuo* and partition the residue between saturated aqueous $NaHCO_3$ and dichloromethane. Extract the aqueous phase with dichloromethane (2 x 15

mL) and EtOAc (2 x 15 mL). Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo* to obtain the title compound (37 mg, 95%) that was used without any further purification.

Preparation 271

2-Bromo-5-*tert*-butoxycarbonylaminomethyl-pyridine



2-Bromo-pyridine-5-carbaldehyde oxime: Add hydroxylamine hydrochloride (1.494 g, 21.504 mmol) and a solution of $NaHCO_3$ (2.71 g, 32.256 mmol) in water (15 mL) to a solution of 2-bromo-5-formyl-pyridine (2 g, 10.752 mmol, prepared by following the procedure described in *J. Org. Chem.* 2004, *69*, 250-262) in absolute ethanol (100 mL). Stir the mixture at room temperature for 2 h. Concentrate *in vacuo* and partition the residue between EtOAc and water. Extract the aqueous phase with EtOAc. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane and hexane/EtOAc (9:1, 4:1) to afford the desired intermediate as a solid (1.362 g, 63%).

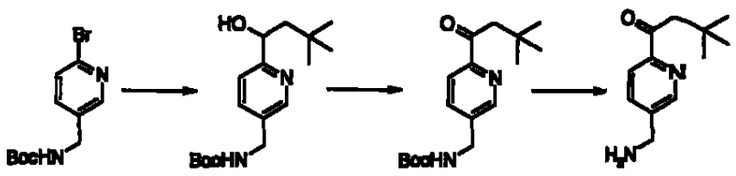
5-Aminomethyl-2-bromo-pyridine: Add dropwise a solution of 2-bromo-pyridine-5-carbaldehyde oxime (0.5 g, 2.487 mmol) in DME (10 mL) to a solution of titanium(IV) chloride (0.573 mL, 5.223 mmol) and sodium borohydride (395 mg, 10.445 mmol) in DME (20 mL) at 0 °C. Allow the mixture to warm to room temperature and stir for 3 h. Add water and remove the solvent *in vacuo*. Basify the mixture to pH 12 with 1N aqueous NaOH and extract with dichloromethane. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo* to afford the desired intermediate (340 mg, 73%) that was used without further purification.

2-Bromo-5-*tert*-butoxycarbonylaminomethyl-pyridine: Add di-*tert*-butyl-dicarbonate (397 mg, 1.818 mmol) and triethylamine (0.507 mL, 3.636 mmol) to a solution of 5-

aminomethyl-2-bromo-pyridine (340 mg, 1.818 mmol) in anhydrous dichloromethane (15 mL). Stir the solution overnight at room temperature. Dilute the reaction mixture with dichloromethane and wash with water. Extract the aqueous phase with dichloromethane. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane and hexane/EtOAc (4:1) to afford the title compound as a solid (322 mg, 62%).

Preparation 272

5-Aminomethyl-2-(3,3-dimethyl-butyryl)-pyridine



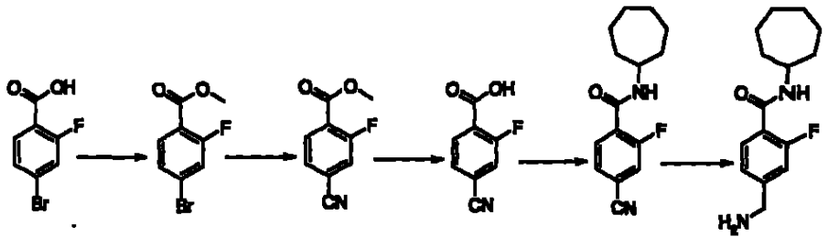
5-*tert*-Butoxycarbonylaminomethyl-2-(1-hydroxy-3,3-dimethyl-butyl)-pyridine: Add slowly butyllithium (1.088 mL, 1.741 mmol, 1.6M solution in hexane) to a solution of 2-bromo-5-*tert*-butoxycarbonylaminomethyl-pyridine (200 mg, 0.696 mmol) in anhydrous THF (10 mL) at –78 °C. Stir the mixture at this temperature for 35 min. Add 3,3-dimethylbutyraldehyde (0.219 mL, 1.741 mmol) and stir the mixture at –78 °C for 3 h. Quench the reaction mixture at –78 °C with brine. Extract the aqueous phase with EtOAc (3 x 15 mL). Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane and hexane/EtOAc (3:2) to afford the desired intermediate as a colorless oil (118 mg, 55%). MS (ES+) *m/z*: 309 $(M+H)^+$.

5-*tert*-Butoxycarbonylaminomethyl-2-(3,3-dimethyl-butyryl)-pyridine: Add manganese dioxide (472 mg, 5.429 mmol) to a solution of 5-*tert*-butoxycarbonylaminomethyl-2-(1-hydroxy-3,3-dimethyl-butyl)-pyridine (118 mg, 0.383 mmol) in anhydrous 1,4-dioxane (5 mL) at room temperature. Heat the reaction mixture at 70 °C overnight. Filter the reaction mixture over Celite® and concentrate *in vacuo* to obtain the desired intermediate (104 mg, 89%).

5-Aminomethyl-2-(3,3-dimethyl-butyryl)-pyridine: Add 4N hydrogen chloride in dioxane (1 mL) to a solution of 5-*tert*-butoxycarbonylaminomethyl-2-(3,3-dimethyl-butyryl)-pyridine (104 mg, 0.339 mmol) in anhydrous dichloromethane (4 mL) and stir the solution overnight. Concentrate *in vacuo* and partition the residue between saturated aqueous $NaHCO_3$ and dichloromethane. Extract the aqueous phase with dichloromethane (2 x 15 mL) and EtOAc (2 x 15 mL). Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo* to obtain the title compound as an oil (62 mg, 88%) that was used without any further purification. MS (ES+) *m/z*: 207 $(M+H)^+$.

Preparation 273

4-Aminomethyl-*N*-cycloheptyl-2-fluoro-benzamide



Methyl 4-bromo-2-fluoro-benzoate: Dissolve 4-bromo-2-fluoro-benzoic acid (15 g, 68.5 mmol) in methanol (70 mL). Add concentrated sulfuric acid (500 µl) to the solution and heat the mixture to reflux for 20 h under a nitrogen atmosphere. Cool the mixture to room temperature and concentrate *in vacuo*. Dissolve the residue in EtOAc (200 mL) and wash successively with saturated aqueous $NaHCO_3$ (50 mL) and water (2 x 50 mL). Dry the organic layer over Na_2SO_4, filter and concentrate *in vacuo* to obtain the desired intermediate (15.4 g, 96%). GC-MS *m/z*: 232 (M^+).

Methyl 4-cyano-2-fluoro-benzoate: Slurry methyl 4-bromo-2-fluoro-benzoate (5 g, 21.5 mmol) and copper(I) cyanide (3.8 g, 42.9 mmol) in anhydrous DMF (90 mL). Heat the mixture to reflux for 20 h under a nitrogen atmosphere. Cool the mixture to room temperature, dilute with hexane/EtOAc (1:1, 300 mL) and water (150 mL). Filter the mixture through Celite® washing with hexane/EtOAc (1:1) to reduce the emulsion layer.

Separate the organic layer and extract the aqueous layer with hexane/EtOAc (1:1, 2 x 200 mL). Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane/EtOAc (9:1 to 1:1 gradient) to obtain the desired intermediate (2.9 g, 76%). GC-MS *m/z*: 179 (M^+).

4-Cyano-2-fluoro-benzoic acid: Dissolve methyl 4-cyano-2-fluoro-benzoate (2.9 g, 16.2 mmol) in absolute ethanol (100 mL). Add potassium hydroxide (4.5 g, 80.2 mmol) and stir the milky white mixture for 1.5 h. Dilute the mixture with water (125 mL) and wash with diethyl ether (50 mL). Collect the aqueous layer and concentrate *in vacuo* until solids start to appear in the flask, then adjust the mixture to pH 1 with concentrated HCl. Extract the aqueous mixture with diethyl ether (3 x 500 mL). Combine the organic extracts and concentrate *in vacuo* to obtain the desired intermediate as a white solid (2.2 g, 83%).

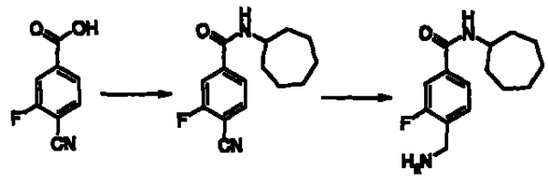
4-Cyano-*N*-cycloheptyl-2-fluoro-benzamide: Dissolve 4-cyano-2-fluoro-benzoic acid (1 g, 6.1 mmol) in anhydrous toluene (25 mL) and thionyl chloride (15 mL). Stir the mixture for 1 h at 90 °C under a nitrogen atmosphere (quench aliquots with methanol and assay by HPLC to determine if starting material has been consumed). Cool the reaction to room temperature and concentrate *in vacuo* to obtain the acid chloride as a yellow oil (1.25 g). Dissolve the acid chloride (1.25 g) in diethyl ether (75 mL), add triethylamine (0.85 mL, 6.1 mmol) and cycloheptylamine (0.78 mL, 6.1 mmol). Stir the mixture at room temperature for 16 h under a nitrogen atmosphere. Quench the reaction with saturated aqueous Na_2CO_3 (20 mL). Extract the mixture with EtOAc (30 mL). Dry the organic layer over Na_2SO_4, filter and concentrate *in vacuo* to obtain the desired intermediate (1.45 g, 91%). GC-MS *m/z*: 260 (M^+).

4-Aminomethyl-*N*-cycloheptyl-2-fluoro-benzamide: Add 4-cyano-*N*-cycloheptyl-2-fluoro-benzamide (1.4 g, 5.4 mmol), 10% Pd/C (Degussa type E101, 415 mg), ethanol (40 mL), water (15 mL) and acetic acid (1.8 mL) to a pressure vessel. Pressurize the vessel to 55 psi with hydrogen, and stir the mixture for 0.5 h (monitor the reaction by TLC). Filter the mixture through Celite® and wash the cake with warm ethanol followed

by dichloromethane under a nitrogen atmosphere. Concentrate the filtrate *in vacuo* to obtain the product as the acetic acid salt. Use SCX chromatography to obtain the title compound (1.36 g, 95%). GC-MS *m/z*: 264 (M^+).

Preparation 274

4-Aminomethyl-*N*-cycloheptyl-3-fluoro-benzamide

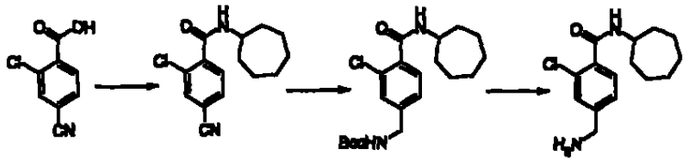


4-Cyano-*N*-cycloheptyl-3-fluoro-benzamide: Dissolve 4-cyano-3-fluoro-benzoic acid (1 g, 6.1 mmol) in anhydrous toluene (20 mL) and thionyl chloride (10 mL). Stir the mixture for 1.5 h at 90 °C under a nitrogen atmosphere (quench aliquots with methanol and assay by HPLC to determine if starting material has been consumed). Cool the reaction to room temperature and concentrate *in vacuo* to obtain the acid chloride as a yellow oil. Dissolve the yellow oil in diethyl ether (50 mL), add triethylamine (0.86 mL, 6.1 mmol) and cycloheptylamine (0.79 mL, 6.1 mmol). Stir the mixture at room temperature for 16 h under a nitrogen atmosphere. Quench the reaction with saturated aqueous Na_2CO_3 (20 mL). Extract the mixture with EtOAc (2 x 50 mL). Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo* to obtain the desired intermediate (1.24 g, 77%). MS (ES-) *m/z*: 259.2 $(M-H)^+$.

4-Aminomethyl-*N*-cycloheptyl-3-fluoro-benzamide: Add 4-cyano-*N*-cycloheptyl-3-fluoro-benzamide (0.86 g, 3.3 mmol), 10% Pd/C (Degussa type E101, 250 mg), ethanol (25 mL), water (9 mL) and acetic acid (1 mL) to a pressure vessel under a nitrogen atmosphere. Pressurize the vessel to 50 psi with hydrogen, and stir the mixture for 0.5 h. Filter the mixture through Celite® and wash the cake with warm ethanol followed by dichloromethane under a nitrogen atmosphere. Concentrate the filtrate *in vacuo* to obtain the title compound as the acetic acid salt. Use SCX chromatography to obtain the title compound (805 mg, 92%). MS (ES+) *m/z*: 265.3 $(M+H)^+$.

Preparation 275

4-Aminomethyl-2-chloro-*N*-cycloheptyl-benzamide



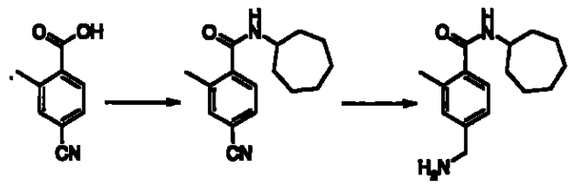
2-Chloro-4-cyano-*N*-cycloheptyl-benzamide: Dissolve 2-chloro-4-cyano-benzoic acid (1.1 g, 6 mmol) in anhydrous toluene (20 mL) and thionyl chloride (15 mL). Stir the mixture for 1 h at 90 °C under a nitrogen atmosphere (quench aliquots with methanol and assay by HPLC to determine if starting material has been consumed). Cool the reaction to room temperature and concentrate *in vacuo* to obtain the acid chloride as an oil. Dissolve the oil in diethyl ether (40 mL), add triethylamine (0.84 mL, 6 mmol) and cycloheptylamine (0.77 mL, 6 mmol). Stir the mixture at room temperature for 1 h under a nitrogen atmosphere. Quench the reaction with saturated aqueous Na_2CO_3 (20 mL). Extract the mixture with EtOAc (100 mL). Dry the organic layer over Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with dichloromethane to obtain the desired intermediate (1.1 g, 66%). MS (ES+) *m/z*: 277.2 $(M+H)^+$.

4-*tert*-Butoxycarbonylaminomethyl-2-chloro-*N*-cycloheptyl-benzamide: Dissolve 2-chloro-4-cyano-*N*-cycloheptyl-benzamide (460 mg, 1.7 mmol) in methanol (15 mL). Cool the solution to 0 °C under a nitrogen atmosphere and add di-*tert*-butyl dicarbonate (726 mg, 3.3 mmol) and nickel(II) chloride hexahydrate (40 mg, 0.17 mmol). Add then sodium borohydride (360 mg, 9.5 mmol) portionwise over 30 min. Stir at 0 °C for 1 h then concentrate the mixture *in vacuo*. Dilute the residue with EtOAc (100 mL), wash with saturated aqueous $NaHCO_3$ (40 mL). Extract the aqueous layer with EtOAc (3 x 40 mL). Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with EtOAc to obtain the desired intermediate (627 mg, 99%). MS (ES+) *m/z*: 381.3 $(M+H)^+$.

4-Aminomethyl-2-chloro-*N*-cycloheptyl-benzamide: Dissolve 4-*tert*-butoxycarbonylaminomethyl-2-chloro-*N*-cycloheptyl-benzamide (624 mg, 1.6 mmol) in dichloromethane (30 mL) then add trifluoroacetic acid (2 mL). Stir the solution at room temperature under a nitrogen atmosphere for 1 h. Concentrate the mixture *in vacuo*. Purify the crude mixture by SCX chromatography to obtain the desired intermediate (395 mg, 85%). MS (ES+) *m/z*: 281.2 $(M+H)^+$.

Preparation 276

4-Aminomethyl-*N*-cycloheptyl-2-methyl-benzamide



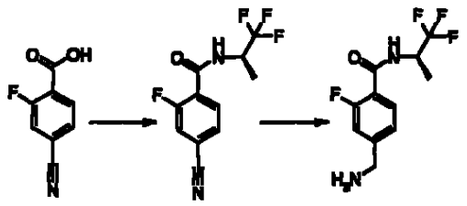
4-Cyano-*N*-cycloheptyl-2-methyl-benzamide: Add cycloheptylamine (0.83 mL, 6.5 mmol), HOBT (838 mg, 6.2 mmol), EDC (1.2 g, 6.2 mmol) and diisopropylethylamine (3.2 mL, 18.6 mmol) to a solution of 4-cyano-2-methyl-benzoic acid (1 g, 6.2 mmol) in dichloromethane (20 mL) at room temperature under a nitrogen atmosphere. Stir the mixture for 16 h at room temperature. Wash the mixture with water (20 mL), separate and concentrate the organic layer *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane/EtOAc (19:1 to 3:2 gradient) to obtain the desired intermediate (830 mg, 52%). MS (ES+) *m/z*: 257.3 $(M+H)^+$.

4-Aminomethyl-*N*-cycloheptyl-2-methyl-benzamide: Add 4-cyano-*N*-cycloheptyl-2-methyl-benzamide (0.82 g, 3.2 mmol), ethanol (23 mL), water (8 mL) and acetic acid (1 mL) to a pressure vessel. Heat vessel to 50 °C to dissolve all solids. Add 10% Pd/C (Degussa type E101, 250 mg) under a nitrogen atmosphere, then pressurize the vessel to 55 psi with hydrogen at ambient temperature. Stir the mixture for 40 min. Filter the mixture through Celite® and wash the cake with warm ethanol (50 mL) followed by dichloromethane (100 mL) under a nitrogen atmosphere. Concentrate the filtrate *in vacuo*

to obtain the title compound as the acetic acid salt. Use SCX chromatography to obtain the title compound (820 mg, 98%). MS (ES+) *m/z*: 261.3 $(M+H)^+$.

Preparation 277

(*R*)-4-Aminomethyl-2-fluoro-*N*-(2,2,2-trifluoro-1-methyl-ethyl)-benzamide

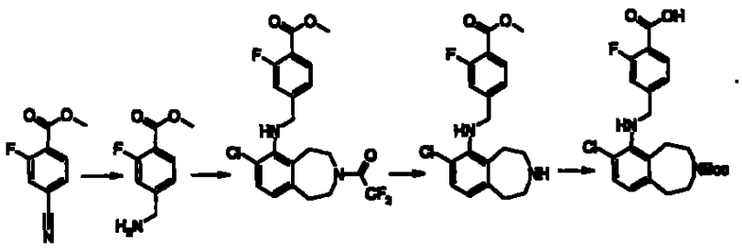


(*R*)-4-Cyano-2-fluoro-*N*-(2,2,2-trifluoro-1-methyl-ethyl)-benzamide: Add (*R*)-(2,2,2-trifluoro-1-methyl)-ethylamine (0.909 g, 6.08 mmol), HOBT (0.82 g, 6.1 mmol), diisopropylethylamine (2.1 mL, 12 mmol) and EDC (1.17 g, 6.08 mmol) to a mixture of 4-cyano-2-fluorobenzoic acid (1.004 g, 6.08 mmol) in anhydrous THF (40 mL) at room temperature. Stir overnight and partition the mixture between EtOAc (250 mL) and saturated aqueous $NaHCO_3$ (100 mL). Dry the organic extract over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with dichloromethane/hexane (1:1 to 1:0 gradient over 71 min; 50 mL/min) to afford the desired intermediate as a white solid (0.985 g, 62%).

(*R*)-4-Aminomethyl-2-fluoro-*N*-(2,2,2-trifluoro-1-methyl-ethyl)-benzamide: Combine a solution of (*R*)-4-cyano-2-fluoro-*N*-(2,2,2-trifluoro-1-methyl-ethyl)-benzamide (0.904 g, 3.475 mmol) in absolute ethanol (26 mL), water (9.7 mL) and glacial acetic acid (1.2 mL) with 10% Pd/C (Degussa type E101, 0.27 g, 0.13 mmol) under nitrogen. Purge the mixture with nitrogen and then with hydrogen. Stir the slurry at room temperature under hydrogen at 55 psi for 30 min. Purge the reaction mixture with nitrogen and then filter the slurry over Celite®. Wash the filter cake with ethanol (100 mL) and THF (100 mL). Concentrate the filtrate and purify by SCX chromatography eluting with dichloromethane/methanol (1:1) to remove impurities and then with dichloromethane/2M ammonia in methanol (1:1) to elute product. Concentrate to afford the title compound as a colorless oil (0.86 g, 94%).

Preparation 278

3-*tert*-Butoxycarbonyl-6-(4-carboxy-3-fluoro-benzylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine



Methyl 4-aminomethyl-2-fluoro-benzoate: Combine a solution of methyl 4-cyano-2-fluoro-benzoate (1 g, 5.58 mmol) in absolute ethanol (42 mL) and acetic acid (1.9 mL) with a mixture of 10% Pd/C (Degussa type E101, 0.17 g, 0.078 mmol) in water (15.6 mL) at room temperature under nitrogen. Purge with nitrogen and then with hydrogen at 55 psi and stir for 1 h. Purge the reaction with nitrogen, filter through Celite® and wash the filter cake with ethanol (100 mL), THF (100 mL) and isopropanol (100 mL). Concentrate *in vacuo* and purify by SCX chromatography and then chromatography on silica gel (40 g RediSep® column) eluting with dichloromethane/2M ammonia in methanol (99:1 to 9:1 gradient over 30 min; 35 mL/min) to afford the desired intermediate as a white solid (0.602 g, 59%).

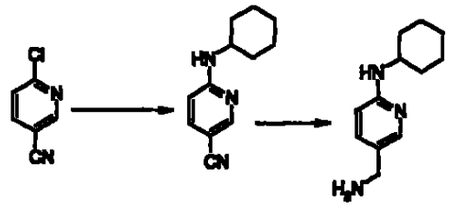
7-Chloro-6-(3-fluoro-4-methoxycarbonyl-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.24 g, 2.91 mmol) with methyl 4-aminomethyl-2-fluoro-benzoate (1.065 g, 5.821 mmol) by using tris(dibenzylideneacetone)dipalladium(0) (0.533 g, 0.582 mmol), BINAP (0.725 g, 1.16 mmol) and cesium carbonate (3.32 g, 10.2 mmol) under nitrogen in anhydrous toluene (20 mL). Purify by chromatography on silica gel eluting with hexane/EtOAc (19:1 to 1:1 gradient over 71 min; 50 mL/min) to afford the desired intermediate as a yellow oil (1.3 g, 100%).

7-Chloro-6-(3-fluoro-4-methoxycarbonyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Add 1*M* aqueous NaOH (2.8 mL, 2.8 mmol) to a solution of 7-chloro-6-(3-fluoro-4-methoxycarbonyl-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.31 g, 2.86 mmol) in 1,4-dioxane (13.3 mL) and water (2.6 mL) at 11 °C. Allow mixture to warm to room temperature and stir for 1 h. Concentrate *in vacuo* and partition the residue between dichloromethane (250 mL) and saturated aqueous $NaHCO_3$ (100 mL). Dry the organic phase over Na_2SO_4, filter and concentrate *in vacuo* to afford the desired intermediate that was used without further purification.

3-*tert*-Butoxycarbonyl-6-(4-carboxy-3-fluoro-benzylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Add 1M aqueous NaOH (5.7 mL, 5.7 mmol) to a mixture of 7-chloro-6-(3-fluoro-4-methoxycarbonyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.04 g, 2.86 mmol) in 1,4-dioxane (13.3 mL) and water (2.6 mL) at room temperature. Heat the mixture at 50 °C for 2 h. Cool the mixture to 0 °C, add a solution of di-*tert*-butyl-dicarbonate (0.62 g, 2.9 mmol) in 1,4-dioxane (2 mL) and stir at 0 °C for 2 h. Concentrate *in vacuo*, add EtOAc (50 mL), 1N aqueous $KHSO_4$ (5.7 mL, 5.7 mmol) and water (20 mL) to pH=1. Dry the organic phase over Na_2SO_4, filter and concentrate *in vacuo* to afford the title compound as a yellow oil (1.25 g, 98%) that was used without further purification. MS (ES+) *m/z*: 449.1 $(M+H)^+$.

Preparation 279

5-Aminomethyl-2-cyclohexylamino-pyridine



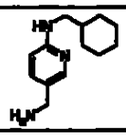
6-Cyclohexylamino-nicotinonitrile: Add cyclohexylamine (7.1 g, 72 mmol) to a mixture of 6-chloronicotinitrile (1 g, 7.2 mmol), potassium carbonate (3 g, 21.7 mmol) and anhydrous DMF (10 mL). Heat the mixture in a sealed flask at 120 °C for 1.5 h.

Cool the reaction to ambient temperature, dilute with hexane/EtOAc (1:1, 100 mL) and wash the mixture with aqueous 5% sodium chloride (3 x 30 mL). Collect the organic layer and concentrate *in vacuo* to obtain the desired intermediate (1.4 g, 97%). GC-MS *m/z*: 201 (M^+).

5-Aminomethyl-2-cyclohexylamino-pyridine: Charge a solution of 6-cyclohexylamino-nicotinonitrile (1.4 g, 7.1 mmol) in methanol (70 mL) and trifluoroacetic acid (5 mL) to a pressure vessel containing 10% Pd/C (Degussa type E101, 600 mg). Pressurize the vessel to 40 psi with hydrogen and stir for 2 h. Filter the mixture through Celite®, wash with warm ethanol, and dichloromethane. Concentrate the filtrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with dichloromethane/2M ammonia in methanol (99:1 to 90:10 gradient) to obtain the title compound (920 mg, 54%). MS (ES+) *m/z*: 206.1 $(M+H)^+$.

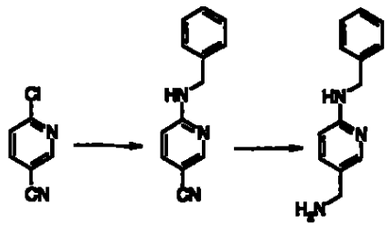
Preparation 280

The compound of Preparation 280 may be prepared essentially as described in Preparation 279 using 6-chloronicotinonitrile and cyclohexylmethylamine. Overall yield and MS (ES+) data are shown in the Table below.

Prep.	Structure	Compound	Yield (%)	MS (ES+) *m/z*
280		5-Aminomethyl-2-cyclohexylmethylamino-pyridine	95	220.3 $(M+H)^+$

Preparation 281

6-Benzylamino-pyridin-3-ylmethylamine

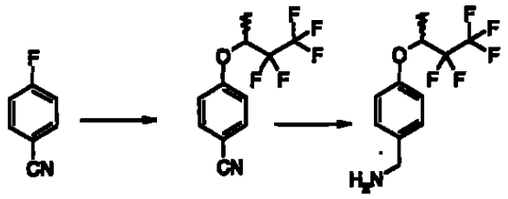


6-Benzylamino-nicotinonitrile: Heat 6-chloroniconitrile (0.58 g, 4.2 mmol) and benzylamine (4.6 mL, 42 mmol) in anhydrous DMF (3 mL) at 120 °C for 4.5 h. Cool at room temperature. Dilute with water and extract with EtOAc. Wash the organic phase with brine, dry over $MgSO_4$, filter, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting sequentially with hexane/EtOAc (4:1, 2:1, 1:2) to give the desired intermediate as a white solid (840 mg, 96%). MS (ES+) *m/z*: 210 $(M+H)^+$.

6-Benzylamino-pyridin-3-ylmethylamine: Stir 6-benzylamino-nicotinonitrile (680 mg, 3.3 mmol) and 10% Pd/C (Degussa type E101) vigorously in absolute ethanol (80 mL) under hydrogen at 25 psi for 1 h. Filter the solution through Celite® and concentrate *in vacuo*. Purify by chromatography on silica gel eluting sequentially with 2M ammonia in methanol/dichloromethane (4:96, 9:91) to give the title compound as a white solid (320 mg, 45%). MS (ES+) *m/z*: 214 $(M+H)^+$.

Preparation 282

(±)-4-[1-(1,1,2,2,2-Pentafluoroethyl)-ethoxy]-benzylamine



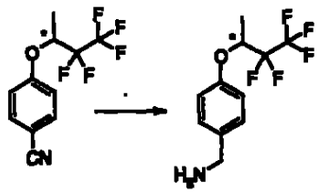
(±)-4-[1-(1,1,2,2,2-Pentafluoroethyl)-ethoxy]-benzonitrile: Add potassium carbonate (27.4 g, 198 mmol) to a mixture of 4-fluorobenzonitrile (8 g, 66 mmol) and (±)-3,3,4,4,4-pentafluoro-2-butanol (17.2 g, 105 mmol) in anhydrous DMF (60 mL). Heat the mixture in a sealed flask for 4 h at 130 °C. Cool the reaction to ambient temperature, dilute with

hexane/EtOAc (1:1, 350 mL) and wash with aqueous 5% sodium chloride (3 x 100 mL). Collect the organic layer, dry over Na_2SO_4, filter and concentrate *in vacuo* to obtain the desired intermediate (17.1 g, 98%). GC-MS *m/z*: 432 (M^+).

(±)-4-[1-(1,1,2,2,2-Pentafluoroethyl)-ethoxy]-benzylamine: Add (±)-4-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-benzonitrile (1 g, 3.8 mmol) to a slurry of lithium aluminum hydride (400 mg, 10 mmol) in diethyl ether (30 mL) at 0 °C under a nitrogen atmosphere. Stir the mixture at ambient temperature for 2 h, and then quench the reaction sequentially with water (1 mL) and 5N sodium hydroxide (1 mL). Filter the slurry through Celite®, dry the filtrate over Na_2SO_4, filter and concentrate *in vacuo* to obtain the title compound (990 mg, 98%). GC-MS *m/z*: 268 (M^+).

Preparation 283

4-[1-(1,1,2,2,2-Pentafluoroethyl)-ethoxy]-benzylamine Isomer



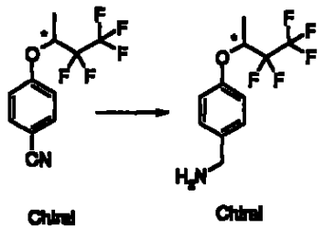
2 Chiral Chiral

4-[1-(1,1,2,2,2-Pentafluoroethyl)-ethoxy]-benzonitrile Isomer 2: Separate (±)-4-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-benzonitrile by normal phase chiral chromatography (Chiralcel OJ, 8 x 33 cm, elute with heptane/3A ethanol 97:3, flow rate 375 mL/min). Collect the 2nd eluting isomer as the desired intermediate (11.3 g, 40% recovery, 98.6% ee (Chiralcel OJ, 4.6 x 250 mm, elute with heptane/3A ethanol 97:3, 1 mL/min). GC-MS *m/z*: 265 (M^+).

4-[1-(1,1,2,2,2-Pentafluoroethyl)-ethoxy]-benzylamine Isomer 2: Reduce 4-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-benzonitrile isomer 2 (11.4 g, 43 mmol) using General Procedure 6-4 to obtain the title compound (11.38 g, 98%). GC-MS *m/z*: 268 (M^+).

Preparation 284

4-[1-(1,1,2,2,2-Pentafluoroethyl)-ethoxy]-benzylamine Isomer 1

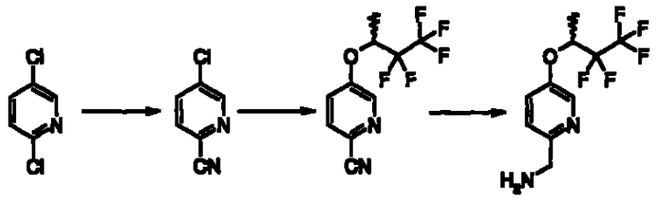


4-[1-(1,1,2,2,2-Pentafluoroethyl)-ethoxy]-benzonitrile Isomer 1: Separate (±)-4-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-benzonitrile by normal phase chiral chromatography (Chiralcel OJ, 8 x 33 cm, elute with heptane/3A ethanol 97:3, flow rate 375 mL/min). Collect the 1st eluting isomer as the desired intermediate (4.5 g, 33% recovery, 99.3% ee (Chiralcel OJ, 4.6 x 250 mm, elute with heptane/3A ethanol 97:3, 1 mL/min). GC-MS *m/z*: 265 (M^+).

4-[1-(1,1,2,2,2-Pentafluoroethyl)-ethoxy]-benzylamine Isomer 1: Reduce 4-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-benzonitrile isomer 1 (4.5 g, 17 mmol) using General Procedure 6-4 to obtain the title compound (4.3 g, 94%). GC-MS *m/z*: 268 (M^+).

Preparation 285

(±)-2-Aminomethyl-5-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-pyridine



5-Chloro-pyridine-2-carbonitrile: Slurry 2,5-dichloropyridine (6 g, 40.5 mmol), zinc cyanide (2.9 g, 24.7 mmol), zinc (dust) (116 mg, 1.8 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (720 mg, 0.98 mmol) in anhydrous DMF (40 mL). Heat the mixture to reflux under a nitrogen atmosphere for 4.5 h. Cool the mixture to room temperature, dilute with EtOAc

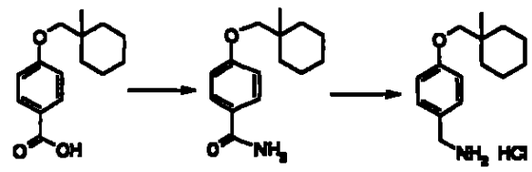
(300 mL), wash with aqueous 10% sodium chloride (3 x 75 mL). Collect organic layer, dry over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1 to 1:1 gradient) to obtain the desired intermediate (2.6 g, 46%). GC-MS *m/z*: 138 (M^+).

(±)-4-[1-(1,1,2,2,2-Pentafluoroethyl)-ethoxy]-pyridine-2-carbonitrile: Add (±)-3,3,4,4,4-pentafluoro-2-butanol (710 mg, 4.3 mmol) slowly to a slurry of sodium hydride (104 mg, 1.2 equiv, 60% mineral oil, washed with hexane) in hexamethylphosphoramide (2 mL) under nitrogen at 0 °C. Allow the slurry to warm to ambient temperature and stir for 5 min. Add 5-chloro-pyridine-2-carbonitrile (300 mg, 2.2 mmol), then heat the mixture in a sealed flask at 130 °C for 4 h (monitor reaction by GC/MS). Cool the reaction to room temperature, adjust the mixture to pH 9 with saturated aqueous Na_2CO_3, then extract with diethyl ether (2 x 50 mL). Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane/EtOAc (19:1 to 7:3 gradient) to obtain the desired intermediate (380 mg, 66%). GC-MS *m/z*: 266 (M^+).

(±)-2-Aminomethyl-5-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-pyridine: Add (±)-4-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-pyridine-2-carbonitrile (280 mg, 1 mmol), 10% Pd/C (Degussa type E101, 100 mg), methanol (20 mL) and trifluoroacetic acid (3 mL) to a pressure vessel. Pressurize the vessel to 40 psi with hydrogen, and stir the mixture for 1 h (monitor the reaction by TLC). Filter the mixture through Celite® and wash the cake with warm ethanol followed by dichloromethane under a nitrogen atmosphere. Concentrate the filtrate *in vacuo* to obtain the crude product as a trifluoroacetic acid salt. Prepare the free base using SCX chromatography, then purify by chromatography on silica gel eluting with dichloromethane/2M ammonia in methanol (20:1) to obtain the title compound (172 mg, 61%). GC-MS *m/z*: 270 (M^+).

Preparation 286

4-(1-Methyl-cyclohexylmethoxy)-benzylamine hydrochloride

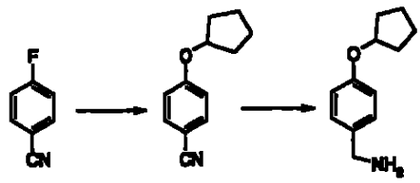


4-(1-Methyl-cyclohexylmethoxy)-benzamide: Add a drop of anhydrous DMF to a mixture of 4-(1-methyl-cyclohexylmethoxy)-benzoic acid (prepared by following the procedure described in *Chem. Pharm. Bull.* 1982, *30*, 3601-3616) (1 g, 4.03 mmol) and thionyl chloride (3.5 mL) at room temperature. Stir the mixture for 1.5 h and then remove the excess of thionyl chloride *in vacuo*. Take-up the crude acid chloride in anhydrous THF (10 mL) and add the resulting solution to cold concentrated NH_4OH (50 mL). Stir for 2.5 h at room temperature and concentrate *in vacuo*. Collect the solid formed *via* filtration and dry *in vacuo* to obtain the desired intermediate (0.94 g, 94%). MS (ES+) *m/z*: 248 $(M+H)^+$.

4-(1-Methyl-cyclohexylmethoxy)-benzylamine hydrochloride: Add a solution of 4-(1-methyl-cyclohexylmethoxy)-benzamide (6.82 g, 27.6 mmol) in anhydrous THF (75 mL) dropwise over 45 min to a slurry of lithium aluminium hydride (1.57 g, 41.3 mmol) in diethyl ether (100 mL) at room temperature. After the addition is completed, heat the mixture at reflux for 5.5 h. Cool the reaction mixture with an ice bath and quench sequentially with water (1.6 mL), 5N aqueous NaOH (1.6 mL) and water (4.8 mL). Stir the resulting suspension for 1 h and remove the solids formed *via* filtration through Celite® eluting with THF. Dry the filtrate over Na_2SO_4 and treat the solution with an excess of hydrogen chloride in diethyl ether. Concentrate the mixture *in vacuo* to obtain the title compound (6.68 g, 90%). MS (ES+) *m/z*: 233 $(M+H)^+$.

Preparation 287

4-Cyclopentyloxy-benzylamine

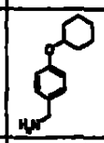
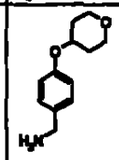
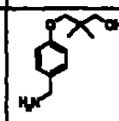
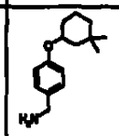
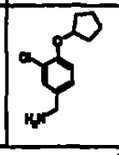


4-Cyclopentyloxy-benzonitrile: Suspend sodium hydride (336 mg, 2.8 mmol, 60% suspension in mineral oil) in anhydrous 1,4-dioxane (10 mL) under nitrogen atmosphere. Add cyclopentanol (620 mg, 7.2 mmol) and stir the resulting solution for 30 min. Add the preformed solution (3.35 mL, 2.4 mmol) to neat 4-fluorobenzonitrile (240 mg, 2 mmol) in a microwave tube and heat the sealed mixture at 100 °C for 30 min. Cool to room temperature and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with isohexane/EtOAc (95:5 to 1:1 gradient) to obtain the desired intermediate (300 mg, 80%). GC-MS *m/z*: 187 (M^+).

4-Cyclopentyloxy-benzylamine: Add a solution of 1M BH_3-THF complex in THF (4.8 mL, 4.8 mmol) to neat 4-cyclopentyloxy-benzonitrile (300 mg, 1.6 mmol) and stir the mixture for 3 h at room temperature and then for 3 h at reflux. Cool to room temperature, pour the reaction into 2N aqueous HCl (10 mL) and stir the mixture for 1 h at room temperature then concentrate *in vacuo*. Dissolve the crude mixture in methanol and filter through SCX column eluting with methanol followed by 3M ammonia in methanol to obtain the title compound (223 mg, 73%).

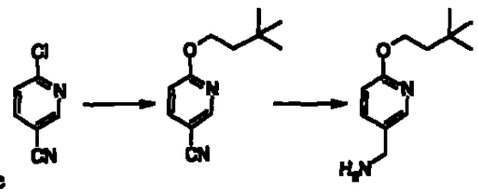
Preparations 288-292

The compounds of Preparations 288-292 may be prepared essentially as described in Preparation 287 using the appropriate alcohols. For Preparations 288, 290 and 291, sodium bis(trimethylsilyl)amide (1.2 equiv., 2M solution in THF) was used as base in the first step. Overall yields and MS (EI) data are shown in the Table below.

Prep.	Structure	Compound	Yield (%)	MS (EI) m/z
288		4-Cyclohexyloxy-benzylamine	52	205 (M^+)
289		4-(Tetrahydro-pyran-4-yloxy)-benzylamine	42	207 (M^+)
290		3-(4-Aminomethyl-phenoxy)-2,2-dimethyl-propan-1-ol	38	209 (M^+)
291		(±)-4-(3,3-Dimethyl-cyclohexyloxy)-benzylamine	37	233 (M^+)
292		3-Chloro-4-cyclopentyloxy-benzylamine	42	225 (M^+)

Preparation 293

5-Aminomethyl-2-(3,3-dimethyl-butoxy)-pyridine



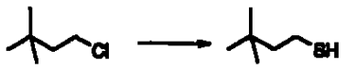
<u>6-(3,3-Dimethyl-butoxy)-nicotinonitrile</u>: Add sodium bis(trimethylsilyl)amide (3.95 mL, 7.9 mmol, 2M solution in THF) to a solution of 3,3-dimethyl-butan-1-ol (960 □L, 7.9 mmol) in anhydrous THF (10 mL). Stir for 30 min at room temperature and then add a solution of 6-chloro-nicotinonitrile (1 g, 7.2 mmol) in anhydrous THF (5 mL). Stir at room temperature overnight and then quench the reaction mixture with saturated aqueous

$NaHCO_3$ (100 mL). Extract the aqueous layer with dichloromethane (3 x 100 mL) and wash the organic layer with brine (100 mL). Dry the combined organic extracts over $MgSO_4$ and concentrate *in vacuo* to give the desired intermediate as a yellow solid (1.4 g, 94%). GC-MS *m/z*: 204 (M^+).

5-Aminomethyl-2-(3,3-dimethyl-butoxy)-pyridine: Dissolve 6-(3,3-dimethyl-butoxy)-nicotinonitrile (1.4 g, 6.86 mmol) in anhydrous THF (10 mL) under nitrogen and add 1M BH_3-THF complex in THF (20.6 mL, 20.6 mmol). Stir the mixture overnight under nitrogen and then pour the reaction carefully into 5N aqueous HCl (20 mL). Stir the resulting suspension for 6 h at room temperature. Then basify by adding 2N aqueous NaOH (50 mL) and extract with dichloromethane (3 x 100 mL). Dry the combined organic extracts over $MgSO_4$, filter and concentrate *in vacuo*. Take-up the resulting oil in methanol and filter it through an SCX column eluting with methanol followed by 3M ammonia in methanol. Concentrate *in vacuo* to obtain the title compound (754 g, 50%). GC-MS *m/z*: 208 (M^+).

Preparation 294

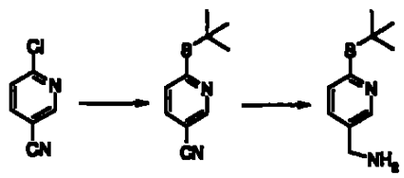
3,3-Dimethylbutanethiol



Into four separate microwave tubes add thiourea (630 mg, 8.3 mmol) to a solution of 1-chloro-3,3-dimethylbutane (0.5 g, 4.4 mmol) in ethanol (5 mL) and heat in a sealed tube in a microwave reactor at 150 W at 100 °C for 4 h. Cool to room temperature then stand over three days. Combine the reactions and concentrate *in vacuo* to afford a white solid. Add 2M aqueous NaOH (50 mL) and heat at reflux overnight. Cool to room temperature then acidify to pH 2 with 5M aqueous HCl (20 mL). Extract into diethyl ether (50 mL), wash with brine (30 mL) then dry over $MgSO_4$ and concentrate *in vacuo* to give the title compound as a clear oil (2 g, 100%).

Preparation 295

5-Aminomethyl-2-*tert*-butylthio-pyridine



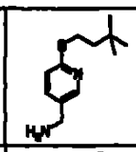
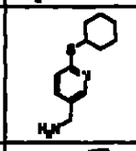
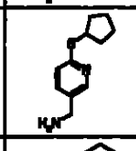
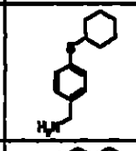
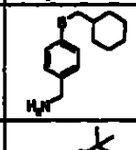
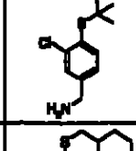
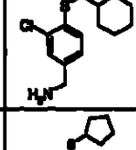
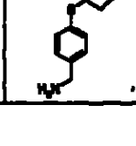
6-(*tert*-Butylthio)nicotinonitrile: Add sodium ethoxide (12 mL of 21% w/v in ethanol, 36 mmol) to a solution of 2-methyl-2-propanethiol (4.06 mL, 36 mmol) in anhydrous ethanol (90 mL) at 0 °C under nitrogen atmosphere. Stir the solution and allow it to warm to room temperature over 30 min. Add 6-chloronicotinonitrile (5 g, 36 mmol) and then heat the reaction to reflux overnight. Cool to room temperature, add saturated aqueous $NaHCO_3$ and concentrate *in vacuo*. Extract into EtOAc or dichloromethane and wash with brine. Dry over $MgSO_4$ and concentrate *in vacuo* to give the desired intermediate as orange crystals (6.31 g, 91%). MS (ES+) *m/z*: 193 $(M+H)^+$.

5-Aminomethyl-2-*tert*-butylthio-pyridine: Use a method similar to the General Procedure 6-5 to react 6-(*tert*-butylthio)nicotinonitrile (4.4 g, 22.7 mmol) in anhydrous THF (25 mL) with 1M BH_3-THF complex in THF (25 mL, 25 mmol). Add 5M aqueous HCl (10 mL) cautiously and stir the mixture overnight at room temperature. Extract into EtOAc, wash with brine, dry over $MgSO_4$ and concentrate *in vacuo* to give an orange solid. Dissolve the crude mixture in methanol and filter through an SCX column eluting with methanol followed by 3M ammonia in methanol to obtain the title compound (2.74 g, 61%). MS (ES+) *m/z*: 197 $(M+H)^+$.

Preparations 296-303

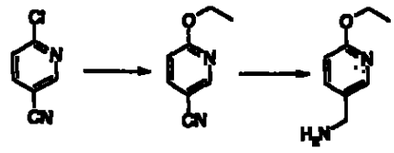
The compounds of Preparations 296-303 may be prepared essentially as described in Preparation 295 using the appropriate thiol and 6-chloronicotinonitrile (Preparations 296-298) or the appropriate aryl fluoride (Preparations 299-303). Overall yields and MS (ES+) data are shown in the Table below.

Prep.	Structure	Compound	Yield (%)	MS (ES+) *m/z*

296		5-Aminomethyl-2-(3,3-dimethyl-butylthio)-pyridine	5	225 $(M+H)^+$
297		5-Aminomethyl-2-cyclohexylthio-pyridine	47	223 $(M+H)^+$
298		5-Aminomethyl-2-cyclopentylthio-pyridine	63	209 $(M+H)^+$
299		4-Cyclohexylthio-benzylamine	30	205 $(M+H-NH_3)^+$
300		4-Cyclohexylmethylthio-benzylamine	30	219 $(M+H-NH_3)^+$
301		4-*tert*-Butylthio-3-chloro-benzylamine	52	213 $(M+H-NH_3)^+$
302		4-Cyclohexylmethylthio-3-chloro-benzylamine	31	253 $(M+H-NH_3)^+$
303		4-Cyclopentylthio-benzylamine	61	208 $(M+H)^+$

Preparation 304

5-Aminomethyl-2-ethoxy-pyridine

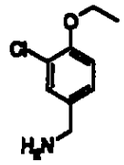


6-(Ethoxy)nicotinonitrile: Add sodium ethoxide (1.6 mL of 21% w/v in ethanol, 4.8 mmol) to a solution of 6-chloronicotinonitrile (612 mg, 4.41 mmol) in anhydrous ethanol (15 mL) and heat the reaction at reflux for 3 h. Cool to room temperature and stir overnight under nitrogen atmosphere. Concentrate *in vacuo* and dissolve the residue into dichloromethane. Wash with saturated aqueous $NaHCO_3$, dry over $MgSO_4$ and concentrate *in vacuo* to give the desired intermediate as an off-white solid (545 mg, 83%).

5-Aminomethyl-2-ethoxy-pyridine: Add a solution of 1M BH_3-THF complex in THF (7 mL, 7 mmol) to a solution of 6-(ethoxy)nicotinonitrile (911 mg, 4.41 mmol) in anhydrous THF (7 mL) and stir the mixture overnight at reflux. Add a second aliquot of 1M BH_3-THF complex in THF (7 mL, 7 mmol) and stir the mixture overnight at reflux. Add 5N aqueous HCl (10 mL) cautiously and stir the mixture overnight at room temperature. Concentrate *in vacuo* then dissolve the crude mixture in methanol and filter through an SCX column eluting with methanol followed by 3M ammonia in methanol to obtain the title compound (250 mg, 40%). MS (ES+) *m/z*: 153 $(M+H)^+$.

Preparation 305

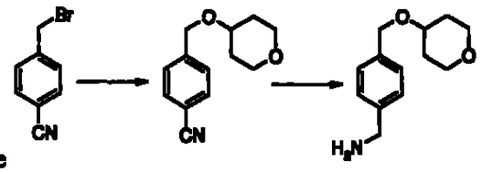
4-Ethoxy-3-chloro-benzylamine



The compound of Preparation 305 may be prepared essentially as described in Preparation 304 using the appropriate aryl fluoride (38% yield, MS (ES+) *m/z* 169 $(M+H-NH_3)^+$).

Preparation 306

4-(Tetrahydro-pyran-4-yloxymethyl)-benzylamine

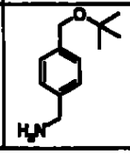


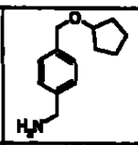
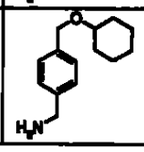
4-(Tetrahydro-pyran-4-yloxymethyl)-benzonitrile: Add sodium bis(trimethylsilyl)amide (2.8 mL, 5.61 mmol, 2M solution in THF) to a solution of tetrahydro-pyran-4-ol (572 mg, 5.61 mmol) in anhydrous THF (20 mL) and stir for 30 min. Add a solution of 4-bromomethyl-benzonitrile (1 g, 5.1 mmol) in anhydrous THF (5 mL) and stir the resulting mixture overnight at room temperature. Concentrate *in vacuo* and purify the crude mixture by chromatography on silica gel eluting with cyclohexane/EtOAc (98:2 to 1:1 gradient) to obtain the desired intermediate as a white solid (845 mg, 76%). GC-MS *m/z*: 217 (M^+).

4-(Tetrahydro-pyran-4-yloxymethyl)-benzylamine: Use a method similar to the General Procedure 6-5 to reduce 4-(tetrahydro-pyran-4-yloxymethyl)-benzonitrile (845 mg, 4 mmol). Reflux overnight to obtain the title compound (812 mg, 91%). MS (ES+) *m/z*: 222.2 $(M+H)^+$.

Preparations 307-309

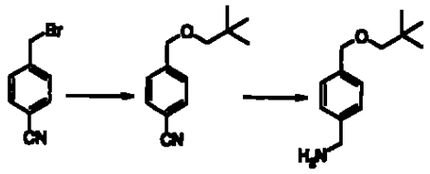
The compounds of Preparations 307-309 may be prepared essentially as described in Preparation 306 using 4-bromomethyl-benzonitrile and the appropriate alcohol. Overall yields and MS (ES+) data are shown in the Table below.

Prep.	Structure	Compound	Yield (%)	MS (ES+) *m/z*
307		4-*tert*-Butoxymethyl-benzylamine	22	194 $(M+H)^+$

308		4-Cyclopentyloxymethyl-benzylamine	72	206 $(M+H)^+$
309		4-Cyclohexyloxymethyl-benzylamine	58	220 $(M+H)^+$

Preparation 310

4-(2,2-Dimethyl-propoxymethyl)-benzylamine

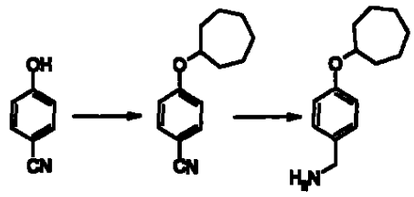


4-(2,2-Dimethyl-propoxymethyl)-benzonitrile: Add sodium bis(trimethylsilyl)amide (3 mL, 6 mmol, 2M solution in THF) to a solution of 2,2-dimethyl-1-propanol (528 mg, 6 mmol) in anhydrous 1,4-dioxane. Stir until the suspension becomes homogenous. Then add a solution of 4-cyanobenzyl bromide (980 mg, 5 mmol) in anhydrous 1,4-dioxane (3 mL). Heat the mixture in a microwave oven at 100 °C for 30 min. Cool to room temperature, add water (50 mL) and extract with EtOAc (3 x 50 mL). Dry the combined organic extracts over $MgSO_4$, and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with isohexane/EtOAc (95:5 to 1:1 gradient) to obtain the desired intermediate (811 mg, 80%).

4-(2,2-Dimethyl-propoxymethyl)-benzylamine: Add 1M BH_3-THF complex in THF (16 mL, 16 mmol) to neat 4-(2,2-dimethyl-propoxymethyl)-benzonitrile (3.043 g, 15 mmol) and stir the mixture overnight at room temperature. Add methanol and stir until hydrogen evolution stops. Concentrate the solution *in vacuo*. Dissolve the crude mixture in methanol and filter through an SCX column eluting with methanol followed by 3M ammonia in methanol. Concentrate *in vacuo* to obtain the title compound (3 g, 96%).

Preparation 311

4-Cycloheptyloxy-benzylamine

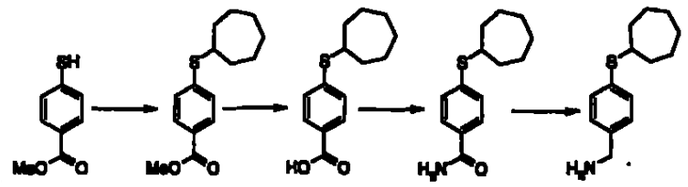


4-Cycloheptyloxy-benzonitrile: Under a nitrogen atmosphere, add 4-hydroxybenzonitrile (4 g, 33.5 mmol), cycloheptanol (2.55 g, 22.3 mmol), tri-*n*-butylphosphine (8.25 mL, 33.5 mmol), and azodicarboxylate dipiperidine (8.45 g, 33.5 mmol) to anhydrous THF (60 mL) at 0 °C. Stir the mixture at 0 °C for 1 h and then at room temperature for 12 h. Dilute with EtOAc (50 mL) and water (50 mL). Separate the layers and extract the aqueous phase with EtOAc (4 × 30 mL). Wash the combined organic extracts with water (30 mL) and brine (20 mL). Dry over Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel (120 g RediSep column) eluting with hexane/EtOAc (1:0 to 1:1 gradient over 1.25 h; 80 mL/min) to provide the desired intermediate as a colorless oil (2.77 g, 58%). MS (APCI) *m/z*: 216 $(M+H)^+$.

4-Cycloheptyloxy-benzylamine: Dissolve 4-cycloheptyloxy-benzonitrile (2 g, 9.29 mmol) in anhydrous THF (20 mL) and cool to 0 °C. Add borane dimethylsulfide complex (2.8 mL, 27.9 mmol, 10-12 M solution), stir at 0 °C for 0.5 h and then heat at reflux for 1 h. Cool the mixture to 0 °C, add methanol (5 mL) and stir for 15 min. Add 2M aqueous HCl (15 mL) and stir for 30 min at room temperature. Concentrate the mixture *in vacuo* and purify the residue by chromatography on silica gel (45 g RediSep column) eluting with a gradient of dichloromethane in chloroform/methanol/concentrated ammonium hydroxide (80:18:2) over 30 min (80 mL/min) to provide the title compound as a colorless oil (1.87 g, 97%). MS (APCI) *m/z*: 220 $(M+H)^+$.

Preparation 312

4-Cycloheptylthio-benzylamine



Methyl 4-cycloheptylthio-benzoate: Under a nitrogen atmosphere, add methyl 4-mercaptobenzoate (2.5 g, 15 mmol), cycloheptanol (2.55 g, 22.3 mmol), tri-*n*-butylphosphine (5.26 g, 26 mmol) and azodicarboxylate dipiperidine (6.56 g, 26 mmol) to anhydrous THF (50 mL) at 0 °C. Stir the mixture at 0 °C for 1 h and then at room temperature for 12 h. Dilute with EtOAc (50 mL) and water (50 mL) and extract the aqueous phase with EtOAc (4 × 30 mL). Wash the combined organic extracts with water (30 mL) and brine (20 mL). Dry the organic phase over Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel (120 g RediSep column) eluting with hexane/EtOAc (1:0 to 1:1 gradient over 1.25 h; 80 mL/min) to provide the desired intermediate as a colorless oil (1.12 g, 40%). MS (APCI) *m/z*: 265 $(M+H)^+$.

4-Cycloheptylthio-benzoic acid: Add methyl 4-cycloheptylthio-benzoate (1.1 g, 4.16 mmol) and sodium hydroxide (500 mg, 12.5 mmol) to methanol (20 mL) and stir overnight. Add 2M aqueous HCl (20 mL) and extract the aqueous phase with dichloromethane. Wash the combined organic extracts with water (20 mL) and brine (20 mL). Dry the organic solution over Na_2SO_4, filter and concentrate *in vacuo* to provide the desired intermediate as a white solid (984 mg, 94%). MS (APCI) *m/z*: 251 $(M+H)^+$.

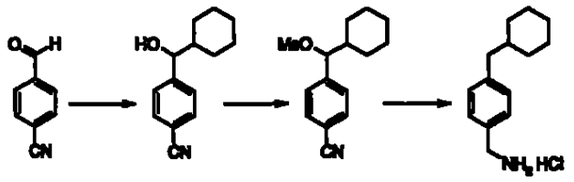
4-Cycloheptylthio-benzamide: Add thionyl chloride (1.35 mL, 18.4 mmol) to a mixture of 4-cycloheptylthio-benzoic acid (984 mg, 3.93 mmol) in dichloromethane (15 mL) at 0 °C. Heat the mixture to reflux for 1 h. Cool the mixture to room temperature and concentrate *in vacuo*. Dissolve the residue in dichloromethane (20 mL) and cool to 0 °C. Add triethylamine (1.1 mL, 7.86 mmol) and bubble ammonia gas through the solution.

Warm the mixture to room temperature and stir for 1 h. Dilute with water (20 mL) and extract the aqueous phase with dichloromethane (3 × 20 mL). Wash the combined organic extracts with saturated aqueous $NaHCO_3$ (20 mL). Dry the organic solution over Na_2SO_4, filter and concentrate *in vacuo* to provide the desired intermediate as an off-white solid (976 mg, 99%). MS (APCI) *m/z*: 250 $(M+H)^+$.

4-Cycloheptylthio-benzylamine: Under a nitrogen atmosphere, add 4-cycloheptylthio-benzamide (976 mg, 3.91 mmol) to a slurry of lithium aluminum hydride (0.398 mg, 11.7 mmol) in anhydrous THF (25 mL) at 0 °C. Heat the mixture for 1 h. Cool the mixture to 0 °C and add diethyl ether (50 mL). Carefully add water (0.4 mL), 3M aqueous NaOH (0.4 mL) and water (1.2 mL). Filter the solid residue and concentrate the filtrate *in vacuo*. Purify the crude mixture by chromatography on silica gel (45 g RediSep column) eluting with a gradient of dichloromethane in chloroform/methanol/concentrated ammonium hydroxide (80:18:2) over 45 min (80 mL/min) to give the title compound as a colorless oil (530 mg, 57%). MS (ES+) *m/z*: 236 $(M+H)^+$.

Preparation 313

4-Cyclohexylmethyl-benzylamine hydrochloride



4-(Cyclohexyl-hydroxy-methyl)-benzonitrile: Dissolve 4-formyl-benzonitrile (5 g, 38.1 mmol) in anhydrous toluene (50 mL). Add chlorodicyclohexylborane (39 mL, 39 mmol, 1M solution in hexane) and 2,6-lutidine (4.25 mL, 39 mmol) and stir the mixture overnight at room temperature. Cool to 0 °C, add aqueous hydrogen peroxide (5.4 mL, 48 mmol, 30%) and 3M aqueous NaOH (16 mL, 48 mmol) and stir for 15 min. Add EtOAc and extract the aqueous phase with EtOAc. Wash the combined organic extracts with water and brine. Dry the organic solution over Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel (45 g RediSep column)

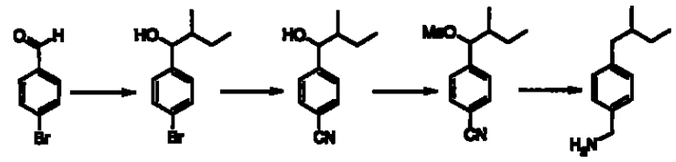
eluting with hexane/EtOAc (1:0 to 1:1 gradient over 60 min; 80 mL/min) to provide the desired intermediate as a clear oil (2.3 g, 23%). MS (APCI) *m/z*: 197 $(M-H_2O)^+$.

4-(Cyclohexyl-methanesulfonyloxy-methyl)-benzonitrile: Dissolve 4-(cyclohexyl-hydroxy-methyl)-benzonitrile (1 g, 4.66 mmol), and triethylamine (1.3 mL, 9.3 mmol) in dichloromethane (20 mL). Cool the mixture to 0 °C, add methanesulfonyl chloride (1.49 mL, 5.34 mmol) and stir the solution for 2 h at 0 °C. Add water (10 mL) and saturated aqueous $NaHCO_3$ (10 mL). Separate the layers and extract back the aqueous phase with dichloromethane (3 × 20 mL). Combine the organic layers, wash with water (20 mL), dry over Na_2SO_4, filter and concentrate *in vacuo* to provide the desired intermediate as a yellow oil (1.29 g, 94%). MS (APCI) *m/z*: 294 $(M+H)^+$.

4-Cyclohexylmethyl-benzylamine hydrochloride: Dissolve 4-(cyclohexyl-methanesulfonyloxy-methyl)-benzonitrile (1.36 g, 4.64 mmol) in diethyl ether (20 mL) and cool the solution to 0 °C. Add lithium aluminum hydride (528 mg, 13.9 mmol) and stir the mixture at 0 °C for 2 h and then at room temperature for 3 h. Cool the mixture to 0 °C and carefully add water (0.5 mL), 3M aqueous NaOH (0.55 mL), and water (1.5 mL). Filter the solid residue and concentrate the filtrate *in vacuo*. Dissolve the crude mixture in diethyl ether and bubble hydrogen chloride to form a white precipitate. Filter and dry the solid *in vacuo* to provide the title compound as a white solid (420 mg, 44%). MS (APCI) *m/z*: 204 $(M+H)^+$.

Preparation 314

4-(2-Methyl-butyl)-benzylamine



4-(1-Hydroxy-2-methyl-butyl)-1-bromo-benzene: Add slowly a solution of 2-bromo-butane (4.8 g, 35 mmol) in anhydrous THF (20 mL) to a stirring mixture of magnesium

(980 mg, 37 mmol) and anhydrous THF (10 mL) under a nitrogen atmosphere. Heat the mixture at reflux for 30 min. Cool the mixture to room temperature and add 4-bromo-benzaldehyde (5.36 g, 29 mmol). After stirring for 5 min, cool the mixture in an ice-bath and acidify with 3N aqueous HCl (50 mL). Dilute the mixture with water and extract twice with diethyl ether. Wash the combined organic extracts with water and brine. Dry the organic phase over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 20:1 and 1:1) to provide the desired intermediate as a clear oil (2 g, 28%). MS (APCI) *m/z*: 243 $(M+H)^+$.

4-(1-Hydroxy-2-methyl-butyl)-benzonitrile: Add 4-(1-hydroxy-2-methyl-butyl)-1-bromo-benzene (1.9 g, 7.8 mmol), zinc cyanide (1.82 g, 15.6 mmol), and tetrakistriphenylphosphine palladium(0) (260 mg, 0.22 mmol) to anhydrous DMF (40 mL) under a nitrogen atmosphere. Heat the mixture at 90 °C for 12 h. Cool the mixture to room temperature, dilute with water and extract the aqueous phase twice with dichloromethane. Wash the combined organic extracts with water and brine. Dry the organic solution over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0 and 20:1) to provide the desired intermediate (1.2 g, 75%). MS (APCI) *m/z*: 190 $(M+H)^+$.

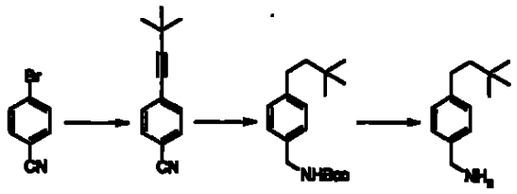
4-(1-Methanesulfonyloxy-2-methyl-butyl)-benzonitrile: Add methanesulfonyl chloride (540 mg, 4.72 mmol) to a solution of 4-(1-hydroxy-2-methyl-butyl)-benzonitrile (800 mg, 4.23 mmol) and triethylamine (0.88 mL, 6.35 mmol) in dichloromethane (10 mL) at 0 °C. Warm the mixture to room temperature and stir for 1 h. Dilute the mixture with water and dichloromethane. Extract the aqueous layer with dichloromethane. Wash the combined organic extracts with water. Dry the organic solution over Na_2SO_4, filter and concentrate *in vacuo* to provide the desired intermediate as a clear oil (1.38 g) that was used without further purification. MS (APCI) *m/z*: 268 $(M+H)^+$.

4-(2-Methyl-butyl)-benzylamine: Under a nitrogen atmosphere, add a mixture of 4-(1-methanesulfonyloxy-2-methyl-butyl)-benzonitrile (1.3 g, 4.9 mmol) in diethyl ether (5 mL) to a slurry of lithium aluminum hydride (820 mg, 19.5 mmol) in diethyl ether (25

mL) at 0 °C. Heat the mixture under reflux for 1 h. Cool the mixture in an ice-bath and add water (0.9 mL), 15% aqueous NaOH (0.9 mL) and water (2.8 mL). Apply the mixture to a silica gel column eluting with dichloromethane and 5:1 dichloromethane in chloroform/methanol/concentrated ammonium hydroxide (80:18:2) to provide the title compound (450 mg, 52%). MS (ES+) *m/z*: 178 $(M+H)^+$.

Preparation 315

4-(3,3-Dimethyl-butyl)-benzylamine



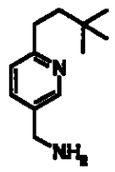
4-(3,3-Dimethyl-but-1-ynyl)-benzonitrile: Dissolve 4-bromobenzonitrile (3 g, 16.48 mmol) in anhydrous DMF (30 mL) in a sealed tube. Degas the solution, purge with nitrogen and add tris(dibenzylideneacetone)dipalladium(0) (453 mg, 0.49 mmol), copper(I) iodide (188 mg, 0.99 mmol), triphenylphosphine (1.08 g, 4.12 mmol), triethylamine (10 mL) and 3,3-dimethylbutyne (6.1 mL, 49.44 mmol). Heat the mixture at 90 °C overnight. Cool to room temperature, add water and extract the aqueous phase twice with EtOAc. Dry the combined organic extracts over $MgSO_4$, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane and hexane/EtOAc (19:1, 9:1) to give the desired intermediate as a solid (2.75 g, 92%).

N-(*tert*-Butoxycarbonyl)-4-(3,3-dimethyl-butyl)-benzylamine: Dissolve 4-(3,3-dimethyl-but-1-ynyl)-benzonitrile (0.85 g, 4.64 mmol) in methanol (50 mL). Add 10% Pd/C (Degussa type E101, 0.68 g) and di-*tert*-butyl-dicarbonate (1.21 g, 5.57 mmol). Submit the mixture to hydrogenation under atmospheric pressure (balloon) for 6 h. Filter the catalyst through Celite® and concentrate the filtrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane and hexane/EtOAc (9:1, 4:1) to provide the desired intermediate as an oil (1.25 g, 93%). MS (ES+) *m/z*: 314 $(M+Na)^+$.

4-(3,3-Dimethyl-butyl)-benzylamine: Add 4N hydrogen chloride in dioxane (15 mL) to a stirred solution of *N*-(*tert*-butoxycarbonyl)-4-(3,3-dimethyl-butyl)-benzylamine (1.25 g, 4.29 mmol) in methanol (20 mL) and stir at room overnight. Concentrate *in vacuo* and wash the solid with diethyl ether. Suspend the solid in dichloromethane and saturated aqueous $NaHCO_3$ and stir until both phases are clear (15 min). Extract the aqueous phase twice with dichloromethane. Dry the combined organic extracts over $MgSO_4$, filter and concentrate *in vacuo* to give the title compound as an oil (0.654 g, 80%) that was used without any further purification. MS (ES+) *m/z*: 192 $(M+H)^+$.

Preparation 316

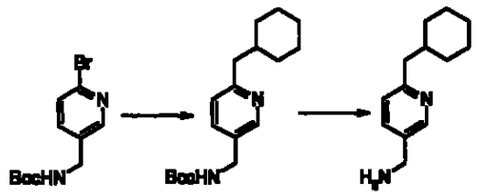
3-Aminomethyl-6-(3,3-dimethyl-butyl)-pyridine



The title compound may be prepared essentially as described in Preparation 315 by using 6-bromonicotinonitrile (45% yield, MS (ES+) *m/z* 193 $(M+H)^+$).

Preparation 317

3-Aminomethyl-6-cyclohexylmethyl-pyridine



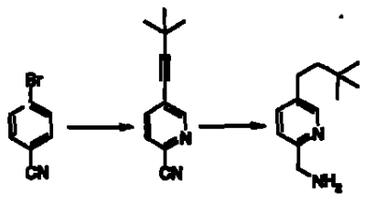
3-*tert*-Butoxycarbonylaminomethyl-6-cyclohexylmethyl-pyridine: Dissolve 2-bromo-5-*tert*-butoxycarbonylaminomethyl-pyridine (500 mg, 1.74 mmol) in anhydrous THF (5 mL) in a sealed tube. Degas the solution, purge with nitrogen and add 1,1'-[bis(diphenylphosphino)ferrocene]dichloropalladium(II) (127 mg, 0.174 mmol) and 0.5M cyclohexylmethylzinc bromide in THF (10.4 mL, 5.22 mmol). Heat the mixture at 60 °C

overnight. Cool to room temperature and dilute the reaction mixture with EtOAc. Add water and filter the precipitate over Celite®. Dry the organic phase over $MgSO_4$, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane and hexane/EtOAc (4:1, 3:2) to give the desired intermediate as an oil (359 mg, 68%). MS (ES+) *m/z*: 305 $(M+H)^+$.

3-Aminomethyl-6-cyclohexylmethyl-pyridine: Add 4N hydrogen chloride in dioxane (10 mL) to a solution of 3-*tert*-butoxycarbonylaminomethyl-6-cyclohexylmethyl-pyridine (345 mg, 1.13 mmol) in EtOAc (10 mL) and stir overnight. Concentrate *in vacuo*, suspend the solid obtained in diethyl ether and add hexane. Filter and wash the solid with hexane. Suspend the solid into dichloromethane, add saturated aqueous $NaHCO_3$ and stir until both phases are clear (15 min). Extract the aqueous phase twice with dichoromethane. Dry the combined organic extracts over $MgSO_4$, filter and concentrate *in vacuo* to obtain the title compound as an oil (205 mg, 97%) that was used without any further purification. MS (ES+) *m/z*: 205 $(M+H)^+$.

Preparation 318

2-Aminomethyl-5-(3,3-dimethyl-butyl)-pyridine



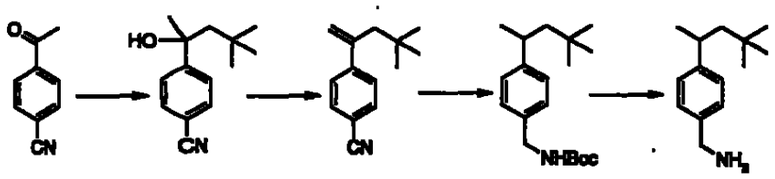
5-(3,3-Dimethyl-but-1-ynyl)-2-cyano-pyridine: Dissolve 5-bromo-2-cyano-pyridine (316 mg, 1.72 mmol) in anhydrous DMF (7 mL) in a sealed tube. Degas the solution, purge with nitrogen and add tris(dibenzylideneacetone)dipalladium(0) (47 mg, 0.05 mmol), copper(I) iodide (20 mg, 0.1 mmol), triphenylphosphine (113 mg, 0.43 mmol), triethylamine (2 mL) and 3,3-dimethylbutyne (0.64 mL, 5.16 mmol). Heat the mixture at 90 °C overnight. Cool to room temperature, add water and extract the aqueous phase twice with EtOAc. Dry the combined organic extracts over $MgSO_4$, filter and concentrate

in vacuo. Purify the crude mixture by chromatography on silica gel eluting with hexane and hexane/EtOAc (19:1) to give the desired intermediate as a solid (310 mg, 97%).

2-Aminomethyl-5-(3,3-dimethyl-butyl)-pyridine: Dissolve 5-(3,3-dimethyl-but-1-ynyl)-2-cyano-pyridine (255 mg, 1.5 mmol) in methanol (15 mL). Add 10% Pd/C (Degussa type E101, 230 mg) and submit the mixture to hydrogenation under atmospheric pressure (balloon) overnight. Filter the catalyst through Celite® and concentrate the filtrate *in vacuo* to provide the title compound as a solid (231 mg, 87%) that was used without any further purification. MS (ES+) *m/z*: 193 $(M+H)^+$.

Preparation 319

4-(1,3,3-Trimethyl-butyl)-benzylamine



4-(1-Hydroxy-1,3,3-trimethyl-butyl)-benzonitrile: Dissolve 4-acetylbenzonitrile (1 g, 6.88 mmol) in diethyl ether/THF (1:1, 60 mL) and cool the solution to 0 °C. Add 1M neopentylmagnesium chloride in diethyl ether (8.3 mL, 8.3 mmol) under nitrogen and stir the mixture at room temperature overnight. Add saturated aqueous NH_4Cl and extract the mixture twice with EtOAc. Dry the combined organic extracts over $MgSO_4$, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane and hexane/EtOAc (19:1, 9:1) to give the desired intermediate (364 mg, 24%).

4-(3,3-Dimethyl-1-methylene-butyl)-benzonitrile: Add *p*-toluenesulfonic acid monohydrate (308 mg, 1.62 mmol) to a solution of 4-(1-hydroxy-1,3,3-trimethyl-butyl)-benzonitrile (352 mg, 1.62 mmol) in toluene (10 mL). Heat the solution to 100 °C for 30 min. Cool the reaction mixture to room temperature, dilute the reaction mixture with EtOAc and wash the organic phase with saturated aqueous $NaHCO_3$. Dry the organic phase over $MgSO_4$, filter and concentrate *in vacuo*. Purify the crude mixture by

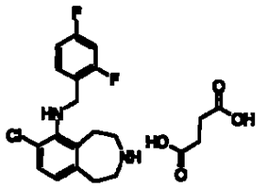
chromatography on silica gel eluting with hexane and hexane/EtOAc (98:2, 19:1) to give the desired intermediate as an oil (200 mg, 62%).

N-(*tert*-Butoxycarbonyl)-4-(1,3,3-trimethyl-butyl)-benzylamine: Dissolve 4-(3,3-dimethyl-1-methylene-butyl)-benzonitrile (164 mg, 0.82 mmol) in methanol (15 mL). Add 10% Pd/C (Degussa type E101, 130 mg) and di-*tert*-butyl-dicarbonate (197 mg, 0.902 mmol). Submit the mixture to hydrogenation under atmospheric pressure (balloon) for 3 h. Filter the catalyst through Celite® and concentrate the filtrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane and hexane/EtOAc (19:1, 9:1) to provide the desired intermediate as an oil (227 mg, 90%). MS (ES+) *m/z*: 328 $(M+Na)^+$.

4-(1,3,3-Trimethyl-butyl)-benzylamine: Add 4N hydrogen chloride in dioxane (10 mL) to a stirred solution of *N*-(*tert*-butoxycarbonyl)-4-(1,3,3-trimethyl-butyl)-benzylamine (225 mg, 0.74 mmol) in EtOAc (15 mL) and stir the mixture at ambient temperature overnight. Concentrate *in vacuo* and wash the solid with diethyl ether. Suspend the solid in dichloromethane and saturated aqueous $NaHCO_3$ and stir until both phases are clear (15 min). Extract the aqueous phase twice with dichloromethane. Dry the combined organic extracts over $MgSO_4$, filter and concentrate *in vacuo* to give the title compound as an oil (0.136 g, 90%) that was used without any further purification. MS (ES+) *m/z*: 206 $(M+H)^+$.

Example 537

7-Chloro-6-(2,4-difluorobenzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



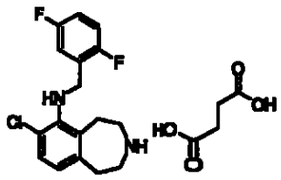
Use a method similar to the General Procedure 5-1 to react 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (3

g, 7.06 mmol), palladium(II) acetate (0.16 g, 0.71 mmol), BINAP (0.88 g, 1.41 mmol), 2,4-difluorobenzylamine (3.03 g, 21.18 mmol) and cesium carbonate (3.22 g, 9.88 mmol) in degassed toluene (120 mL). Degas the mixture with vacuum/nitrogen purge and heat to 100 °C for 16 h. Cool the mixture to room temperature, dilute with EtOAc, filter through Celite® and concentrate *in vacuo* to give a brown oil. Purify the crude mixture by chromatography on silica gel eluting with hexane and then hexane/THF (95:5) to obtain 7-chloro-6-(2,4-difluorobenzylamino)-3-(2,2,2,trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as oil (2.25 g, 76%). MS (ES+) *m/z*: 419 $(M+H)^+$.

Use a method similar to the General Procedure 1-2, using 7-chloro-6-(2,4-difluorobenzylamino)-3-(2,2,2,trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (2.2 g, 5.26 mmol), to give the free base of the title compound as an oil (1.66 g, 98%) that solidified upon standing at room temperature and was used without further purification. MS (ES+) *m/z*: 323 $(M+H)^+$. Use a method similar to the General Procedure 2-1, using 7-chloro-6-(2,4-difluorobenzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.66 g, 5.14 mmol) to give the title compound as a white solid (2.03 g, 90%). MS (ES+) *m/z*: 323 $(M+H)^+$.

Example 538

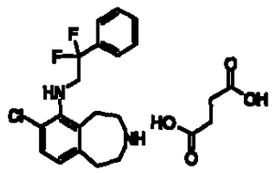
7-Chloro-6-(2,5-difluorobenzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Example 538 may be prepared essentially as described in Example 537 using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 2,5-difluorobenzylamine (68% yield, MS (ES+) *m/z* 323 $(M+H)^+$).

Example 539

7-Chloro-6-(2,2-difluoro-2-phenyl-ethylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

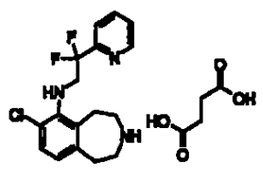


Use a method similar to the General Procedure 5-3 to react 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (541 mg, 1.274 mmol), palladium(II) acetate (57 mg, 0.225 mmol), tris(dibenzylideneacetone)dipalladium(0) (117 mg, 0.127 mmol), BINAP (0.506 g, 0.764 mmol), 2,2-difluoro-2-phenyl-ethylamine (400 mg, 2.547 mmol) and cesium carbonate (830 mg, 2.548 mmol) in degassed toluene (35 mL). Degas the mixture with vacuum/nitrogen purge and heat to 100 °C for 16 h. Cool the mixture to room temperature, dilute with EtOAc and filter over Celite®. Purify the crude mixture by chromatography on silica gel eluting with hexane and hexane/EtOAc (19:1) to obtain 7-chloro-6-(2,2-difluoro-2-phenyl-ethylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as oil (335 mg, 61%). MS (ES+) *m/z*: 433 $(M+H)^+$.

Use a method similar to the General Procedure 1-2, using 7-chloro-6-(2,2-difluoro-2-phenyl-ethylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (317 mg, 0.734 mmol), to give the free base of the title compound as an oil (215 mg, 87%) that was used without further purification. MS (ES+) *m/z*: 337 $(M+H)^+$. Use a method similar to the General Procedure 2-1, using 7-chloro-6-(2,2-difluoro-2-phenyl-ethylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (215 mg, 0.64 mmol) to give the title compound as a white solid (220 mg, 76%). MS (ES+) *m/z*: 337 $(M+H)^+$.

Example 540

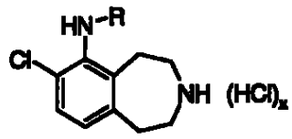
7-Chloro-6-(2,2-difluoro-2-pyridin-2-yl-ethylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

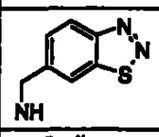
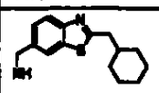
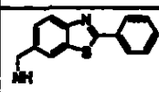
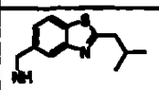


Example 540 may be prepared essentially as described in Example 539 using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 2,2-difluoro-2-pyridin-2-yl-ethylamine (prepared by following the procedure described in *J. Med. Chem.* 2003, *46*, 461-473), (37% yield, MS (ES+) *m/z* 338 $(M+H)^+$).

Examples 541-544

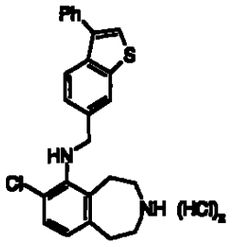
Examples 541-544 may be prepared essentially as described in Example 262 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. Overall yields and MS (ES+) data are shown in the Table below.



Ex.	NH-R	Compound	Yield (%)	MS (ES+) *m/z*
541		7-Chloro-6-(benzo[1,2,3]thiadiazol-6-yl-methylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	12	345 $(M+H)^+$
542		7-Chloro-6-(2-cyclohexylmethyl-benzothiazol-6-yl-methylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	50	441 $(M+H)^+$
543		7-Chloro-6-[(2-phenyl-benzothiazol-6-yl-methyl)-amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	27	420 $(M+H)^+$
544		7-Chloro-6-(2-isobutyl-benzothiazol-5-yl-methylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	37	400 $(M+H)^+$

Example 545

7-Chloro-6-(3-phenyl-benzothiophen-6-yl-methylamino)-2,3,4,5-tetrahydro-1*H*-benzo [*d*]azepine Hydrochloride

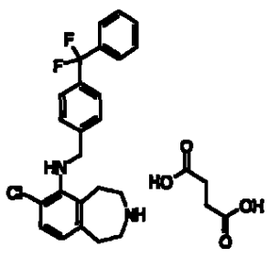


Use a method similar to the General Procedure 5-2, using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.28 g, 0.66 mmol) and 6-aminomethyl-3-phenyl-benzothiophene (0.19 g, 0.8 mmol) with tris(dibenzylideneacetone)dipalladium(0) (120 mg, 0.13 mmol), BINAP (165 mg, 0.26 mmol) and cesium carbonate (0.3 g, 0.93 mmol) at 90 °C for 17 h, to obtain 7-chloro-6-(3-phenyl-benzothiophen-6-yl-methylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo [*d*]azepine that is used without further purification (234 mg, 69%). MS (ES+) *m/z*: 515 (M+H)+.

Use a procedure similar to General Procedure 1-1 to deprotect 7-chloro-6-(3-phenyl-benzothiophen-6-yl-methylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo [*d*]azepine (234 mg, 0.45 mmol) in 7M ammonia in methanol (20 mL). Purify by reverse phase HPLC (Vydac C18 5 x 25 cm, 30% to 100% acetonitrile in 0.1% TFA-water solution). Recover the free base by SCX chromatography and form the salt according to General Procedure 2-3 to obtain the title compound (38 mg, 17%). HRMS (ES+) *m/z*: 419.1340 $(M+H)^+$.

Example 546

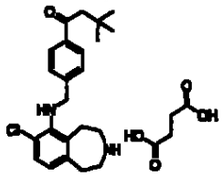
7-Chloro-6-[(difluoro-phenyl-methyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Use a procedure similar to Example 262 using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 4-(difluoro-phenyl-methyl)-benzylamine, followed by deprotection according to General Procedure 1-2 and salt formation according to General Procedure 2-1 to obtain the title compound (175 mg, 77%). MS (ES+) *m/z* 413 $(M+H)^+$.

Example 547

7-Chloro-6-[4-(3,3-dimethyl-butyryl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



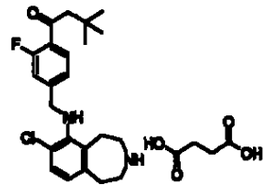
Use a method similar to the General Procedure 5-3 to react 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (250 mg, 0.588 mmol), palladium(II) acetate (26 mg, 0.118 mmol), tris(dibenzylideneacetone)dipalladium(0) (53 mg, 0.059 mmol), BINAP (0.22 g, 0.353 mmol), 4-(3,3-dimethyl-butyryl)-benzylamine (241 mg, 1.176 mmol) and cesium carbonate (383 mg, 1.176 mmol) in degassed toluene (10 mL). Degas the mixture with vacuum/nitrogen purge and heat to 100 °C for 16 h. Cool the mixture to room temperature, dilute with EtOAc and wash with saturated aqueous $NaHCO_3$. Dry the organic layer over Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane and then hexane/EtOAc (90:10, 85:15) to obtain 7-chloro-6-[4-(3,3-dimethyl-butyryl)-benzylamino]-3-(2,2,2-trifluoroacetyl)-

2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as oil (185 mg, 65%). MS (ES+) *m/z*: 481 $(M+H)^+$.

Use a method similar to the General Procedure 1-2, using 7-chloro-6-[4-(3,3-dimethyl-butyryl)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (165 mg, 0.343 mmol), to give the free base of the title compound as an oil (130 mg, 98%) that was used without further purification. MS (ES+) *m/z*: 385 $(M+H)^+$. Use a method similar to the General Procedure 2-1, using 7-chloro-6-[4-(3,3-dimethyl-butyryl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (130 mg, 0.338 mmol) to give the title compound as a white solid (128 mg, 76%). MS (ES+) *m/z*: 385 $(M+H)^+$.

Example 548

7-Chloro-6-[4-(3,3-dimethyl-butyryl)-3-fluoro-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

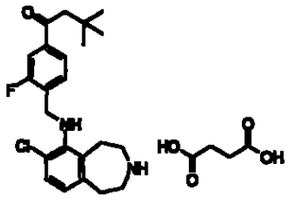


Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (96 mg, 0.225 mmol) with 4-(3,3-dimethyl-butyryl)-3-fluoro-benzylamine (105 mg, 0.45 mmol) by using tris(dibenzylideneacetone)dipalladium(0) (41 mg, 0.045 mmol), BINAP (56 mg, 0.09 mmol) and cesium carbonate (103 mg, 0.315 mmol) in anhydrous toluene (15 mL). Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to give 7-chloro-6-[4-(3,3-dimethyl-butyryl)-3-fluoro-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow oil (54 mg, 49%). MS (ES+) *m/z*: 499 $(M+H)^+$.

Use a method similar to the General Procedure 1-2, using 7-chloro-6-[4-(3,3-dimethyl-butyryl)-3-fluoro-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (53 mg, 0.11 mmol) to give the free base of the title compound as a yellow oil (42 mg, 96%) that was used without further purification. Use a method similar to the General Procedure 2-1, using 7-chloro-6-[4-(3,3-dimethyl-butyryl)-3-fluoro-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (42 mg, 0.105 mmol) to give the title compound as a white solid (30 mg, 60%). MS (ES+) *m/z*: 403 $(M+H)^+$.

Example 549

7-Chloro-6-[4-(3,3-dimethyl-butyryl)-2-fluoro-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



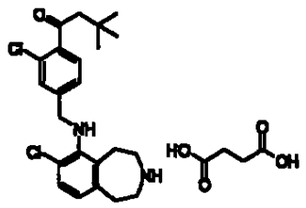
Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (127 mg, 0.3 mmol) with 4-(3,3-dimethyl-butyryl)-2-fluoro-benzylamine (120 mg, 0.54 mmol) by using tris(dibenzylideneacetone)dipalladium(0) (27 mg, 0.03 mmol), BINAP (40 mg, 0.06 mmol) and cesium carbonate (137 mg, 0.42 mmol) in anhydrous toluene (20 mL). Purify by chromatography on silica gel eluting with hexane/EtOAc (19:1 and 9:1) followed by reverse phase HPLC [Zorbax Bonus RP, 5 □M 21.2 x 100 mm, eluting with water/acetonitrile (0.05% TFA in each) (35:65 to 15:85 gradient over 5 min), flow rate 25 mL/min, UV detector (230 nm)] to give 7-chloro-6-[4-(3,3-dimethyl-butyryl)-2-fluoro-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (72 mg, 49%). MS (ES+) *m/z*: 499 $(M+H)^+$.

Use a method similar to the General Procedure 1-2, using 7-chloro-6-[4-(3,3-dimethyl-butyryl)-2-fluoro-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-

benzo[*d*]azepine (26 mg, 0.052 mmol) to give the free base of the title compound as a yellow oil (19 mg, 91%) that was used without further purification. Use a method similar to the General Procedure 2-1, using 7-chloro-6-[4-(3,3-dimethyl-butyryl)-2-fluoro-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (18 mg, 0.045 mmol) to give the title compound as a white solid (20 mg, 86%). MS (ES+)m/z: 403 $(M+H)^+$.

Example 550

7-Chloro-6-[3-chloro-4-(3,3-dimethyl-butyryl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



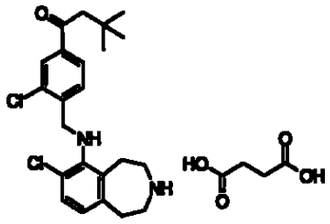
Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (90 mg, 0.212 mmol) with 3-chloro-4-(3,3-dimethyl-butyryl)-benzylamine (102 mg, 0.43 mmol) by using tris(dibenzylideneacetone)dipalladium(0) (39 mg, 0.0424 mmol), BINAP (53 mg, 0.0848 mmol) and cesium carbonate (97 mg, 0.297 mmol) in anhydrous toluene (10 mL). Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to give 7-chloro-6-[3-chloro-4-(3,3-dimethyl-butyryl)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (72 mg, 49%). MS (ES+) *m/z*: 516 $(M+H)^+$.

Use a method similar to the General Procedure 1-2, using 7-chloro-6-[3-chloro-4-(3,3-dimethyl-butyryl)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (70 mg, 0.136 mmol) to give the free base of the title compound as a yellow oil (57 mg, 99%) that was used without further purification. Use a method similar to the General Procedure 2-1, using 7-chloro-6-[3-chloro-4-(3,3-dimethyl-butyryl)-

benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (57 mg, 0.136 mmol) to give the title compound as a white solid (50 mg, 68%). MS (ES+) *m/z*: 420 $(M+H)^+$.

Example 551

7-Chloro-6-[2-chloro-4-(3,3-dimethyl-butyryl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

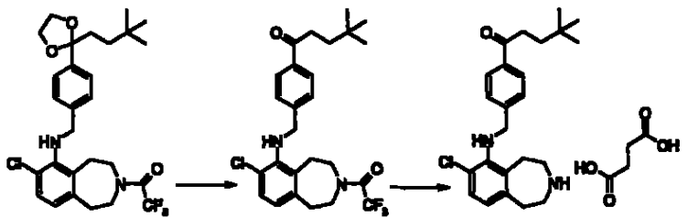


Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (300 mg, 0.71 mmol) with 1-(4-aminomethyl-3-chloro-phenyl)-3,3-dimethyl-butan-1-one (338 mg, 1.41 mmol) by using tris(dibenzylideneacetone)dipalladium(0) (130 mg, 0.142 mmol), BINAP (177 mg, 0.284 mmol) and cesium carbonate (324 mg, 0.994 mmol) in anhydrous toluene (31 mL). Purify by chromatography on silica gel eluting with hexane/EtOAc (92:8) followed by reverse phase HPLC [Hichrom Kromasil C18, 5 □M 21.2 x 100 mm, eluting with water/acetonitrile (0.05% TFA in each) (1:4 to 1:19 gradient over 5 min), flow rate 25 mL/min, UV detector (230 nm)] to give 7-chloro-6-[2-chloro-4-(3,3-dimethyl-butyryl)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (77 mg, 21%). MS (ES+) *m/z*: 516 $(M+H)^+$.

Use a method similar to the General Procedure 1-2, using 7-chloro-6-[2-chloro-4-(3,3-dimethyl-butyryl)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (77 mg, 0.15 mmol) to give the free base of the title compound as a yellow oil (93 mg, 99%) that was used without further purification. Use a method similar to the General Procedure 2-1, using 7-chloro-6-[2-chloro-4-(3,3-dimethyl-butyryl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (63 mg, 0.15 mmol) to give the title compound as a white solid (52 mg, 65%). MS (ES+) *m/z*: 420 $(M+H)^+$.

Example 552

7-Chloro-6-[4-(4,4-dimethyl-pentanoyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Use a method similar to the General Procedure 5-2 to react 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (233 mg, 0.55 mmol), tris(dibenzylideneacetone)dipalladium(0) (50 mg, 0.055 mmol), BINAP (73 mg, 0.11 mmol), 4-[2-(3,3-dimethyl-butyl)-[1,3]dioxolan-2-yl]-benzylamine (263 mg, 1 mmol) and cesium carbonate (250 mg, 0.77 mmol) in degassed toluene (20 mL). Degas the mixture with vacuum/nitrogen purge and heat to 100 °C for 14 h. Cool the mixture to room temperature, dilute with EtOAc and filter through Celite®. Purify the crude mixture by chromatography on silica gel eluting with hexane and then hexane/EtOAc (19:1, 9:1 and 4:1) to obtain 7-chloro-6-{4-[2-(3,3-dimethyl-butyl)-[1,3]dioxolan-2-yl]-benzylamine}-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as oil (185 mg, 63%). MS (ES+) *m/z*: 539 $(M+H)^+$.

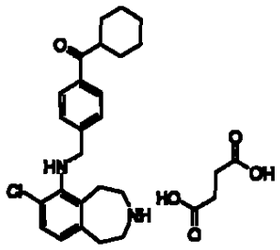
Dissolve 7-chloro-6-{4-[2-(3,3-dimethyl-butyl)-[1,3]dioxolan-2-yl]-benzylamine}-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (185 mg, 0.34 mmol) in methanol (10 mL) and add 1N aqueos HCl (2 mL). Stir the mixture for 2 h and concentrate *in vacuo*. Dissolve the residue in dichloromethane and wash with saturated aqueous $NaHCO_3$. Dry the organic phase over $MgSO_4$, filter and concentrate *in vacuo* to obtain 7-chloro-6-[4-(4,4-dimethyl-pentanoyl)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (150 mg, 89%).

Use a method similar to the General Procedure 1-2, using 7-chloro-6-[4-(4,4-dimethyl-pentanoyl)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-

benzo[*d*]azepine (150 mg, 0.3 mmol), to give the free base of the title compound as an oil (100 mg, 83%) that was used without further purification. Use a method similar to the General Procedure 2-1, using 7-chloro-6-[4-(4,4-dimethyl-pentanoyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (100 mg, 0.25 mmol) to give the title compound as a solid (100 mg, 78%). MS (ES+) *m/z*: 399 $(M+H)^+$.

Example 553

7-Chloro-6-(4-cyclohexanecarbonyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



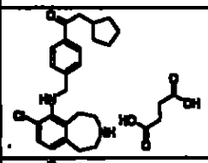
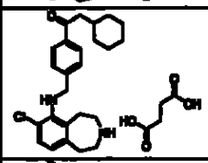
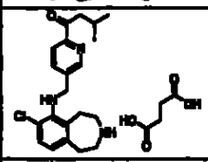
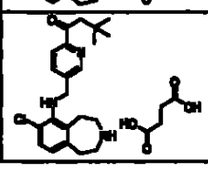
Use a method similar to the General Procedure 5-2 to react 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (150 mg, 0.353 mmol), tris(dibenzylideneacetone)dipalladium(0) (64 mg, 0.071 mmol), BINAP (88 mg, 0.141 mmol), 4-cyclohexanecarbonyl-benzylamine (125 mg, 0.576 mmol) and cesium carbonate (230 mg, 0.706 mmol) in degassed toluene (10 mL). Degas the mixture with vacuum/nitrogen purge and heat to 100 °C for 6 h. Cool the mixture to room temperature, dilute with EtOAc and filter through Celite®. Purify the crude mixture by chromatography on silica gel eluting with hexane and then hexane/EtOAc (90:10 and 85:15) to obtain 7-chloro-6-(4-cyclohexanecarbonyl-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as oil (130 mg, 75%). MS (ES+) *m/z*: 493 $(M+H)^+$.

Use a method similar to the General Procedure 1-2, using 7-chloro-6-(4-cyclohexanecarbonyl-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (120 mg, 0.243 mmol), to give the free base of the title compound as an oil (86 mg, 89%) that was used without further purification. MS (ES+) *m/z*: 397 $(M+H)^+$.

Use a method similar to the General Procedure 2-1, using 7-chloro-6-(4-cyclohexanecarbonyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (86 mg, 0.217 mmol) to give the title compound as a solid (85 mg, 77%). MS (ES+) *m/z*: 397 $(M+H)^+$.

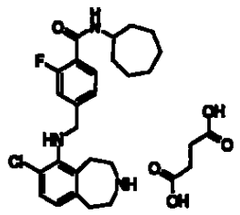
Examples 554-557

Examples 554-557 may be prepared essentially as described in Example 553 using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. Overall yields and MS (ES+) data are shown in the Table below.

Ex.	Structure	Compound	Yield (%)	MS (ES+) *m/z*
554		7-Chloro-6-[4-(2-cyclopentyl-acetyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	64	397 $(M+H)^+$
555		7-Chloro-6-[4-(2-cyclohexyl-acetyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	30	411 $(M+H)^+$
556		7-Chloro-6-[6-(3-methyl-butyryl)-pyridin-3-yl-methylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	35	372 $(M+H)^+$
557		7-Chloro-6-[6-(3,3-dimethyl-butyryl)-pyridin-3-yl-methylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	30	386 $(M+H)^+$

Example 558

7-Chloro-6-(4-cycloheptylcarbamoyl-3-fluoro-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

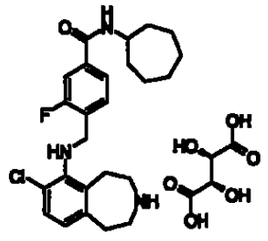


Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.1 g, 2.5 mmol) with 4-aminomethyl-*N*-cycloheptyl-2-fluoro-benzamide (1.35 g, 5.1 mmol) in anhydrous toluene (25 mL). Purify by chromatography on silica gel eluting with hexane/EtOAc (19:1 to 1:1 gradient) followed by SCX chromatography to obtain 7-chloro-6-[4-cycloheptylcarbamoyl-3-fluoro-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (720 mg, 53%). MS (ES+) *m/z*: 540.2 $(M+H)^+$.

Use a method similar to the General Procedure 1-2 to deprotect 7-chloro-6-[4-cycloheptylcarbamoyl-3-fluoro-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Purify by chromatography on silica gel eluting with dichloromethane/2M ammonia in methanol (99:1 to 90:10 gradient) to obtain the free base of the title compound. Use a method similar to the General Procedure 2-1 to obtain the title compound (665 mg, 89%). MS (ES+) *m/z*: 444.2 $(M+H)^+$.

Example 559

7-Chloro-6-(4-cycloheptylcarbamoyl-2-fluoro-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate



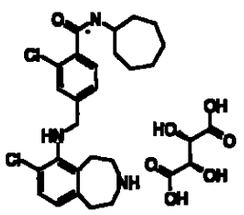
Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine

(640 mg, 1.5 mmol) with 4-aminomethyl-*N*-cycloheptyl-3-fluoro-benzamide (795 mg, 3 mmol) in anhydrous toluene (20 mL). Purify the crude mixture by chromatography on silica gel eluting with hexane/EtOAc (19:1 to 3:2 gradient) to obtain 7-chloro-6-(4-cycloheptylcarbamoyl-2-fluoro-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (568 mg, 70%). MS (ES+) *m/z*: 540.2 $(M+H)^+$.

Use a method similar to the General Procedure 1-2 to deprotect 7-chloro-6-(4-cycloheptylcarbamoyl-2-fluoro-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Purify by chromatography on silica gel eluting with dichloromethane/2M ammonia in methanol (99/1 to 93/7 gradient) to give the free base of the title compound. Dissolve the free base (400 mg, 0.9 mmol) and *L*-tartaric acid (135 mg, 0.9 mmol) in methanol. Concentrate *in vacuo* to an oil. Triturate oil with dichloromethane and remove solvent *in vacuo* to obtain the title compound as a solid (460 mg, 74%). MS (ES+) *m/z*: 444.2 $(M+H)^+$.

Example 560

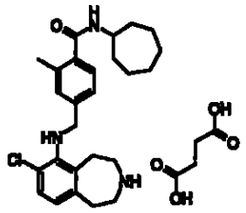
7-Chloro-6-(3-chloro-4-cycloheptylcarbamoyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate



Example 560 may be prepared essentially as described in Example 559 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 4-aminomethyl-2-chloro-*N*-cycloheptyl-benzamide (50% yield, MS (ES+) *m/z* 460.2 $(M+H)^+$).

Example 561

7-Chloro-6-(4-cycloheptylcarbamoyl-3-methyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

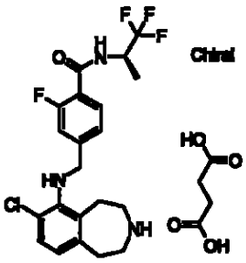


Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (660 mg, 1.6 mmol) with 4-aminomethyl-*N*-cycloheptyl-2-methyl-benzamide (810 mg, 3.1 mmol) in anhydrous toluene (18 mL). Purify the crude mixture by chromatography on silica gel eluting with hexane/THF (19:1 to 7:3 gradient) to obtain 7-chloro-6-(4-cycloheptylcarbamoyl-3-methyl-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (690 mg, 83%). MS (ES+) *m/z*: 536.3 $(M+H)^+$.

Use a method similar to the General Procedure 1-3 to deprotect 7-chloro-6-(4-cycloheptylcarbamoyl-3-methyl-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (680 mg, 1.3 mmol). Purify by chromatography on silica gel eluting with dichloromethane/2M ammonia in methanol (99:1 to 97:3 gradient) to give the free base of the title compound. Use a method similar to the General Procedure 2-1 to obtain the title compound (473 mg, 65%). MS (ES+) *m/z*: 440.3 $(M+H)^+$.

Example 562

(*R*)-7-Chloro-6-[3-fluoro-4-(2,2,2-trifluoro-1-methyl-ethylcarbamoyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



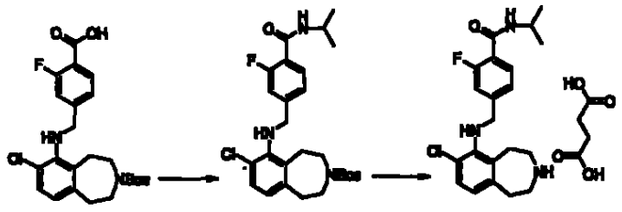
Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine

(0.561 g, 1.319 mmol) with (*R*)-4-aminomethyl-2-fluoro-*N*-(2,2,2-trifluoro-1-methyl-ethyl)-benzamide (0.698 g, 2.642 mmol) by using tris(dibenzylideneacetone)dipalladium(0) (0.241 g, 0.264 mmol), BINAP (0.33 g, 0.53 mmol) and cesium carbonate (1.51 g, 4.63 mmol) in anhydrous toluene (13 mL). Purify by chromatography on silica gel (40 g RediSep® column) eluting with hexane/EtOAc (19:1 to 1:1 gradient over 30 min; 35 mL/min) and then by SCX chromatography to afford (*R*)-7-chloro-6-[3-fluoro-4-(2,2,2-trifluoro-1-methyl-ethylcarbamoyl)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a colorless oil (0.444 g, 62%). MS (ES+) *m/z*: 540.1 $(M+H)^+$.

Use a method similar to the General Procedure 1-3 to deprotect (*R*)-7-chloro-6-[3-fluoro-4-(2,2,2-trifluoro-1-methyl-ethylcarbamoyl)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.224 g, 0.415 mmol). Purify by chromatography on silica gel (12 g RediSep® column) eluting with dichloromethane/2M ammonia in methanol (99:1 to 90:10 gradient over 30 min; 35 mL/min) to afford the free base of the title compound as a white foam (0.142 g, 77%). Use a method similar to the General Procedure 2-1, using (*R*)-7-chloro-6-[3-fluoro-4-(2,2,2-trifluoro-1-methyl-ethylcarbamoyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.132 g, 0.299 mmol) to afford the title compound as a white solid (0.135 g, 80%). MS (ES+) *m/z*: 444.2 $(M+H)^+$.

Example 563

7-Chloro-6-(3-fluoro-4-isopropylcarbamoyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



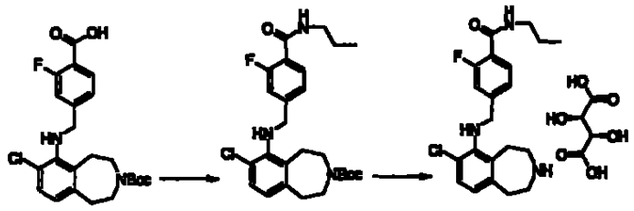
Add isopropylamine (0.15 mL, 1.8 mmol), HOBT (0.24 g, 1.8 mmol), diisopropylethylamine (0.63 mL, 3.6 mmol) and EDC (0.34 g, 1.8 mmol) to a mixture of

3-*tert*-butoxycarbonyl-6-(4-carboxy-3-fluoro-benzylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.403 g, 0.9 mmol) in anhydrous THF (11.8 mL) at room temperature. Stir overnight at room temperature and partition the mixture between EtOAc (250 mL) and saturated aqueous $NaHCO_3$ (100 mL). Dry the organic phase over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel (40 g RediSep® column) eluting with hexane/EtOAc (19:1 to 1:1 gradient over 30 min; 50 mL/min) to afford 3-*tert*-butoxycarbonyl-7-chloro-6-(3-fluoro-4-isopropylcarbamoyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a thick colorless oil (0.439 g, 100%). MS (ES+) *m/z*: 490.2 $(M+H)^+$.

Use a method similar to the General Procedure 1-4 to deprotect 3-*tert*-butoxycarbonyl-7-chloro-6-(3-fluoro-4-isopropylcarbamoyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.406 g, 0.83 mmol) in 1,4-dioxane (12.8 mL). Purify by SCX chromatography eluting with dichloromethane and dichloromethane/2M ammonia in methanol (1:1) followed by chromatography on silica gel (40 g RediSep column) eluting with dichloromethane/2M ammonia in methanol (99:1 to 90:10 over 30 min) and then dichloromethane/2M ammonia in methanol (90:10 over 30 min; 35 mL/min) to afford 7-chloro-6-(3-fluoro-4-isopropylcarbamoyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a colorless oil (0.3237 g). MS (ES+) *m/z*: 390.1 $(M+H)^+$. Use a method similar to the General Procedure 2-1, using 7-chloro-6-(3-fluoro-4-isopropylcarbamoyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.301 g, 0.772 mmol) to provide the title compound as a beige solid (0.328 g, 84%). MS (ES+) *m/z*: 390.1 $(M+H)^+$.

Example 564

7-Chloro-6-(3-fluoro-4-propylcarbamoyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate

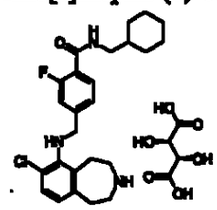


Add a solution of *n*-propylamine (6.3 mg, 0.11 mmol) in anhydrous THF (0.5 mL), HOBT (14.5 mg, 0.11 mmol), a solution of diisopropylamine (27.7 mg, 0.21 mmol) in anhydrous THF (0.5 mL) and EDC (20.5 mg, 0.11 mmol) to a mixture of 3-*tert*-butoxycarbonyl-6-(4-carboxy-3-fluoro-benzylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (48.1 mg, 0.11 mmol) in anhydrous THF (1.4 mL) at room temperature. Stir overnight at room temperature and partition the mixture between EtOAc (50 mL) and saturated aqueous $NaHCO_3$ (20 mL). Dry the organic phase over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel (12 g RediSep® column) eluting with hexane/EtOAc (19:1 to 1:1 gradient over 30 min; 35 mL/min) to afford 3-*tert*-butoxycarbonyl-7-chloro-6-(3-fluoro-4-propylcarbamoyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a thick colorless oil (37.1 mg, 71%). MS (ES+) *m/z*: 490.2 $(M+H)^+$.

Use a method similar to the General Procedure 1-4 to deprotect 3-*tert*-butoxycarbonyl-7-chloro-6-(3-fluoro-4-propylcarbamoyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (33.1 mg, 0.83 mmol) in 1,4-dioxane (1 mL). Purify by SCX chromatography eluting with dichloromethane and dichloromethane/2M ammonia in methanol (1:1) to afford 7-chloro-6-(3-fluoro-4-propylcarbamoyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a colorless oil (25.2 mg, 96%). MS (ES+) *m/z*: 390.1 $(M+H)^+$. Use a method similar to the General Procedure 2-6, using 7-chloro-6-(3-fluoro-4-propylcarbamoyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (25 mg, 0.064 mmol) to provide the title compound as a white foam (31.4 mg, 91%). MS (ES+) *m/z*: 390.1 $(M+H)^+$.

Example 565

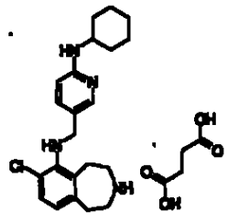
7-Chloro-6-[4-(cyclohexylmethylcarbamoyl)-3-fluoro-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate



Example 565 may be prepared essentially as described in Example 564 by using 3-*tert*-butoxycarbonyl-6-(4-carboxy-3-fluoro-benzylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and cyclohexylmethylamine (67% yield, MS (ES+) *m/z* 444 $(M+H)^+$).

Example 566

7-Chloro-6-(6-cyclohexylamino-pyridin-3-ylmethylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

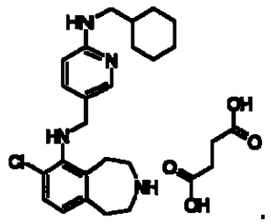


Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (800 mg, 1.9 mmol) with 5-aminomethyl-2-cyclohexylamino-pyridine (910 mg, 4.4 mmol) in anhydrous toluene (15 mL). Purify the residue by chromatography on silica gel eluting with hexane/EtOAc (19:1 to 3:2 gradient) to obtain 7-chloro-6-(6-cyclohexylamino-pyridin-3-ylmethylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (520 mg, 58%). MS (ES+) *m/z*: 481.0 $(M+H)^+$.

Use a method similar to the General Procedure 1-3 to deprotect 7-chloro-6-(6-cyclohexylamino-pyridin-3-ylmethylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Purify by chromatography on silica gel eluting with dichloromethane/2M ammonia in methanol (99/1 to 85/15 gradient) to give the free base of the title compound. Use a method similar to the General Procedure 2-1 to obtain the title compound (360 mg, 66%). MS (ES+) *m/z*: 385.1 $(M+H)^+$.

Example 567

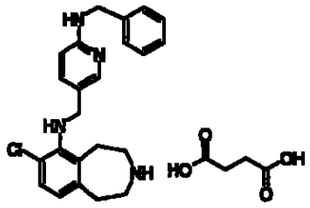
7-Chloro-6-(6-cyclohexylmethylamino-pyridin-3-ylmethylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



The title compound may be prepared essentially as described in Example 566 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 5-aminomethyl-2-cyclohexylmethylamino-pyridine (22% yield, MS (ES+) *m/z* 399.1 $(M+H)^+$).

Example 568

6-[6-(Benzylamino)-pyridin-3-ylmethylamino]-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

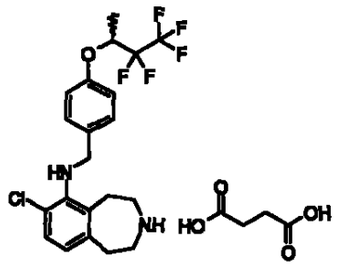


Use a method similar to General Procedure 5-2 to couple 6-benzylamino-pyridin-3-ylmethylamine and 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-

2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine to give, after deprotection and salt formation by methods similar to the General Procedures 1-3 and 2-1, the title compound as an off-white solid (45% overall yield). HRMS (ES+) *m/z*: 393.1836 $(M+H)^+$.

Example 569

(±)-7-Chloro-6-{4-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-benzylamino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

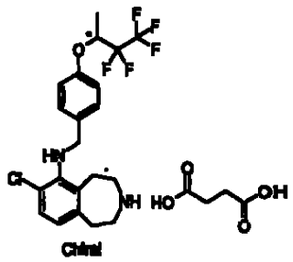


Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (751 mg, 1.8 mmol) with (±)-4-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-benzylamine (950 mg, 3.5 mmol) in anhydrous toluene (20 mL). Purify the crude mixture by chromatography on silica gel eluting sequentially with hexane/EtOAc (10:1, 5:1, 3:1) to obtain (±)-7-chloro-6-{4-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-benzylamino}-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (990 mg, 99%).

Use a method similar to the General Procedure 1-3 to deprotect (±)-7-chloro-6-{4-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-benzylamino}-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (980 mg, 1.8 mmol). Purify by chromatography on silica gel eluting with dichloromethane/2*M* ammonia in methanol (99:1 to 90:10 gradient) to give the free base of the title compound. Use a method similar to the General Procedure 2-1 to obtain the title compound (650 mg, 64%). MS (ES+) *m/z*: 449.1 $(M+H)^+$.

Example 570

(-)-7-Chloro-6-{4-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-benzylamino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

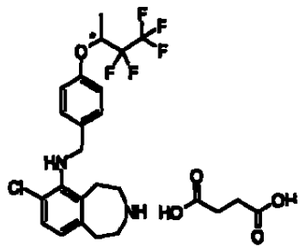


Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (9 g, 21.1 mmol) with 4-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-benzylamine isomer 2 (11.4 g, 42.3 mmol) in anhydrous toluene (270 mL). Purify the crude mixture by chromatography on silica gel eluting with hexane/EtOAc (19:1 to 4:1 gradient) to obtain 7-chloro-6-{4-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-benzylamino}-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine isomer 2 (9.5 g, 83%).

Use a method similar to the General Procedure 1-3 to deprotect 7-chloro-6-{4-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-benzylamino}-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine isomer 2 (9.5 g, 17.4 mmol). Purify by chromatography on silica gel eluting with dichloromethane/2M ammonia in methanol (99:1 to 90:10 gradient) to give the free base of the title compound. Use a method similar to the General Procedure 2-1 to obtain the title compound (5.9 g, 60%). MS (ES+) *m/z*: 449.1 $(M+H)^+$. $[\alpha]^{20}_D$ –11.6° (c 0.5, MeOH).

Example 571

(+)-7-Chloro-6-{4-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-benzylamino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



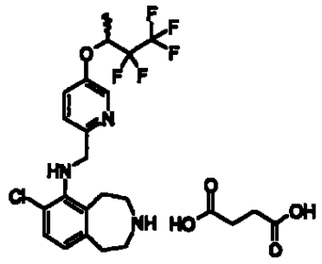
Chiral

Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (3.4 g, 8 mmol) with 4-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-benzylamine isomer 1 (4.3 g, 16 mmol) in anhydrous toluene (100 mL). Purify the crude mixture by chromatography on silica gel eluting with hexane/EtOAc (19:1 to 3:1 gradient) to obtain 7-chloro-6-{4-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-benzylamino}-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine isomer 1 (3.7 g, 85%).

Use a method similar to the General Procedure 1-3 to deprotect 7-chloro-6-{4-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-benzylamino}-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine isomer 1 (3.7 g, 6.8 mmol). Purify by chromatography on silica gel eluting with dichloromethane/2M ammonia in methanol (99:1 to 97:3 gradient) to give the free base of the title compound. Use a method similar to the General Procedure 2-1 to obtain the title compound (2.8 g, 74%). MS (ES+) *m/z*: 449.1 $(M+H)^+$. $[\alpha]^{20}_D$ +13.0° (c 0.5, MeOH).

Example 572

(±)-7-Chloro-6-{4-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-pyridin-2-ylmethylamino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

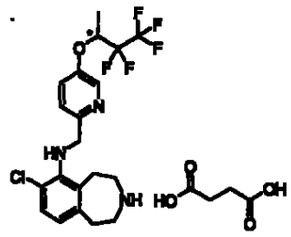


Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (268 mg, 0.6 mmol) with (±)-2-aminomethyl-5-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-pyridine (170 mg, 0.6 mmol) in anhydrous toluene (3 mL). Purify the crude mixture by chromatography on silica gel eluting sequentially with hexane/EtOAc (10:1, 5:1, 3:1) to obtain (±)-7-chloro-6-{4-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-pyridin-2-ylmethylamino}-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (270 mg, 79%). MS (ES+) *m/z*: 546.1 $(M+H)^+$.

Use a method similar to the General Procedure 1-3 to deprotect (±)-7-chloro-6-{4-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-pyridin-2-ylmethylamino}-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (265 mg, 0.5 mmol). Purify by chromatography on silica gel eluting with dichloromethane/2M ammonia in methanol (99:1 to 90:10 gradient) to give the free base of the title compound. Use a method similar to the General Procedure 2-1 to obtain the title compound (172 mg, 63%). MS (ES+) *m/z*: 450.1 $(M+H)^+$.

Example 573

(-)-7-Chloro-6-{4-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-pyridin-2-ylmethylamino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

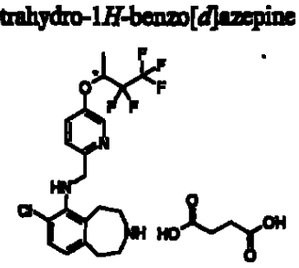


Chiral

Separate (±)-7-chloro-6-{4-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-pyridin-2-ylmethylamino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine succinate (172 mg) by normal phase chiral chromatography (Chiralcel OD, 8 x 35 cm, eluting with heptane/isopropanol 4:1 with 0.2% DMEA). Collect the 1st eluting isomer, then use a method similar to the General Procedure 2-1 to obtain the title compound [50 mg, 96.3% ee (Chiralcel OD-H, 4.6 x 150 mm, eluting with heptane/isopropanol 4:1 with 0.2% DMEA, 0.6 mL/min)]. MS (ES+) *m/z*: 450.1 $(M+H)^+$. $[\alpha]^{20}_D$ –10.5° (c 0.5, MeOH).

Example 574

(+)-7-Chloro-6-{4-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-pyridin-2-ylmethylamino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

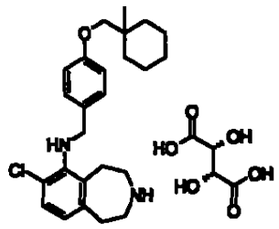


Chiral

Separate (±)-7-chloro-6-{4-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-pyridin-2-ylmethylamino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine succinate (172 mg) by normal phase chiral chromatography (Chiralcel OD, 8 x 35 cm, eluting with heptane/isopropanol 4:1 with 0.2% DMEA). Collect the 2nd eluting isomer, then use a method similar to the General Procedure 2-1 to obtain the title compound [41 mg, 95.6% ee (Chiralcel OD-H, 4.6 x 150 mm, eluting with heptane/isopropanol 4:1 with 0.2% DMEA, 0.6 mL/min)]. MS (ES+) *m/z*: 450.1 $(M+H)^+$. $[\alpha]^{20}_D$ +13.1° (c 0.5, MeOH).

Example 575

7-Chloro-6-[4-(1-methyl-cyclohexylmethoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate

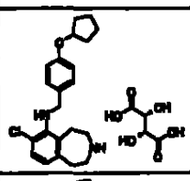
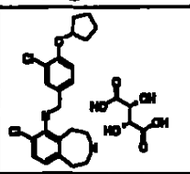
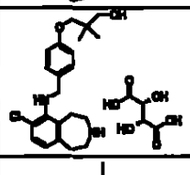
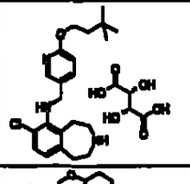
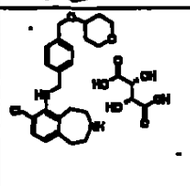


Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (200 mg, 0.47 mmol) with 4-(1-methyl-cyclohexylmethoxy)-benzylamine (120 mg, 0.51 mmol) in anhydrous 1,4-dioxane (7 mL). Purify the crude mixture by chromatography on silica gel eluting with isohexane/EtOAc (19:1 to 4:1 gradient) to obtain 7-chloro-6-[4-(1-methyl-cyclohexylmethoxy)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (101 mg, 39%).

Use a method similar to the General Procedure 1-1 to deprotect 7-chloro-6-[4-(1-methyl-cyclohexylmethoxy)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (100 mg, 0.19 mmol). Purify by SCX chromatography eluting with methanol and 3M ammonia in methanol. Use a method similar to the General Procedure 2-6 to obtain the title compound (78 mg, 73%). MS (ES+) *m/z*: 413.2 $(M+H)^+$.

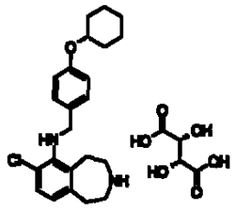
Examples 576-580

Examples 576-580 may be prepared essentially as described in Example 575 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. Overall yields and MS (ES+) data are shown in the Table below.

Ex.	Structure	Compound	Yield (%)	MS (ES+) m/z
576		7-Chloro-6-(4-cyclopentyloxy-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate	39	371 $(M+H)^+$
577		7-Chloro-6-(3-chloro-4-cyclopentyloxy-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate	6	405 $(M+H)^+$
578		7-Chloro-6-[4-(2,2,dimethyl-3-hydroxy-propoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate	6	389 $(M+H)^+$
579		7-Chloro-6-[6-(3,3-dimethyl-butoxy)-pyridin-3-ylmethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate	50	388 $(M+H)^+$
580		7-Chloro-6-[4-(tetrahydro-pyran-4-yloxymethyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate	37	401 $(M+H)^+$

Example 581

7-Chloro-6-(4-cyclohexyloxy-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate

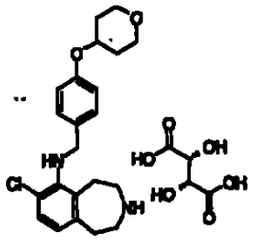


Use a method similar to the General Procedure 5-1 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (100 mg, 0.43 mmol) with 4-cyclohexyloxy-benzylamine (58 mg, 0.285 mol) in anhydrous toluene (1 mL). Purify the crude mixture by chromatography on silica gel eluting with cyclohexane/EtOAc (9:1) to give 7-chloro-6-(4-cyclohexyloxy-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (78 mg, 69%).

Use a method similar to the General Procedure 1-1 to deprotect 7-chloro-6-(4-cyclohexyloxy-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (237 mg, 0.49 mmol) to obtain the free base of the title compound. Use a method similar to the General Procedure 2-6 to obtain the title compound (208 mg, 80%). MS (ES+) *m/z*: 385.2 $(M+H)^+$.

Example 582

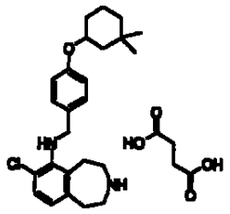
7-Chloro-6-[4-(tetrahydro-pyran-4-yloxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate



Example 582 may be prepared essentially as described in Example 581 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 4-(tetrahydro-pyran-4-yloxy)-benzylamine (4% yield, MS (ES+) *m/z* 387 $(M+H)^+$).

Example 583

(±)-7-Chloro-6-[4-(3,3-dimethyl-cyclohexyloxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

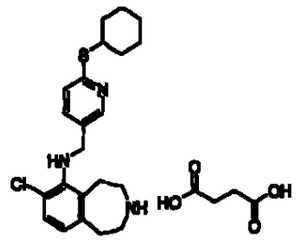


Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (387 mg, 0.91 mmol) with (±)-4-(3,3-dimethyl-cyclohexyloxy)-benzylamine (233 mg, 1 mmol) in anhydrous 1,4-dioxane (14 mL). Purify the crude mixture by chromatography on silica gel eluting with cyclohexane/EtOAc (19:1 to 1:1 gradient) to obtain (±)-7-chloro-6-[4-(3,3-dimethyl-cyclohexyloxy)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (227 mg, 50%).

Use a method similar to the General Procedure 1-1 to deprotect (±)-7-chloro-6-[4-(3,3-dimethyl-cyclohexyloxy)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (220 mg, 0.43 mmol). Purify by SCX chromatography eluting with methanol and 3M ammonia in methanol. Further purify the residue by preparative HPLC. Use a method similar to the General Procedure 2-1 to obtain the title compound (65 mg, 13%). MS (ES+) *m/z*: 413.2 $(M+H)^+$.

Example 584

7-Chloro-6-(4-cyclohexylthio-pyridin-3-ylmethylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

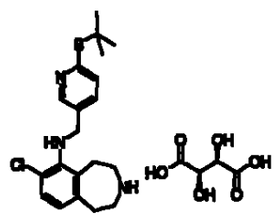


Add cesium carbonate (2.04 g, 6.27 mmol), palladium(II) acetate (46 mg, 0.209 mmol) and BINAP (195.21 mg, 0.313 mmol) to a solution of 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.79 g, 4.18 mmol) and 5-aminomethyl-2-cyclohexylthio-pyridine (1.11 g, 5.02 mmol) in anhydrous toluene (30 mL). Sonicate the resulting suspension for 30 min then heat at 100 °C for 18 h. Cool the reaction to room temperature. Purify the crude mixture by chromatography on silica gel eluting with cyclohexane/EtOAc (98:2 to 60:40 gradient) to give 7-chloro-6-(4-cyclohexylthio-pyridin-3-ylmethylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (1.1 g, 53%).

Use a method similar to the General Procedure 1-1 to deprotect 7-chloro-6-(4-cyclohexylthio-pyridin-3-ylmethylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.1 g, 2.21 mmol). Purify by SCX chromatography eluting with methanol and 3M ammonia in methanol. Use a method similar to the General Procedure 2-1 to obtain the title compound as a white solid (0.884 g, 77%). MS (ES+) *m/z*: 402 $(M+H)^+$.

Example 585

6-(4-*tert*-Butylthio-pyridin-3-ylmethylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-tartrate

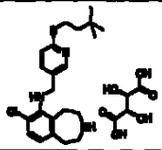
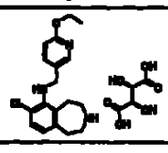


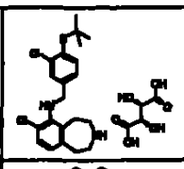
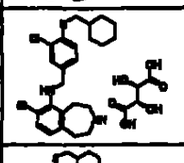
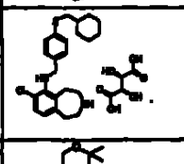
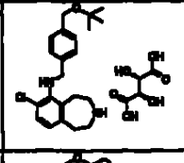
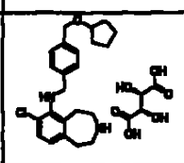
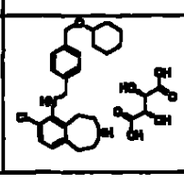
Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (990 mg, 2.32 mmol) with 5-aminomethyl-2-*tert*-butylthio-pyridine (500 mg, 2.55 mmol) in anhydrous toluene (15 mL). Purify the crude mixture by chromatography on silica gel eluting with isohexane/EtOAc (1:0 to 3:1 gradient) to obtain 6-(4-*tert*-butylthio-pyridin-3-ylmethylamino)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (650 mg, 59%). MS (ES+) *m/z*: 472 $(M+H)^+$.

Use a method similar to the General Procedure 1-2 to deprotect 6-(4-*tert*-butylthio-pyridin-3-ylmethylamino)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (650 mg, 1.37 mmol). Purify by SCX chromatography eluting with methanol and 3M ammonia in methanol. Use a method similar to the General Procedure 2-6 to obtain the title compound (362 mg, 50%). MS (ES+) *m/z*: 376 $(M+H)^+$.

Examples 586-593

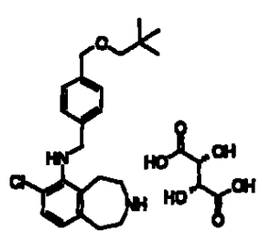
Examples 586-593 may be prepared essentially as described in Example 585 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. Overall yields and MS (ES+) data are shown in the Table below.

Ex.	Structure	Compound	Yield (%)	MS (ES+) *m/z*
586		7-Chloro-6-[4-(3,3-dimethylbutylthio)-pyridin-3-ylmethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate	25	404 $(M+H)^+$
587		7-Chloro-6-(4-ethoxy-pyridin-3-ylmethylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate	30	332 $(M+H)^+$

588		6-(4-*tert*-Butylthio-3-chloro-benzylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate	37	409 $(M+H)^+$
589		7-Chloro-6-(3-chloro-4-cyclohexylmethylthio-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate	27	472 $(M+Na)^+$
590		7-Chloro-6-(4-cyclohexylmethylthio-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate	13	415 $(M+H)^+$
591		6-(4-*tert*-Butoxymethyl-benzylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate	16	373 $(M+H)^+$
592		7-Chloro-6-(4-cyclopentyloxymethyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate	39	385 $(M+H)^+$
593		7-Chloro-6-(4-cyclohexyloxymethyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate	33	399 $(M+H)^+$

Example 594

7-Chloro-6-[4-(2,2-dimethyl-propoxymethyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate

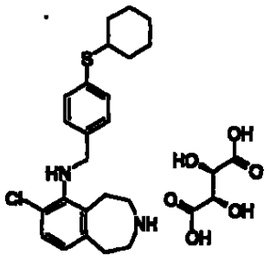


Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (426 mg, 1 mmol) with 4-(2,2-dimethyl-propoxymethyl)-benzylamine (230 mg, 1.1 mmol) in anhydrous toluene (20 mL). Purify the crude mixture by chromatography on silica gel eluting with isohexane/EtOAc (1:0 to 4:1 gradient) to obtain 7-chloro-6-[4-(2,2-dimethyl-propoxymethyl)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (380 mg, 79%). MS (ES+) *m/z*: 483 $(M+H)^+$.

Use a method similar to the General Procedure 1-2 to deprotect 7-chloro-6-[4-(2,2-dimethyl-propoxymethyl)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (380 mg, 0.88 mmol). Purify by SCX chromatography eluting with methanol and 3M ammonia in methanol. Use a method similar to the General Procedure 2-6 to obtain the title compound (319.2 mg, 70%). MS (ES+) *m/z*: 387 $(M+H)^+$.

Example 595

7-Chloro-6-(4-cyclohexylthio-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate

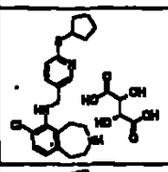
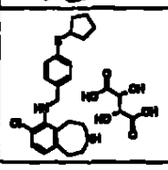


Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (167 mg, 0.392 mmol) with 4-cyclohexylthio-benzylamine (95.4 mg, 0.431 mmol) in anhydrous 1,4-dioxane (5 mL). Purify the crude mixture by chromatography on silica gel eluting with isohexane/EtOAc (1:0 to 13:7 gradient) to obtain 7-chloro-6-(4-cyclohexylthio-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (155 mg, 79%). MS (ES+) *m/z*: 519 $(M+Na)^+$.

Use a method similar to the General Procedure 1-2 to deprotect 7-chloro-6-(4-cyclohexylthio-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (155 mg, 0.312 mmol). Purify by SCX chromatography eluting with methanol and 3M ammonia in methanol. Use a method similar to the General Procedure 2-6 to obtain the title compound (95 mg, 75%). MS (ES+) *m/z*: 401 $(M+H)^+$.

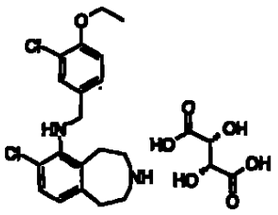
Examples 596-597

Examples 596-597 may be prepared essentially as described in Example 595 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. Overall yields and MS (ES+) data are shown in the Table below.

Ex.	Structure	Compound	Yield (%)	MS (ES+) *m/z*
596		7-Chloro-6-(4-cyclopentylthio-pyridin-3-ylmethylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate	58	388 $(M+H)^+$
597		7-Chloro-6-(4-cyclopentylthio-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate	66	387 $(M+H)^+$

Example 598

7-Chloro-6-(3-chloro-4-ethoxy-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate

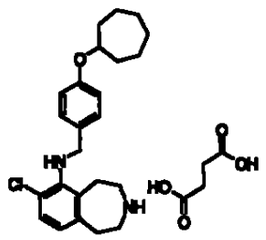


Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (150 mg, 0.35 mmol) with 4-ethoxy-3-chloro-benzylamine (94.7 mg, 0.51 mmol) in anhydrous 1,4-dioxane (10 mL). Purify the crude mixture by chromatography on silica gel eluting with isohexane/EtOAc (100:0 to 77:23 gradient) to obtain 7-chloro-6-(3-chloro-4-ethoxy-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (111.3 mg, 68%). MS (ES+) *m/z*: 483 $(M+Na)^+$.

Use a method similar to the General Procedure 1-1, but adding water (10 mL) to the 7M ammonia in methanol solution (20 mL), to deprotect 7-chloro-6-(3-chloro-4-ethoxy-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (27 mg, 0.072 mmol) to give the free base of the title compound. Use a method similar to the General Procedure 2-6 to give the title compound as a solid (29 mg, 78%). MS (ES+) *m/z*: 365 $(M+H)^+$.

Example 599

7-Chloro-6-(4-cycloheptyloxy-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



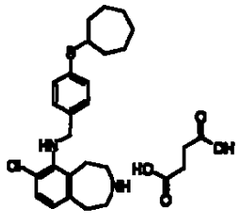
Under a nitrogen atmosphere, add 4-cycloheptyloxy-benzylamine (451 mg, 2.06 mmol), 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (500 mg, 1.17 mmol), palladium(II) acetate (26 mg, 0.117 mmol), BINAP (110 mg, 0.176 mmol), and cesium carbonate (1.15 g, 3.52 mmol) to toluene (20 mL). Heat the mixture at 90 °C for 12 h. Cool the mixture to room temperature and dilute with EtOAc (25 mL). Filter the solids through cellulose (20 g) and

concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel (45 g RediSep column) eluting with hexane/EtOAc (1:0 to 4:1 gradient over 1 h; 80 mL/min) to provide 7-chloro-6-(4-cycloheptyloxy-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a colorless oil (384 mg, 61%). MS (APCI) *m/z*: 495 $(M+H)^+$.

Dissolve 7-chloro-6-(4-cycloheptyloxy-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (370 mg, 0.747 mmol) and lithium hydroxide monohydrate (153 mg, 3.73 mmol) in methanol (5 mL) and stir for 6 h. Concentrate the mixture *in vacuo* and dissolve the residue in water (20 mL). Extract the mixture with EtOAc (3 × 20 mL). Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by reverse phase HPLC [Phenomonex C18(2) column, 5 × 25 cm, eluting with a gradient of water/acetonitrile (0.1% TFA in each) (9:1 through 1:9 over 40 min), 118 mL/min] to provide the trifluoroacetate salt of the title compound. Dissolve the residue in methanol and elute through an SCX column with saturated ammonia in methanol to provide the free base of the title compound (197 mg, 65%). Use a method similar to the General Procedure 2-1 to give the title compound as an off-white solid (250 mg, 100%). MS (APCI) *m/z*: 399 $(M+H)^+$.

Example 600

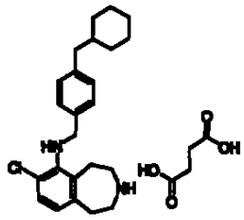
7-Chloro-6-(4-cycloheptylthio-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Example 600 may be prepared essentially as described in Example 599 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 4-cycloheptylthio-benzylamine (6% yield, MS (ES+) *m/z* 415 $(M+H)^+$).

Example 601

7-Chloro-6-(4-cyclohexylmethyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



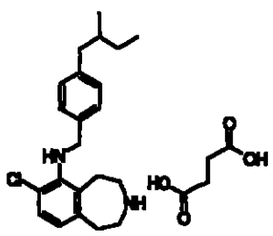
Under a nitrogen atmosphere, add 4-cyclohexylmethyl-benzylamine hydrochloride (352 mg, 1.47 mmol), 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (500 mg, 1.17 mmol), palladium(II) acetate (52.7 mg, 0.235 mmol), BINAP (293 mg, 0.47 mmol) and cesium carbonate (1.53 g, 4.7 mmol) to toluene (20 mL). Heat the mixture at 90 °C for 12 h. Cool the mixture to room temperature and dilute with EtOAc (25 mL). Filter the solids through cellulose (20 g) and concentrate the filtrate *in vacuo*. Purify the crude mixture by chromatography on silica gel (45 g RediSep column) eluting with hexane/EtOAc (1:0 to 4:1 gradient over 1 h; 80 mL/min) to provide 7-chloro-6-(4-cyclohexylmethyl-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a colorless oil (354 mg, 63%). MS (APCI) *m/z*: 479 $(M+H)^+$.

Dissolve 7-chloro-6-(4-cyclohexylmethyl-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (354 mg, 0.739 mmol) and lithium hydroxide monohydrate (100 mg, 2.43 mmol) in methanol (5 mL) and stir overnight. Concentrate the mixture *in vacuo* and dissolve the residue in water (20 mL). Extract the mixture with EtOAc (3 × 20 mL). Dry the combined organic extracts over Na_2SO_4, filter, and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel (40 g RediSep column) eluting with a gradient of dichloromethane and chloroform/methanol/concentrated ammonium hydroxide (80:18:2) over 1 h (80 mL/min) followed by reverse phase HPLC [Phenomonex C18(2) column (5 × 25 cm), eluting with water/acetonitrile (0.1% TFA in each) (9:1 to 1:9 gradient over 40 min), 118 mL/min] to obtain the trifluoroacetate salt of the title compound. Dissolve the residue in methanol

and elute through SCX column with saturated ammonia in methanol to provide 7-chloro-6-(4-cyclohexylmethyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (184 mg, 64%). Use a method similar to the General Procedure 2-1 to give the title compound as a white solid (240 mg, 100%). MS (ES) *m/z*: 383 $(M+H)^+$.

Example 602

7-Chloro-6-[4-(2-methyl-butyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



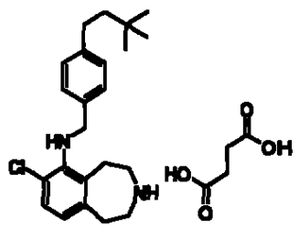
Under a nitrogen atmosphere, add 4-(2-methyl-butyl)-benzylamine (450 mg, 2.54 mmol), 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (720 mg, 1.7 mmol), palladium(II) acetate (40 mg, 0.17 mmol), BINAP (222 mg, 0.34 mmol) and cesium carbonate (1.4 g, 4.3 mmol) to toluene (20 mL). Heat the mixture at 95 °C for 12 h. Cool the mixture to room temperature and apply the mixture to a silica gel column eluting with hexane/EtOAc (10:1) to provide 7-chloro-6-[4-(2-methyl-butyl)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (450 mg, 59%). MS (ES+) *m/z*: 453 $(M+H)^+$.

Dissolve 7-chloro-6-[4-(2-methyl-butyl)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (450 mg, 1 mmol) and concentrated ammonium hydroxide (5 mL) in methanol (10 mL) and stir overnight. Concentrate the mixture *in vacuo*. Purify the crude mixture by SCX chromatography eluting with methanol and 3M ammonia in methanol. Concentrate the product *in vacuo* and purify the residue by reverse phase HPLC [Phenomonex Luna C18(2), 50 mm × 250 mm, eluting with acetonitrile/water with 0.1% TFA (2:3)]. Concentrate *in vacuo*, basify with potassium carbonate and extract into dichloromethane. Dry the organic solution over Na_2SO_4, filter

and concentrate *in vacuo* to provide the free base of the title compound (205 mg, 57%). Use a method similar to the General Procedure 2-1 to give the title compound as a white solid (280 mg, 59%). MS (APCI) *m/z*: 357 $(M+H)^+$.

Example 603

7-Chloro-6-[4-(3,3-dimethyl-butyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



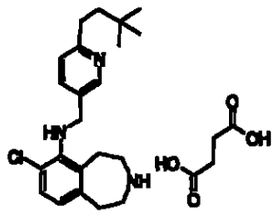
Use a method similar to the General Procedure 5-1 to react 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (623 mg, 1.46 mmol), palladium(II) acetate (33 mg, 0.146 mmol), BINAP (182 mg, 0.292 mmol), 4-(3,3-dimethyl-butyl)-benzylamine (560 mg, 2.93 mmol) and cesium carbonate (666 mg, 2.04 mmol) in degassed toluene (40 mL). Degas the mixture with vacuum/nitrogen purge and heat to 100 °C for 16 h. Cool the mixture to room temperature, dilute with EtOAc and wash with water. Dry the organic phase over $MgSO_4$, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane and then hexane/EtOAc (19:1, 9:1) to obtain 7-chloro-6-[4-(3,3-dimethyl-butyl)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as oil (622 mg, 91%). MS (ES+) *m/z*: 467 $(M+H)^+$.

Use a method similar to the General Procedure 1-2, using 7-chloro-6-[4-(3,3-dimethyl-butyl)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (448 mg, 0.96 mmol), to give the free base of the title compound as an oil (320 mg, 90%) that was used without further purification. MS (ES+) *m/z*: 371 $(M+H)^+$. Use a method similar to the General Procedure 2-1, using 7-chloro-6-[4-(3,3-dimethyl-butyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (315 mg, 0.85

mmol) to give the title compound as a white solid (340 mg, 82%). MS (ES+) *m/z*: 371 $(M+H)^+$.

Example 604

7-Chloro-6-[6-(3,3-dimethyl-butyl)-pyridin-3-yl-methylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

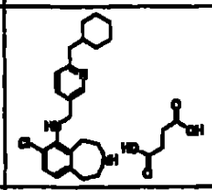
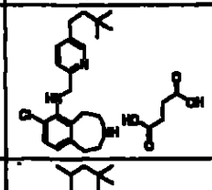
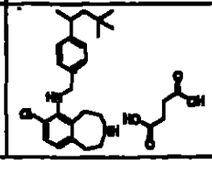


Use a method similar to the General Procedure 5-2 to react 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (166 mg, 0.39 mmol), tris(dibenzylideneacetone)dipalladium(0) (71 mg, 0.078 mmol), BINAP (103 mg, 0.156 mmol), 3-aminomethyl-6-(3,3-dimethyl-butyl)-pyridine (150 mg, 0.78 mmol) and cesium carbonate (178 mg, 0.546 mmol) in degassed toluene (20 mL). Degas the mixture with vacuum/nitrogen purge and heat to 100 °C for 14 h. Cool the mixture to room temperature, dilute with EtOAc and filter through Celite®. Purify the crude mixture by chromatography on silica gel eluting with hexane and then hexane/EtOAc (19:1, 9:1 and 4:1) to obtain 7-chloro-6-[6-(3,3-dimethyl-butyl)-pyridin-3-yl-methylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as oil (149 mg, 82%). MS (ES+) *m/z*: 468 $(M+H)^+$.

Use a method similar to the General Procedure 1-2, using 7-chloro-6-[6-(3,3-dimethyl-butyl)-pyridin-3-yl-methylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (140 mg, 0.29 mmol), to give the free base of the title compound as an oil (96 mg, 86%) that was used without further purification. MS (ES+) *m/z*: 372 $(M+H)^+$. Use a method similar to the General Procedure 2-1, using 7-chloro-6-[6-(3,3-dimethyl-butyl)-pyridin-3-yl-methylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (96 mg, 0.258 mmol) to give the title compound as a solid (119 mg, 94%). MS (ES+) *m/z*: 372 $(M+H)^+$.

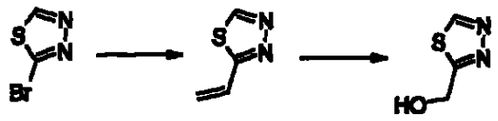
Examples 605-607

Examples 605-607 may be prepared essentially as described in Example 604 using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. Overall yields and MS (ES+) data are shown in the Table below..

Ex.	Structure	Compound	Yield (%)	MS (ES+) *m/z*
605		7-Chloro-6-(6-cyclohexylmethyl-pyridin-3-yl-methylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	42	384 $(M+H)^+$
606		7-Chloro-6-[5-(3,3-dimethyl-butyl)-pyridin-2-yl-methylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	34	372 $(M+H)^+$
607		7-Chloro-6-[4-(1,3,3-trimethyl-butyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	47	385 $(M+H)^+$

Preparation 320

2-Hydroxymethyl-[1,3,4]-thiadiazole



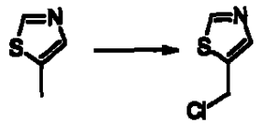
2-Vinyl-[1,3,4]-thiadiazole: Combine 2-bromo-[1,3,4]-thiadiazole (3.5 g, 21.2 mmol), tributylvinyltin (6.20 mL, 21.2 mmol) and tetrakis(triphenylphosphine)palladium(0) (735 mg, 0.6 mmol) in anhydrous toluene (141 mL). Heat the mixture at reflux for 18 h. Add methanol and dichloromethane to dissolve the residue and evaporate onto silica gel.

Purify the residue by chromatography on silica gel eluting with hexane/EtOAc (1:0 to 1:4 gradient) to give the desired intermediate (0.49 g, 21%). GC-MS *m/z*: 112 (M^+).

2-Hydroxymethyl-[1,3,4]-thiadiazole: At –10 °C bubble ozone through a solution of 2-vinyl-[1,3,4]-thiadiazole (400 mg, 3.57 mmol) in methanol (18 mL). After 20 min the starting material is consumed. Add then sodium borohydride (37 mg, 0.98 mmol) and warm to room temperature. Evaporate the mixture and purify the residue by passage through a pad of silica gel eluting with methanol/dichloromethane (98:2 to 96:4 gradient) to give the title compound (0.24 g, 60%). MS (ES+) *m/z*: 117 $(M+H)^+$.

Preparation 321

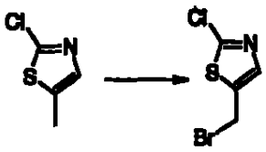
5-Chloromethylthiazole



Combine 5-methylthiazole (1.5 g, 15.1 mmol), *N*-chlorosuccinimide (2.6 g, 19.4 mmol) and AIBN (0.26 g, 1.6 mmol) in carbon tetrachloride (15 mL). Reflux under nitrogen for 3 h. Cool the reaction mixture and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (4:1) to give the title compound as a yellow oil (0.38 g, 19%).

Preparation 322

5-Bromomethyl-2-chlorothiazole

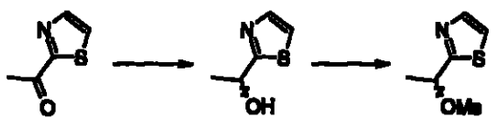


5-Chloromethyl-2-chlorothiazole: Combine 5-methyl-2-chlorothiazole (1.05 g, 7.5 mmol), NBS (1.7 g, 9.6 mmol) and AIBN (0.12 g, 0.73 mmol) in carbon tetrachloride (10 mL). Reflux under nitrogen for 7 h. Cool and concentrate *in vacuo*. Purify by

chromatography on silica gel eluting with hexane/EtOAc (9:1) to give the title compound as a yellow oil (0.82 g, 51%).

Preparation 323

(±)-1-Methanesulfonyloxy-1-thiazol-2-yl-ethyl

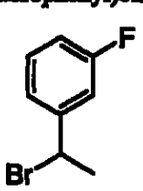


(±)-1-Thiazol-2-yl-ethanol: Add sodium borohydride (357 mg, 9.4 mmol) portionwise, over 5 min, to a solution of 2-acetylthiazole (1.0 g, 7.8 mmol) in methanol (25 mL) at 0 °C under a nitrogen atmosphere. Stir the mixture for 2 h at room temperature. Concentrate the mixture *in vacuo*, dilute the residue with brine (30 mL) and adjust the mixture to pH 6 with 5N aqueous HCl (10 mL). Extract the mixture with EtOAc (40 mL). Dry the organic layer over Na_2SO_4, filter and concentrate *in vacuo* to obtain the desired intermediate (1.0 g, 99%). GC-MS *m/z*: 129 (M^+).

(±)-1-Methanesulfonyloxy-1-thiazol-2-yl-ethyl: Dissolve 1-thiazol-2-yl-ethanol (1.0 g, 7.7 mmol) in dichloromethane (30 mL) and triethylamine (1.2 mL, 8.5 mmol). Cool the solution to 0°C, then add methanesulphony chloride (690 µl, 8.9 mmol) under a nitrogen atmosphere. Stir the solution for 1.5 h at room temperature, then wash with saturated aqueous $NaHCO_3$ (30 mL). Dry the organic layer over Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with dichloromethane/hexane/methanol (50:45:5) to obtain the title compound (1.3 g, 81%). GC-MS *m/z*: 207 (M^+).

Preparation 324

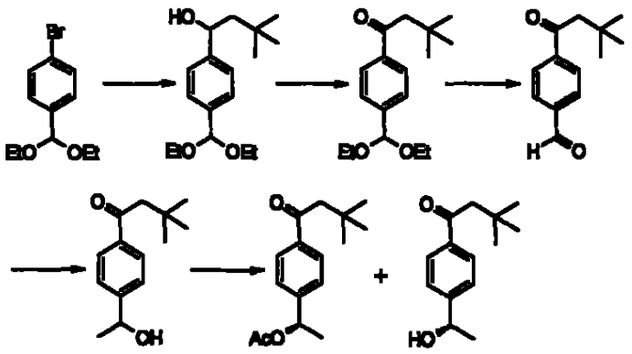
(±)-1-(3-Fluorophenyl)ethyl bromide



Dissolve (±)-1-(3-fluorophenyl)ethanol (250 mg, 1.786 mmol) in carbon tetrachloride (10 mL). Add phosphorus tribromide (0.1 mL, 1.786 mmol) at 0 °C and stir the solution at room temperature overnight. Dilute the reaction mixture with dichloromethane and wash with brine. Dry the organic phase over Na_2SO_4, filter and concentrate *in vacuo* to obtain the title compound (285 mg) that was used without any further purification.

Preparation 325

(*S*)-1-[4-(1-Hydroxyethyl)-phenyl]-3,3-dimethylbutan-1-one



1-[4-(Diethoxymethyl)-phenyl]-3,3-dimethylbutan-1-ol: Dissolve 1-bromo-4-(diethoxymethyl)-benzene (6.1 g, 23.55 mmol) in anhydrous THF (150 mL) and cool the solution to –78 °C. Add *n*-butyllithium (11.3 mL, 28.26 mmol, 2.5M solution in hexane) and stir the mixture for 30 min. Add 3,3-dimethylbutyraldehyde (4.7 mL, 35.33 mmol) and stir the mixture for 1 h. Add water and EtOAc. Warm the solution to room temperature and extract the aqueous layer three times with EtOAc. Dry the combined organic extracts with Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane/EtOAc (93:7) to give the desired intermediate as a colorless oil (3.8 g, 58%).

1-[4-(Diethoxymethyl)-phenyl]-3,3-dimethylbutan-1-one: Dissolve 1-[4-(diethoxymethyl)-phenyl]-3,3-dimethylbutan-1-ol (3.8 g, 13.57 mmol) in hexane (50 mL). Add manganese dioxide (3.5 g, 40.71 mmol) and stir the mixture at 60 °C

overnight. Filter the solid and concentrate the filtrate *in vacuo* to give the desired intermediate as a colorless oil (3.49 g, 93%).

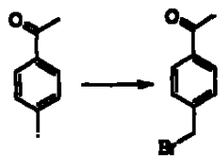
4-(3,3-Dimethyl-butyryl)-benzaldehyde: Dissolve 1-[4-(diethoxymethyl)-phenyl]-3,3-dimethylbutan-1-one (3.49 g, 12.55 mmol) in acetone (50 mL). Add *p*-toluenesulfonic acid monohydrate (238 mg, 1.256 mmol). Heat the mixture under reflux for 3 h. Concentrate *in vacuo* and partition the residue between water and EtOAc. Extract the aqueous phase three times with EtOAc. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane/EtOAc (9:1) to give the desired intermediate as a colorless oil (1.67 g, 65%).

1-[4-(1-Hydroxyethyl)-phenyl]-3,3-dimethylbutan-1-one: Dissolve 4-(3,3-dimethyl-butyryl)-benzaldehyde (1.67 g, 8.186 mmol) in anhydrous THF (20 mL) and cool the solution at –10 °C. Add methyl magnesium bromide (2.7 mL, 8.186 mmol, 3M solution in diethyl ether) and stir the mixture for 30 min. Add water at 0 °C, dilute with EtOAc and extract the aqueous layer three times with EtOAc. Dry the combined organic extracts over Na_2SO_4, filter through a short pad of silica gel and concentrate *in vacuo* to give the desired intermediate as yellow oil (1.519 g, 84%).

(*S*)-1-[4-(1-hydroxyethyl)-phenyl]-3,3-dimethylbutan-1-one: Dissolve 1-[4-(1-hydroxyethyl)-phenyl]-3,3-dimethylbutan-1-one (1.519 g, 6.905 mmol) in diisopropyl ether (20 mL). Add 4Å molecular sieves powder (1.5 g), vinyl acetate (2 mL) and lipase Candida Antarctica acrylic resin (150 mg). Stir the mixture at room temperature overnight. Remove the solid residue by filtration. Concentrate the filtrate *in vacuo* and purify the crude mixture by chromatography on silica gel eluting with hexane/EtOAc (4:1) to give (*R*)-1-(1-acetoxi-ethyl)-4-(3,3-dimethyl-butyryl)-benzene as colorless oil (0.661 g, 36%) and (*S*)-1-[4-(1-hydroxyethyl)-phenyl]-3,3-dimethylbutan-1-one as a light yellow oil (0.737 g, 49%).

Preparation 326

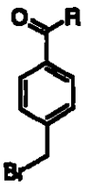
4-Acetyl-benzyl bromide



Heat a mixture of 4'-methylacetophenone (5 g, 37.26 mmol), NBS (6.964 g, 39.12 mmol), and AIBN (153 mg, 0.93 mmol) in carbon tetrachloride (120 mL) for 14 h at reflux. Cool to ambient temperature and wash sequentially with water (100 mL), 1M aqueous HCl (100 mL), 5% aqueous $NaHCO_3$ (100 mL) and brine (100 mL). Dry the organic phase over Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting sequentially with hexane and hexane/EtOAc (19:1, 9:1) to provide the title compound as oil (5.191 g, 65%). GC-MS *m/z*: 213 (M^+).

Preparations 353-354

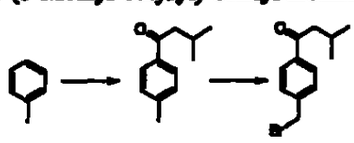
The compounds of Preparations 353-354 may be prepared essentially as described in Preparation 326 using 4'-methylpropiophenone (Preparation 353) and 4'-methylbutyrophenone (Preparation 354). Yields are shown in the Table below.



Prep.	R	Compound	Yield (%)
353	Et	4-Propionyl-benzyl bromide	92
354	*n*-Pr	4-Butyryl-benzyl bromide	42

Preparation 329

4-(3-Methyl-butyryl)-benzyl bromide



3,4'-Dimethylbutyrophenone: Add slowly isovaleryl chloride (3.0 g, 24.88 mmol) to an ice-cold stirred solution of aluminum trichloride (4.976 g, 37.32 mmol) in anhydrous toluene (60 mL). Stir the reaction mixture at ambient temperature overnight. Add slowly ice-cold water and extract the mixture twice with EtOAc. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo* to give the desired intermediate (4.38 g, 100%) that was used without any further purification. GC-MS *m/z*: 176 (M^+).

4-(3-Methyl-butyryl)-benzyl bromide: Heat a mixture of 3,4'-dimethylbutyrophenone (3 g, 17.02 mmol), NBS (3.787 g, 16.18 mmol), and AIBN (70 mg, 0.425 mmol) in carbon tetrachloride (80 mL) for 14 h at reflux. Cool to ambient temperature and filter the mixture. Concentrate the filtrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting sequentially with hexane and hexane/EtOAc (9:1) to provide the title compound as oil (2.802 g, 65%). GC-MS *m/z*: 255 (M^+).

Preparations 356-357

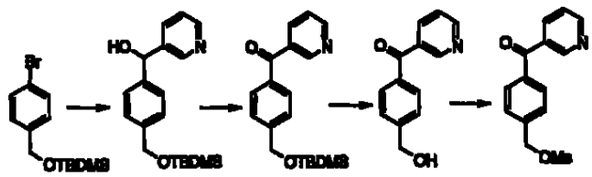
The compounds of Preparations 356-357 may be prepared essentially as described in Preparation 329 using the appropriate acyl chloride. Overall yields and GC-MS data are shown in the Table below.



Prep.	R	Compound	Yield (%)	GC-MS *m/z*
330	*i*-Propyl	4-Isobutyryl-benzyl bromide	32	241 $(M)^+$
357	2-Pyridyl	4-(Pyridine-2-carbonyl)-benzyl bromide	9	276 $(M)^+$

Preparation 332

4-(Pyridine-3-carbonyl)-benzyl methanesulfonate



[4-(*tert*-Butyldimethylsilyloxymethyl)-phenyl-pyridin-3-yl-methanol]: Dissolve 4-(*tert*-butyldimethylsilyloxymethyl)bromobenzene (1 g, 3.319 mmol, prepared by following the procedure described in *J. Am. Chem. Soc.* 1995, *117*, 704-714) in anhydrous THF (20 mL). Cool the solution to –78 °C, add *n*-BuLi (4.149 mL, 6.638 mmol, 1.6M solution in hexane) and stir at this temperature for 1.5 h. Warm to –60°C, stir for an additional 30 min and add 3-pyridine carboxaldehyde. Allow the reaction mixture to warm gradually to room temperature and stir overnight. Add brine and extract with EtOAc. Dry the organic phase over Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting sequentially with hexane and EtOAc to give the desired intermediate (380 mg, 35%). MS (ES+) *m/z*: 330 $(M+H)^+$.

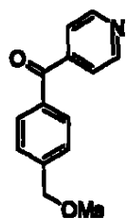
[4-(*tert*-Butyldimethylsilyloxymethyl)-phenyl-pyridin-3-yl-methanone]: Add manganese dioxide (1.44 g) to a stirred solution of [4-(*tert*-butyldimethylsilyloxymethyl)-phenyl]-pyridin-3-yl-methanol (360 mg, 0.303 mmol) in anhydrous 1,4-dioxane (25 mL). Heat the mixture to 70 °C overnight. Cool the reaction mixture to room temperature, filter through Celite® and wash with EtOAc. Concentrate the filtrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting sequentially with hexane and hexane/EtOAc (1:1) to provide the desired intermediate (233 mg, 65%). GC-MS *m/z*: 327 (M^+).

4-(Pyridine-3-carbonyl)-benzyl alcohol: Add tetrabutylammonium fluoride (1.37 mL, 1.37 mmol, 1M solution in THF) to a solution of [4-(*tert*-butyldimethylsilyloxymethyl)-phenyl]-pyridin-3-yl-methanone (225 mg, 0.687 mmol) in anhydrous THF (10 mL) at 0 °C and stir at this temperature for 1 h. Concentrate the solvent *in vacuo* and purify the crude mixture by chromatography on silica gel eluting with EtOAc to provide the desired intermediate (85 mg, 58%). MS (ES+) *m/z*: 214 $(M+H)^+$.

4-(Pyridine-3-carbonyl)-benzyl methanesulfonate: Dissolve 4-(pyridine-3-carbonyl)-benzyl alcohol (85 mg, 0.399 mmol) in dichloromethane (5 mL). Cool to 0 °C and add triethylamine (0.056 mL, 0.438 mmol) and methanesulfonyl chloride (0.033 mL, 0.438 mmol). Allow the mixture to warm to room temperature and stir for 2 h. Dilute the reaction mixture with dichloromethane and wash with saturated aqueous $NaHCO_3$. Dry the organic phase over Na_2SO_4, filter and concentrate *in vacuo* to provide the title compound as oil (115 mg, 100%). GC-MS *m/z*: 291 (M^+).

Preparation 333

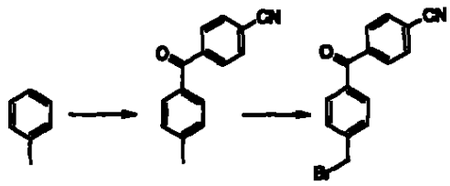
4-(Pyridine-4-carbonyl)-benzyl methanesulfonate



The compound of Preparation 333 may be prepared essentially as described in Preparation 332 using 4-(*tert*-butyldimethylsilyloxymethyl)bromobenzene and 4-pyridine carboxaldehyde (GC-MS *m/z* 291 $(M)^+$).

Preparation 334

4-(4-Cyano-benzoyl)-benzyl bromide



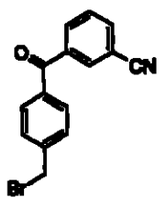
4-(4-Methyl-benzoyl)-benzonitrile: Suspend 4-cyanobenzoyl chloride (2.0 g, 12 mmol) in anhydrous toluene (30 mL). Add aluminum trichloride (2.4 g, 18 mmol) in three portions and stir the reaction mixture at ambient temperature overnight. Cool to 0°C, add carefully water and extract the mixture twice with EtOAc. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo* to give a solid. Suspend the solid in

diethyl ether and filter to obtain the desired intermediate (1.30 g, 49%) that was used without any further purification. GC-MS *m/z*: 221 (M^+).

4-(4-Cyano-benzoyl)-benzyl bromide: Heat a mixture of 4-(4-methyl-benzoyl)-benzonitrile (300 mg, 1.356 mmol), NBS (386 mg, 2.169 mmol), and AIBN (22 mg, 0.136 mmol) in carbon tetrachloride (10 mL) for 14 h at reflux. Add additional NBS (121 mg) and AIBN (11 mg) and reflux the mixture for 3 h. Cool the reaction mixture to ambient temperature and filter the mixture. Concentrate the filtrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting sequentially with hexane and hexane/EtOAc (9:1) to provide the title compound as a solid (286 mg, 70%). GC-MS *m/z*: 300 (M^+).

Preparation 335

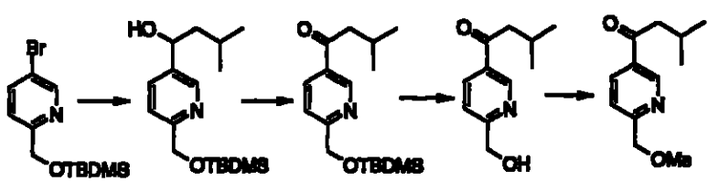
4-(3-Cyano-benzoyl)-benzyl bromide



The compound of Preparation 335 may be prepared essentially as described in Preparation 334 using 3-cyanobenzoyl chloride (GC-MS *m/z* 300 (M^+)).

Preparation 336

2-Methanesulfonyloxymethyl-5-(3-methyl-butyryl)-pyridine



2-(*tert*-Butyldimethylsilyloxymethyl)-5-(1-hydroxy-3-methyl-butyl)-pyridine: Dissolve 5-bromo-2-(*tert*-butyldimethylsilyloxymethyl)-pyridine (0.5 g, 1.654 mmol, prepared by following the procedure described in *J. Med. Chem.* 1987, 30, 871-880) in anhydrous THF (12 mL). Cool the solution to –78 °C, add *n*-BuLi (1.14 mL, 1.819 mmol, 1.6M solution in hexane) and stir at this temperature for 40 min. Add slowly isovaleryl aldehyde (0.284 mL, 2.646 mmol) and stir the mixture for 5 h at –78 °C. Add additional isovaleryl aldehyde (0.089 mL, 0.827 mmol) and stir the mixture for 1.5 h at –78 °C. Add ammonium chloride at –78 °C and warm the mixture to room temperature. Add EtOAc and extract the aqueous layer twice with EtOAc. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane and hexane/EtOAc (4:1) to give the desired intermediate as oil (330 mg, 64%). GC-MS *m/z*: 309 (M^+).

2-(*tert*-Butyldimethylsilyloxymethyl)-5-(3-methyl-butyryl)-pyridine: Add manganese dioxide (1.32 g) to a stirred solution of 2-(*tert*-butyldimethylsilyloxymethyl)-5-(1-hydroxy-3-methyl-butyl)-pyridine (330 mg, 1.066 mmol) in anhydrous 1,4-dioxane (30 mL). Heat the mixture to 70 °C overnight. Cool the reaction mixture to room temperature, filter through Celite® and wash with EtOAc. Concentrate the filtrate *in vacuo* to provide the desired intermediate as oil (327 mg, 100%). GC-MS *m/z*: 307 (M^+).

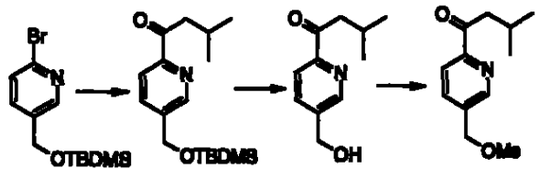
2-Hydroxymethyl-5-(3-methyl-butyryl)-pyridine: Add tetrabutylammonium fluoride (2.13 mL, 2.13 mmol, 1M solution in THF) to a solution of 2-(*tert*-butyldimethylsilyloxymethyl)-5-(3-methyl-butyryl)-pyridine (330 mg, 1.066 mmol) in anhydrous THF (20 mL) at 0 °C and stir at this temperature for 1 h. Concentrate the solvent *in vacuo* and purify the crude mixture by chromatography on silica gel eluting with EtOAc to provide the desired intermediate (327 mg, 100%).

2-Methanesulfonyloxymethyl-5-(3-methyl-butyryl)-pyridine: Dissolve 2-hydroxymethyl-5-(3-methyl-butyryl)-pyridine (190 mg, 0.98 mmol) in dichloromethane (10 mL). Cool to 0 °C and add triethylamine (0.151 mL, 1.08 mmol) and methanesulfonyl chloride (0.083 mL, 1.08 mmol). Allow the mixture to warm to room

temperature and stir for 2 h. Dilute the reaction mixture with dichloromethane and wash with saturated aqueous $NaHCO_3$. Dry the organic phase over Na_2SO_4, filter and concentrate *in vacuo* to provide the title compound as oil (263 mg, 98%).

Preparation 337

5-Methanesulfonyloxymethyl-2-(3-methyl-butyryl)-pyridine



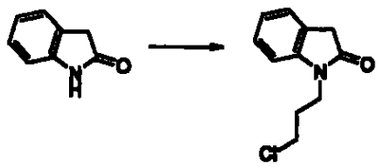
5-(*tert*-Butyldimethylsilyloxymethyl)-2-(3-methyl-butyryl)-pyridine: Dissolve 2-bromo-5-(tert-butyldimethylsilyloxymethyl)pyridine (1.99 g, 6.583 mmol, prepared by following the procedure described in *J. Org. Chem.* 2004, *69*, 250-262) in anhydrous THF (20 mL). Cool the solution to –78 °C, add *n*-BuLi (4.32 mL, 6.912 mmol, 1.6M solution in hexane) and stir at this temperature for 40 min. Add slowly a solution of *N*-methoxy-*N*-methyl-3-methyl-butyramide (0.955 g, 6.583 mmol) in anhydrous THF (5 mL). Stir the mixture for 2 h at –78 °C and then allow the mixture to warm to room temperature. Add brine and extract the aqueous layer twice with EtOAc. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane and hexane/EtOAc (19:1) to give the desired intermediate as yellow oil (890 mg, 44%). GC-MS *m/z*: 307 (M^+).

5-Hydroxymethyl-2-(3-methyl-butyryl)-pyridine: Add tetrabutylammonium fluoride (5.853 mL, 5.853 mmol, 1M solution in THF) to a solution of 5-(*tert*-butyldimethylsilyloxymethyl)-2-(3-methyl-butyryl)-pyridine (900 mg, 2.927 mmol) in anhydrous THF (30 mL) at 0 °C and stir at this temperature for 2 h. Concentrate the solvent *in vacuo* and purify the crude mixture by chromatography on silica gel eluting with hexane and hexane/EtOAc (3:2) to provide the desired intermediate (478 mg, 84%). MS (ES+) *m/z*: 194 $(M+H)^+$.

5-Methanesulfonyloxymethyl-2-(3-methyl-butyryl)-pyridine: Dissolve 5-hydroxymethyl-2-(3-methyl-butyryl)-pyridine (210 mg, 1.086 mmol) in dichloromethane (5 mL). Cool to 0 °C and add triethylamine (0.167 mL, 1.195 mmol) and methanesulfonyl chloride (0.093 mL, 1.195 mmol). Allow the mixture to warm to room temperature and stir for 2 h. Dilute the reaction mixture with dichloromethane and wash with saturated aqueous $NaHCO_3$. Dry the organic phase over Na_2SO_4, filter and concentrate *in vacuo* to provide the title compound (256 mg, 87%). GC-MS *m/z*: 271 (M^+).

Preparation 338

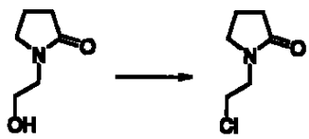
1-(3-Chloro-propyl)-1,3-dihydro-indol-2-one



Reflux together oxindole (2.66 g, 20.0 mmol), 1-bromo-3-chloropropane (2.56 mL, 26.0 mmol) and potassium carbonate (5.52 g, 40.0 mmol) in acetonitrile (300 mL) under nitrogen for 16 h. Cool the suspension to room temperature and filter off the precipitate. Concentrate the filtrate *in vacuo* and purify the crude mixture by chromatography on silica gel eluting with isohexane/EtOAc (1:0 to 3:2 gradient over 40 min) to give the title compound as an orange oil (1.65 g, 39%). MS (ES+) *m/z*: 210 $(M+H)^+$.

Preparation 339

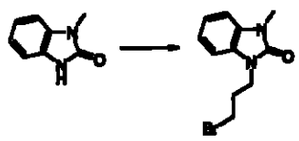
1-(2-Chloro-ethyl)-pyrrolidin-2-one



Add thionyl chloride (5 mL) to 1-(2-hydroxy-ethyl)-pyrrolidin-2-one (1.12 mL, 10.0 mmol) dropwise then stir at room temperature for 10 min. Remove solvent *in vacuo* to give the title compound as an orange oil. MS (ES+) *m/z*: 148 $(M+H)^+$.

Preparation 340

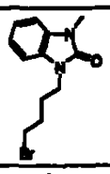
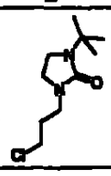
1-(3-Bromo-propyl)-3-methyl-1,3-dihydro-benzoimidazol-2-one



Add portion wise 3-methyl-1,3-dihydro-benzoimidazol-2-one (400 mg, 27.0 mmol) to a suspension of sodium hydride (1.296 g, 32.4 mmol of 60% dispersion in oil) in anhydrous THF (200 mL) under nitrogen over 15 min, then continue to stir for 30 min. Add 1,3-dibromopropane (11.0 mL, 108 mmol) and stir overnight. Then heat at reflux for 3 days. Cool the suspension to room temperature, pour into brine (400 mL), extract with diethyl ether (300 mL), dry over $MgSO_4$ and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with isohexane/EtOAc (1:0 to 1:1 gradient over 40 min) to give the title compound as a colourless oil (2.15 g, 30%).

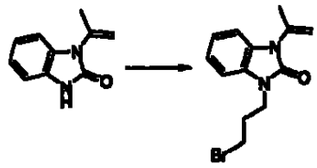
Preparations 341-342

The Compound of Preparation 341 may be prepared essentially as described in Preparation 340 using 3-methyl-1,3-dihydro-benzoimidazol-2-one and 1,4-dibromobutane. The compound of Preparation 342 may be prepared essentially as described in Preparation 340 using 1-*tert*-butyl-imidazolidin-2-one and 1-bromo-3-chloropropane. Yields are shown in the Table below.

Prep.	Structure	Compound	Yield (%)
341		1-(4-Bromo-butyl)-3-methyl-1,3-dihydro-benzoimidazol-2-one	56
342		1-*tert*-Butyl-(3-chloro-propyl)-imidazolidin-2-one	5

Preparation 343

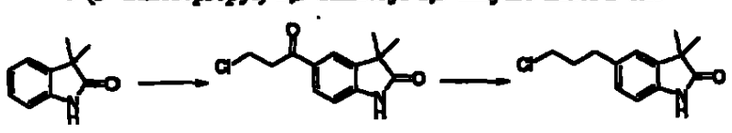
1-(3-Bromo-propyl)-3-isopropenyl-1,3-dihydro-benzoimidazol-2-one



Add sodium hydride (600 mg, 16.5 mmol of 60% dispersion in oil) to a solution of 1-isopropenyl-1,3-dihydro-benzoimidazol-2-one (1.311 g, 7.53 mmol) in anhydrous DMF (10 mL) under nitrogen at room temperature and stir for 2 h. Add 1-bromo-3-chloropropane (900 μL, 9.03 mmol) and stir for 3 days. Pour the suspension into water (100 mL), extract with diethyl ether (2 x 50 mL). Wash the organic extract with brine (100 mL), dry over $MgSO_4$ and concentrate *in vacuo* to give the title compound impurified with 1-(3-chloro-propyl)-3-isopropenyl-1,3-dihydro-benzoimidazol-2-one (2.03 g, 1:1 mixture). MS (ES+) *m/z*: 251 $(M+H)^+$, 293 $(M+H)^+$.

Preparation 344

5-(3-Chloropropyl)-3,3-dimethyl-1,3-dihydro-indol-2-one

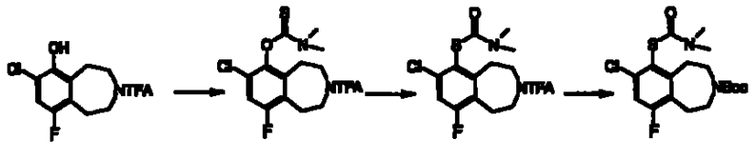


5-(3-Chloropropionyl)-3,3-dimethyl-1,3-dihydro-indol-2-one: Under nitrogen atmosphere, add chloropropionyl chloride (1.54 mL, 16.13 mmol) to a mixture of 3,3-dimethyl-1,3-dihydro-indol-2-one (2.0 g, 12.41 mmol) and aluminium trichloride (10.26 g, 76.92 mmol) in carbon disulphide (70 mL). Heat under reflux for 3 h then allow to cool. Decant off the solvent and replace it carefully with ice/water (200 mL). Allow the resultant suspension to stir for 20 min before filtering off the product and washing with water (80 mL). Dry *in vacuo* to obtain the desired intermediate as a pale brown solid (3.08 g, 99%).

5-(3-Chloropropyl)-3,3-dimethyl-1,3-dihydro-indol-2-one: Under nitrogen atmosphere, add 5-(3-chloropropyl)-3,3-dimethyl-1,3-dihydro-indol-2-one (3.08 g, 12.24 mmol) to trifluoroacetic acid (9.4 mL, 122.4 mmol). Cool the resulting suspension to 0 °C and then add triethylsilane (4.5 mL, 28.2 mmol) dropwise over 2 min. Heat at 45 °C for 30 min then stir at ambient temperature overnight. Pour the reaction mixture onto ice/water (100 mL) and extract with EtOAc (2 x 100 mL). Dry the combined extracts over $MgSO_4$, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane/EtOAc (1:0 to 4:1 gradient), to give the title compound as a yellow-orange solid (2.12 g, 73%).

Preparation 345

3-*tert*-Butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-9-fluoro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine



7-Chloro-6-(*O*-dimethylthiocarbamoyl)-9-fluoro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Heat 7-chloro-9-fluoro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.56 g, 1.8 mmol) at reflux in anhydrous 1,4-dioxane (18 mL) with triethylamine (1.01 mL, 7.2 mmol), *N,N*-dimethyl-4-aminopyridine (22 mg, 0.18 mmol) and dimethylthiocarbamoyl chloride (0.67 g, 5.4

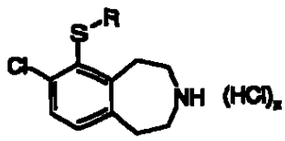
mmol) for 16 h. Cool and wash the mixture with 1N aqueous HCl, saturated aqueous $NaHCO_3$ and brine. Concentrate *in vacuo* and purify by chromatography on silica gel eluting with hexane/EtOAc (1:0 to 3:2 gradient) to give the desired intermediate as a yellow oil that solidifies on standing (0.69 g, 96%). MS (ES+) *m/z*: 399 $(M+H)^+$.

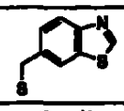
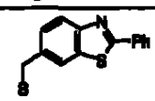
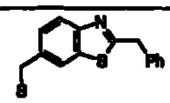
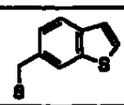
7-Chloro-6-dimethylcarbamoylthio-9-fluoro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Heat 7-chloro-6-(*O*-dimethylthiocarbamoyl)-9-fluoro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.69 g, 1.73 mmol) in diphenyl ether (6 mL) at 245 °C for 2.5 h. Cool the mixture and load onto a column of silica gel. Wash diphenyl ether off with hexane and elute with hexane/EtOAc (1:0 to 3:2 gradient) to give the desired intermediate (0.44 g, 64%). MS (ES+) *m/z*: 399 $(M+H)^+$.

3-*tert*-Butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-9-fluoro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Heat 7-chloro-6-dimethylcarbamoylthio-9-fluoro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.2 g, 0.5 mmol) in methanol (50 mL) with potassium carbonate (0.28 g, 2 mmol) at reflux for 5 h. Cool the mixture, add dropwise a solution of di-*tert*-butyl-dicarbonate (0.22 g, 1.0 mmol) in dichloromethane (20 mL) and stir 17 h. Evaporate the mixture onto silica gel and purify by chromatography eluting with hexane/EtOAc (1:0 to 3:2 gradient) to give the title compound (0.12 g, 62%). MS (ES+) *m/z*: 303 $(M+H\text{-Boc})^+$.

Examples 608-611

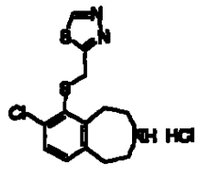
Examples 608-611 may be prepared essentially as described in Example 350 by using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriately substituted chloromethylheterocycle or bromomethylheterocycle. MS (ES+) data are shown in the Table below.



Ex.	SR	Compound	MS (ES+ or APCI+)
608		7-Chloro-6-(benzothiazol-6-yl-methylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	361 $(M+H)^+$
609		7-Chloro-6-(2-phenyl-benzothiazol-6-yl-methylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	437 $(M+H)^+$
610		7-Chloro-6-(2-benzyl-benzothiazol-6-yl-methylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	451 $(M+H)^+$
611		7-Chloro-6-(benzothiophen-6-yl-methylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	360 $(M+H)^+$

Example 612

7-Chloro-6-([1,3,4]thiadiazol-2-yl-methylthio)-2,3,4,5-tetrahydro-1*H*-benzo [*d*]azepine Hydrochloride



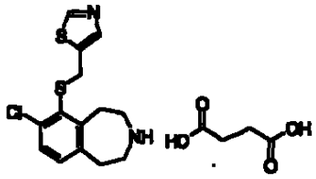
Stir 2-hydroxymethyl-[1,3,4]-thiadiazole (241 mg, 2.1 mmol) in thionylchloride (15 mL) for 1 h and concentrate *in vacuo*. Treat this residue with the thiolate prepared from 3-*tert*-butoxycarbonyl-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.4 g, 1.04 mmol) and potassium hydroxide (1.37 g, 24.5 mmol) in methanol (3.5 mL) according to General Procedure 7 to give 3-*tert*-butoxycarbonyl-7-chloro-6-([1,3,4]thiadiazol-2-yl-methylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.3 g, 70%). Treat an aliquot with trifluoroacetic acid to obtain the mass spectrum. MS (ES+) *m/z*: 312 $(M+H)^+$.

Use a method similar to the General Procedure 1-5 to deprotect 3-*tert*-butoxycarbonyl-7-chloro-6-([1,3,4]thiadiazol-2-yl-methylthio)-2,3,4,5-tetrahydro-1*H*-

benzo[*d*]azepine (300 mg, 0.73 mmol). Use a method similar to the General Procedure 2-2 to give the title compound (208 mg, 82%). MS (ES+) *m/z*: 312 $(M+H)^+$.

Example 613

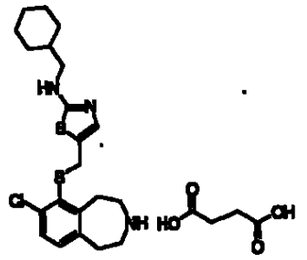
7-Chloro-6-(thiazol-5-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Use a method similar to General Procedure 7, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 5-chloromethylthiazole to give, after deprotection and salt formation by methods similar to the General Procedures 1-5 and 2-1, the title compound as a white solid (700 mg, 80% overall). HRMS (ES+) *m/z*: 311.0427 $(M+H)^+$.

Example 614

7-Chloro-6-[2-(cyclohexylmethylamino)-thiazol-5-ylmethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

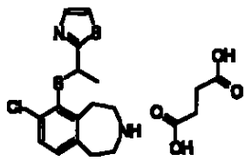


Use a method similar to General Procedure 7 using 3-*tert*-butoxycarbonyl-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 5-bromomethyl-2-chlorothiazole to give 3-*tert*-butoxycarbonyl-7-chloro-6-(2-chlorothiazol-5-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow oil (0.9 g, 71%). Dissolve 3-*tert*-butoxycarbonyl-7-chloro-6-(2-chlorothiazol-5-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (120 mg, 0.27 mmol) and cyclohexylmethylamine (1 mL, 7.7 mmol) in

absolute ethanol (1 mL) in a heavy walled Pyrex tube. Heat the reaction in an oil bath at 82 °C for 24 h. Cool the reaction mixture and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (4:1). Use methods similar to General Procedures 1-5 and 2-1 to deprotect and give the title compound as yellow oil (19 mg, 26% overall). MS (ES+) *m/z*: 422 $(M+H)^+$.

Example 615

(-)-7-Chloro-6-[1-(thiazol-2-yl)-ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



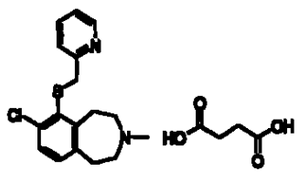
Add potassium hydroxide (3.9 g, 70 mmol) to a solution of 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (900 mg, 2.3 mmol) in methanol (25 mL) under a nitrogen atmosphere. Heat the mixture at 80 °C for 1.5 h. Cool the mixture to ambient temperature, then concentrate *in vacuo* to an oil. Dissolve the oil in EtOAc (50mL) and wash with saturated aqueous ammonium chloride (30 mL). Separate the organic layer and extract the aqueous layer with EtOAc (3 x 50 mL). Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo* to an oil (735 mg). Dissolve the oil in anhydrous DMSO (20 mL), then add triethylamine (1.9 mL, 14 mmol) and (±)-1-methanesulfonyloxy-1-thiazol-2-yl-ethyl (1.3 g, 6.3 mmol) at ambient temperature under nitrogen. Heat the mixture at 40 °C for 1 h. Cool the reaction to room temperature, then dilute the mixture with hexane/EtOAc (1:1, 50 mL) and wash with aqueous 5% sodium chloride (3 x 50 mL). Separate the organic layer and back extract the aqueous layer with EtOAc (3 x 50 mL). Combine the organic extracts and concentrate *in vacuo*. Purify the residue by chromatography on silica gel eluting with hexane/EtOAc (19:1 to 7:3 gradient) to obtain (±)-3-*tert*-butoxycarbonyl-7-chloro-6-[1-(thiazol-2-yl)-ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (779 mg, 79%). MS (ES+) *m/z*: 425.0 $(M+H)^+$.

Separate (±)-3-*tert*-butoxycarbonyl-7-chloro-6-[1-(thiazol-2-yl)-ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (770 mg, 1.8 mmol) by normal phase chiral chromatography [Chiralpak AD, 8 x 30 cm, eluting with heptane/3A ethanol (9:1)]. Collect the 2nd eluting isomer of 3-*tert*-butoxycarbonyl-7-chloro-6-[1-(thiazol-2-yl)-ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine {348 mg, 99% ee [Chiralpak AD-H, 4.6 x 150 mm, eluant heptane/3A ethanol (9:1)]}.

Use a method similar to the General Procedure 1-5 to deprotect 3-*tert*-butoxycarbonyl-7-chloro-6-[1-(thiazol-2-yl)-ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine isomer 2. Purify by chromatography on silica gel eluting with dichloromethane/2M ammonia in methanol (98:2 to 90:10 gradient) to give the free base of the title compound. Use a method similar to the General Procedure 2-1 to obtain the title compound (350 mg, 96%). MS (ES+) *m/z*: 325.0 $(M+H)^+$. $[\alpha]^{20}_D$ –160° (c 0.5, MeOH).

Example 616

7-Chloro-3-methyl-6-(pyridin-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine . Succinate



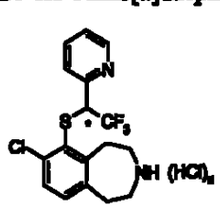
Suspend 7-chloro-6-(pyridin-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine hydrochloride in saturated aqueous $NaHCO_3$ and extract three times with EtOAc. Dry the combined organic extracts over $MgSO_4$. Filter and concentrate in *vacuo* to give the free base as a yellow oil. Combine the free base (0.2 g, 0.66 mmol), sodium triacetoxyborohydride (0.78 g, 3.7 mmol), formaldehyde (37% solution in water, 0.2 mL, 2.7 mmol), and acetic acid (0.45 mL, 7.9 mmol), in 1,2-dichloroethane (5 mL). Stir at room temperature for 12 h. Concentrate the crude reaction mixture *in vacuo* and partition the residue between EtOAc/water. Separate the layers and extract the aqueous phase with EtOAc (3 x 30 mL). Wash the combined organic extracts with 1M aqueous NaOH. Dry

over $MgSO_4$, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with 2M ammonia in methanol/dichloromethane (4:96).

Use a method similar to the General Procedure 2-1 to give the title compound as a sticky glass (140 mg, 48%). HRMS (ES+) *m/z*: 319.1029 $(M+H)^+$.

Examples 617 and 618

7-Chloro-6-(2,2,2-trifluoro-1-pyridin-2-yl-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride Isomer 1 and 7-Chloro-6-(2,2,2-trifluoro-1-pyridin-2-yl-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride Isomer 2



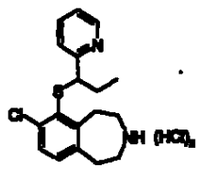
Separate the two enantiomers of (±)-7-chloro-6-(2,2,2-trifluoro-1-pyridin-2-yl-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine hydrochloride by normal phase chiral chromatography (Chiralpak AD, 2 x 25 cm, eluting with heptane/ethanol (85:15) with 0.2% DMEA).

Subject the first eluting isomer to the General Procedure 1-4 to obtain 7-chloro-6-(2,2,2-trifluoro-1-pyridin-2-yl-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine hydrochloride isomer 1 [99% ee (Chiralpak AD-H, 4.6 x 150 mm, eluting with heptane/ethanol (85:15) with 0.2% DMEA, flow rate 0.6 mL/min)]. MS (ES+) *m/z*: 373 .1 $(M+H)^+$.

Subject the second eluting isomer to the General Procedure 1-4 to obtain 7-chloro-6-(2,2,2-trifluoro-1-pyridin-2-yl-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine hydrochloride isomer 2 [99% ee (Chiralpak AD-H, 4.6 x 150 mm, eluting with heptane/ethanol (85:15) with 0.2% DMEA, flow rate 0.6 mL/min)]. MS (ES+) *m/z* 373.1 $(M+H)^+$.

Example 619

(-)-7-Chloro-6-(1-pyridin-2-yl-propylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

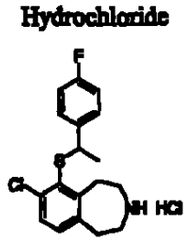


Separate the two enantiomers of (±)-7-chloro-6-(1-pyridin-2-yl-propylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine hydrochloride by normal phase chiral chromatography (Chiralcel OJ, 8 x 33 cm, eluting with heptane/methanol/3A ethanol (85:10:5) with 0.2% DMEA).

Subject the second eluting isomer to the General Procedure 1-4 to obtain the title compound [93% ee (Chiralcel OJ, 4.6 x 250 mm, eluting with heptane/methanol/3A ethanol (90:5:5) with 0.2% DMEA, flow rate 0.6 mL/min)]. MS (ES+) *m/z*: 333.1 $(M+H)^+$. $[\alpha]^{20}_D$ –240.6° (c 0.5, MeOH).

Example 620

(±)-7-Chloro-6-[1-(4-fluorophenyl)ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



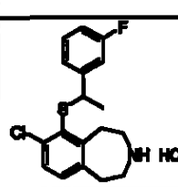
Dissolve 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (415 mg, 1.08 mmol) in methanol (20 mL) and add potassium hydroxide (1.938 g, 34.53 mmol). Heat at 60 °C for 4 h. Cool the reaction mixture to ambient temperature, add aqueous saturated ammonium chloride and concentrate *in vacuo*. Partition the residue between EtOAc and water. Dry the organic phase over anhydrous Na_2SO_4 and concentrate *in vacuo* to give 3-*tert*-butoxycarbonyl-7-

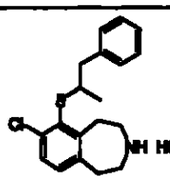
chloro-6-mercapto-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.34 g, 1.086 mmol). Dissolve the crude 3-*tert*-butoxycarbonyl-7-chloro-6-mercapto-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.34 g, 1.086 mmol) in anhydrous DMF (10 mL), add sodium hydride (65 mg, 1.63 mmol, 60% in mineral oil) and stir the mixture for 5 min. Add a solution of (±)-1-(4-fluorophenyl)ethyl bromide (332 mg, 1.63 mmol) in anhydrous DMF (5 mL) and heat the solution at 45 °C overnight. Cool to ambient temperature, add water and extract the aqueous phase twice with EtOAc. Dry the combined organic extracts over anhydrous Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane and hexane/EtOAc (19:1 and 9:1) to give (±)-3-*tert*-butoxycarbonyl-7-chloro-6-[1-(4-fluorophenyl)ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as oil (397 mg, 84%). MS (ES+) *m/z*: 336 $(M+H\text{-Boc})^+$.

Use a method similar to the General Procedure 1-4 to deprotect (±)-3-*tert*-butoxycarbonyl-7-chloro-6-[1-(4-fluorophenyl)ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (47 mg, 0.108 mmol) and give the title compound as a solid (39 mg, 99%). MS (ES+) *m/z*: 336 $(M+H)^+$.

Examples 621-622

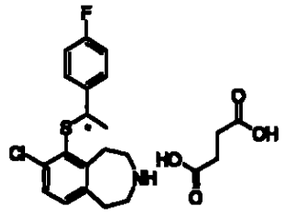
Examples 621-622 may be prepared essentially as described in Example 620 using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate alkyl bromide. Overall yields and MS (ES+) data are shown in the Table below.

Ex.	Structure	Compound	Yield (%)	MS (ES+) *m/z*
621		(±)-7-Chloro-6-[1-(3-fluorophenyl)ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	75	336 $(M+H)^+$

Ex.	Structure	Compound	Yield (%)	MS (ES+) *m/z*
622		(±)-7-Chloro-6-(1-methyl-2-phenyl-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	80	332 $(M+H)^+$

Examples 623 and 624

7-Chloro-6-[1-(4-fluorophenyl)ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate Isomer 1 and 7-chloro-6-[1-(4-fluorophenyl)ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate Isomer 2



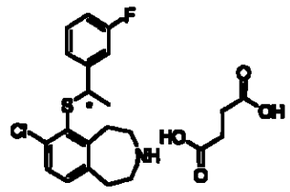
Separate the two enantiomers of (±)-3-*tert*-butoxycarbonyl-7-chloro-6-[1-(4-fluorophenyl)ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine by chiral HPLC (Chiralcel OJ-H 4.6 x 150 mm column, eluting with methanol at 0.6 mL/min).

Subject Isomer 1 (t_R = 7.3 min, ee > 99.9%) to the General Procedure 2-1 to afford 7-chloro-6-[1-(4-fluorophenyl)ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine succinate isomer 1 as a white solid. MS (ES+) *m/z* 336 $(M+H)^+$.

Subject Isomer 2 (t_R = 12.9 min, ee = 99.9%) to the General Procedure 2-1 to afford 7-chloro-6-[1-(4-fluorophenyl)ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine succinate isomer 2 as a white solid. MS (ES+) *m/z* 336 $(M+H)^+$.

Examples 625 and 626

7-Chloro-6-[1-(3-fluorophenyl)ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate Isomer 1 and 7-chloro-6-[1-(3-fluorophenyl)ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate Isomer 2



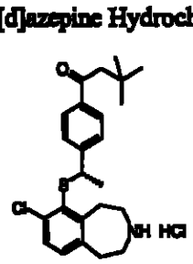
Separate the two enantiomers of (±)-3-*tert*-butoxycarbonyl-7-chloro-6-[1-(3-fluorophenyl)ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine by chiral HPLC (Chiralcel OJ-H 4.6 x 150 mm column, eluting with methanol at 0.6 mL/min).

Subject Isomer 1 (t_R = 5.4 min, ee > 99.9%) to the General Procedure 2-1 to afford 7-chloro-6-[1-(3-fluorophenyl)ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine succinate isomer 1 as a white solid. MS (ES+) *m/z* 336 $(M+H)^+$.

Subject Isomer 2 (t_R = 11.2 min, ee = 99.7%) to the General Procedure 2-1 to afford 7-chloro-6-[1-(3-fluorophenyl)ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine succinate isomer 2 as a white solid. MS (ES+) *m/z* 336 $(M+H)^+$.

Example 627

(S)-7-Chloro-6-{1-[4-(3,3-dimethylbutyryl)-phenyl]-ethylthio}-2,3,4,5-tetrahydro-1H-benzo[d]azepine Hydrochloride



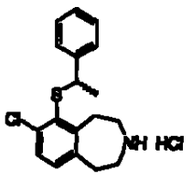
Heat the mixture of 3-tert-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1H-benzo[d]azepine (310 mg, 0.807 mmol) and potassium hydroxide

(1.45 g, 25.83 mmol) in methanol (5 mL) at 50 °C for 3 h. Cool the reaction mixture to room temperature and dilute with saturated aqueous NH_4Cl and EtOAc. Separate the layers and extract the aqueous layer three times with EtOAc. Dry the combined organic extracts over Na_2SO_4, filter and concentrate in vacuo. Dissolve the crude 3-tert-butoxycarbonyl-7-chloro-6-mercapto-2,3,4,5-tetrahydro-1H-benzo[d]azepine in anhydrous DMF (2 mL) and cool at 0 °C. Add sodium hydride (21 mg, 0.888 mmol) and a solution of (R)-1-[4-(1-bromoethyl)-phenyl]-3,3-dimethylbutan-1-one {prepared by the mixture of (S)-1-[4-(1-hydroxyethyl)-phenyl]-3,3-dimethylbutan-1-one (213 mg, 0.969 mmol), triphenylphosphine (296 mg, 1.130 mmol) and NBS (201 mg, 1.13 mmol) in anhydrous THF (5 mL) at 0 °C and then room temperature}. Stir the mixture at 0 °C for 30 min and quench with water. Dilute with EtOAc and extract the aqueous layer three times with EtOAc. Dry the combined organic extracts over Na_2SO_4, filter and concentrate in vacuo. Purify the crude mixture by chromatography on silica gel eluting with hexane/EtOAc (85:15) to give (S)-3-tert-butoxycarbonyl-7-chloro-6-{1-[4-(3,3-dimethylbutyryl)-phenyl]-ethylthio}-2,3,4,5-tetrahydro-1H-benzo[d]azepine as yellow oil (197 mg, 47%).

Use a method similar to the General Procedure 1-4, using (S)-3-tert-butoxycarbonyl-7-chloro-6-{1-[4-(3,3-dimethylbutyryl)-phenyl]-ethylthio}-2,3,4,5-tetrahydro-1H-benzo[d]azepine (197 mg, 0.382 mmol) to give the title compound as a white solid (161 mg, 93%). MS (ES+) m/z: 416 $(M+H)^+$; ee = 92%, t_R = 11.27 min (Chiralcel OJ, 4.6 x 250 mm, 45 °C , eluent: 20% isopropanol with 0.05% triethylamine in SFC, flow rate 2 mL/min, UV detector at 234 nm).

Example 628

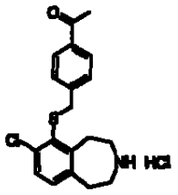
(*S*)-7-Chloro-6-(1-phenyl-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Example 628 may be prepared essentially as described in Example 627 using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and (*R*)-(1-bromo-ethyl)-benzene (64% yield, MS (ES+) *m/z* 318 $(M+H)^+$).

Example 629

6-(4-Acetyl-benzylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



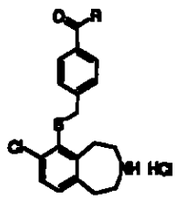
Use a method similar to the General Procedure 7 to react 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (200 mg, 0.521 mmol) with 4-acetylbenzyl bromide (555 mg, 2.605 mmol). Purify the crude mixture by chromatography on silica gel eluting sequentially with hexane and hexane/EtOAc (9:1, 4:1) to obtain 6-(4-acetyl-benzylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (190 mg, 82%).

Use a method similar to the General Procedure 1-4 to deprotect 6-(4-acetyl-benzylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (170 mg, 0.381 mmol) and give the title compound as a white solid (140 mg, 96%). MS (ES+) *m/z*: 346 $(M+H)^+$.

Examples 630-634

Examples 630-634 may be prepared essentially as described in Example 629 using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-

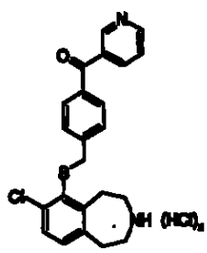
benzo[*d*]azepine and the appropriate benzyl bromide. Overall yields and MS (ES+) data are shown in the Table below.



Ex.	R	Compound	Yield (%)	MS (ES+) *m/z*
630	Ethyl	7-Chloro-6-(4-propionyl-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	87	360 $(M+H)^+$
631	*n*-Propyl	6-(4-Butyryl-benzylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	81	374 $(M+H)^+$
632	*i*-Propyl	7-Chloro-6-(4-isobutyryl-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	69	374 $(M+H)^+$
633	*t*-Butyl	7-Chloro-6-[4-(3-methyl-butyryl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	68	388 $(M+H)^+$
634	2-Pyridyl	7-Chloro-6-[4-(pyridine-2-carbonyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	38	409 $(M+H)^+$

Example 635

7-Chloro-6-[4-(pyridine-3-carbonyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



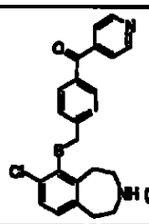
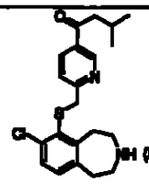
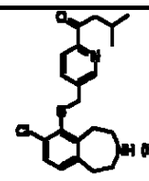
Dissolve 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (150 mg, 0.39 mmol) in methanol (10 mL) and add

potassium hydroxide (0.7 g, 12.47 mmol). Heat at 60 °C for 4 h. Cool the reaction mixture to ambient temperature, add aqueous saturated ammonium chloride and concentrate *in vacuo*. Partition the residue between EtOAc and water. Dry the organic phase over anhydrous Na_2SO_4 and concentrate *in vacuo* to give 3-*tert*-butoxycarbonyl-7-chloro-6-mercapto-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.12 g). Dissolve the crude 3-*tert*-butoxycarbonyl-7-chloro-6-mercapto-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.12 g, 5.2 mmol) in anhydrous DMSO (6 mL) and add triethylamine (0.325 mL, 2.34 mmol) and 4-(pyridine-3-carbonyl)-benzyl methanesulfonate (114 mg, 0.39 mmol). Heat the solution at 40 °C overnight. Cool to ambient temperature, dilute the mixture with hexane/EtOAc (1:1, 100 mL), and wash the organic solution sequentially with brine and ice-cold water. Dry the organic layer over anhydrous Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane and hexane/EtOAc (1:1) to give 3-*tert*-butoxycarbonyl-7-chloro-6-[4-(pyridine-3-carbonyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as oil (123 mg, 64%).

Use a method similar to the General Procedure 1-4 to deprotect 3-*tert*-butoxycarbonyl-7-chloro-6-[4-(pyridine-3-carbonyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (113 mg, 0.22 mmol) and give the title compound as a solid (105 mg, 99%). MS (ES+) *m/z*: 409 $(M+H)^+$.

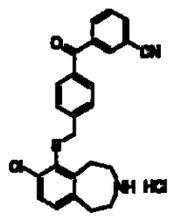
Examples 636-638

Examples 636-638 may be prepared essentially as described in Example 635 using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate methanesulfonate. Overall yields and MS (ES+) data are shown in the Table below.

Ex.	Structure	Compound	Yield (%)	MS (ES+) m/z
636		7-Chloro-6-[4-(pyridine-4-carbonyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	39	409 $(M+H)^+$
637		7-Chloro-6-[5-(3-methyl-butyryl)-pyridin-2-yl-methylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	69	389 $(M+H)^+$
638		7-Chloro-6-[6-(3-methyl-butyryl)-pyridin-3-yl-methylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	57	389 $(M+H)^+$

Example 639

7-Chloro-6-[4-(3-cyanobenzoyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



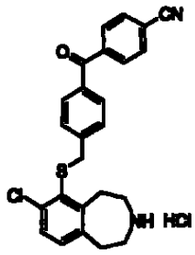
Dissolve 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (200 mg, 0.52 mmol) in methanol (12 mL) and add potassium hydroxide (0.935 g, 16.66 mmol). Heat at 60 °C for 4 h. Cool the reaction mixture to ambient temperature, add aqueous saturated ammonium chloride and concentrate *in vacuo*. Partition the residue between EtOAc and water. Dry the organic phase over anhydrous Na_2SO_4 and concentrate *in vacuo* to give 3-*tert*-butoxycarbonyl-7-chloro-6-mercapto-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.16 g, 5.2 mmol). Dissolve

the crude 3-*tert*-butoxycarbonyl-7-chloro-6-mercapto-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.16 g, 0.52 mmol) in anhydrous DMSO (5 mL) and add triethylamine (0.435 mL, 3.12 mmol) and 4-(3-cyano-benzoyl)benzyl bromide (289 mg, 0.96 mmol). Heat the solution at 40 °C overnight. Cool to ambient temperature, dilute the mixture with hexane/EtOAc (1:1, 100 mL), and wash the organic solution sequentially with brine and ice-cold water. Dry the organic layer over anhydrous Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane and hexane/EtOAc (9:1, 4:1) to give 3-*tert*-butoxycarbonyl-7-chloro-6-[4-(3-cyanobenzoyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as oil (212 mg, 77%).

Use a method similar to the General Procedure 1-4 to deprotect 3-*tert*-butoxycarbonyl-7-chloro-6-[4-(3-cyanobenzoyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (200 mg, 0.37 mmol) and give the title compound as a solid (136 mg, 77%). MS (ES+) *m/z*: 433 $(M+H)^+$.

Example 640

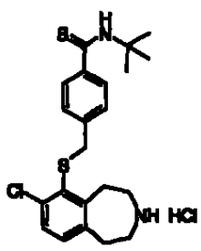
7-Chloro-6-[4-(4-cyanobenzoyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Example 640 may be prepared essentially as described in Example 639 using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 4-(4-cyano-benzoyl)benzyl bromide (49% yield, MS (ES+) *m/z* 433 $(M+H)^+$).

Example 641

7-Chloro-6-(4-*tert*-butylthiocarbamoyl-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

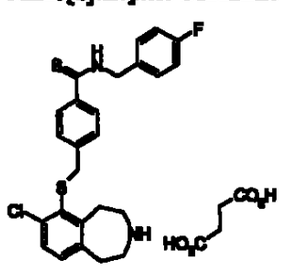


Combine 7-chloro-6-(4-*tert*-butylcarbamoyl-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo [*d*]azepine (53 mg, 0.13 mmol) with 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's reagent) (53 mg, 0.13 mmol) in anhydrous 1,4-dioxane (1 mL) in a sealed tube and heat at 100 °C for 2 h. Cool the reaction mixture to room temperature, concentrate *in vacuo* and purify the residue by SCX chromatography to obtain 7-chloro-6-(4-*tert*-butylthiocarbamoyl-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow oil. Purify by reverse phase preparative HPLC [Zorbax SB-Phenyl 21.2 x 250 mm, 5 micron, 22 mL/min of 0.1% aqueous HCl /acetonitrile (9:1 to 1:9) over 30 min, detector at 230 nm].

Use a method similar to the General Procedure 2-2 to obtain the title compound as a yellow solid (36 mg, 58%). MS (ES+) *m/z*: 419 $(M+H)^+$.

Example 642

7-Chloro-6-[4-(4-fluorobenzylthiocarbamoyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

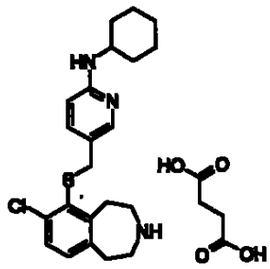


Combine 7-chloro-6-[4-(4-fluorobenzylcarbamoyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (23 mg, 0.05 mmol) with 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's reagent) (23 mg, 0.05 mmol) in anhydrous 1,4-dioxane (1 mL) in a sealed tube and heat at 100 °C for 2 h. Cool the reaction mixture to room temperature, concentrate *in vacuo* and purify the residue by SCX chromatography to obtain 7-chloro-6-[4-(4-fluorobenzylthiocarbamoyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow oil.

Use a method similar to the General Procedure 2-1 to obtain the title compound as a white solid (10 mg, 42%). MS (ES+) *m/z*: 471 $(M+H)^+$.

Example 643

7-Chloro-6-(6-cyclohexylamino-pyridin-3-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Use a method similar to General Procedure 7, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (2 g, 5.2 mmol) and 2-chloro-5-(chloromethyl)pyridine (843 mg, 5.2 mmol) to give 3-*tert*-butoxycarbonyl-7-chloro-6-(6-chloro-pyridin-3-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (2.2 g, 95%). MS (ES+) *m/z*: 439.1 $(M+H)^+$.

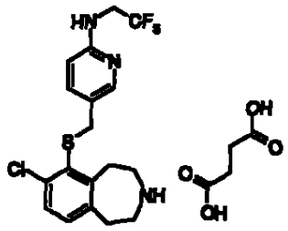
Slurry palladium(II) acetate (434 mg, 1.9 mmol), BINAP (1.2 g, 1.9 mmol), sodium-*tert*-butoxide (644 mg, 6.7 mmol), cyclohexylamine (1.4 g, 14.4 mmol) and 3-*tert*-butoxycarbonyl-7-chloro-6-(6-chloro-pyridin-3-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (2.1 g, 4.8 mmol) in anhydrous toluene (70 mL). Degas the slurry under

house vacuum, then buble nitrogen. Heat the mixture to 95 °C for 16 h under a nitrogen atmosphere. Cool the mixture to room temperature, dilute with EtOAc (50 mL) and filter through Celite®. Concentrate the filtrate to an oil and purify by chromatography on silica gel eluting with hexane/EtOAc (19:1 to 13:7 gradient) to obtain 3-*tert*-butoxycarbonyl-7-chloro-6-(6-cyclohexylamino-pyridin-3-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (800 mg, 33%). MS (ES+) *m/z*: 502.2 $(M+H)^+$.

Use a method similar to the General Procedure 1-5 to deprotect 3-*tert*-butoxycarbonyl-7-chloro-6-(6-cyclohexylamino-pyridin-3-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (790 mg, 1.6 mmol). Purify by chromatography on silica gel eluting with dichloromethane/2M ammonia in methanol (99:1 to 95:5 gradient) to give the free base of the title compound. Use a method similar to the General Procedure 2-1 to obtain the title compound (670 mg, 82%). MS (ES+) *m/z*: 402.1 $(M+H)^+$.

Example 644

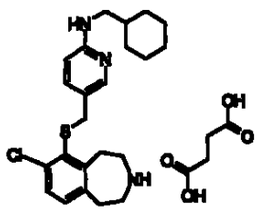
7-Chloro-6-(6-trifluoroethylamino-pyridin-3-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Example 644 may be prepared essentially as described in Example 643 by using 3-*tert*-butoxycarbonyl-7-chloro-6-(6-chloro-pyridin-3-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 2,2,2-trifluoroethylamine (10% yield, MS (ES+) *m/z* 502.2 $(M+H)^+$).

Example 645

7-Chloro-6-(6-cyclohexylmethylamino-pyridin-3-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

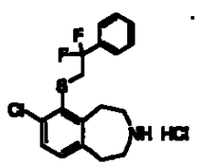


Add cyclohexylmethylamine (3 mL) to a flask containing 3-*tert*-butoxycarbonyl-7-chloro-6-(6-chloro-pyridin-3-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (340 mg, 0.8 mmol) and ammonium chloride (50 mg, 0.92 mmol). Heat the contents in a sealed flask at 170 °C for 7 h. Cool the flask to room temperature, dilute with EtOAc (50 mL) and wash with water (20 mL). Collect the organic layer and concentrate *in vacuo*. Purify the residue by chromatography on silica gel eluting with hexane/EtOAc (19:1 to 4:1 gradient) to obtain 3-*tert*-butoxycarbonyl-7-chloro-6-(6-cyclohexylmethylamino-pyridin-3-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (160 mg, 40%).

Use a method similar to the General Procedure 1-5 to deprotect 3-*tert*-butoxycarbonyl-7-chloro-6-(6-cyclohexylmethylamino-pyridin-3-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Purify by chromatography on silica gel eluting with dichloromethane/2M ammonia in methanol (99:1, 98:2, 96:4 gradient) to give the free base of the title compound. Use a method similar to the General Procedure 2-1 to obtain the title compound (115 mg, 70%). MS (ES+) *m/z*: 416.0 $(M+H)^+$.

Example 646

7-Chloro-6-(2,2-difluoro-2-phenyl-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

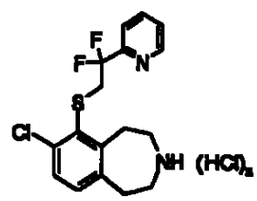


Dissolve 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (200 mg, 0.52 mmol) in methanol (10 mL) and add potassium hydroxide (0.934 g, 16.64 mmol). Heat at 60 °C for 4 h. Cool the reaction mixture to ambient temperature, add aqueous saturated ammonium chloride and concentrate *in vacuo*. Partition the residue between EtOAc and water. Dry the organic phase over anhydrous Na_2SO_4 and concentrate *in vacuo* to give 3-*tert*-butoxycarbonyl-7-chloro-6-mercapto-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.163 g). Dissolve the crude 3-*tert*-butoxycarbonyl-7-chloro-6-mercapto-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.163 g, 0.52 mmol) in anhydrous DMSO (5 mL) and add triethylamine (0.43 mL, 3.12 mmol) and 2,2-difluoro-2-phenylethyl trifluoromethanesulfonate (151 mg, 0.52 mmol). Heat the solution at 40 °C overnight. Cool to ambient temperature, add water and extract the aqueous phase twice with EtOAc. Dry the combined organic extracts over anhydrous Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane and hexane/EtOAc (19:1, 9:1 and 4:1) to give 3-*tert*-butoxycarbonyl-7-chloro-6-(2,2-difluoro-2-phenyl-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as oil (132 mg, 56%).

Use a method similar to the General Procedure 1-4 to deprotect 3-*tert*-butoxycarbonyl-7-chloro-6-(2,2-difluoro-2-phenyl-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (132 mg, 0.29 mmol) and give the title compound as a solid (111 mg, 98%). MS (ES+) *m/z*: 354 $(M+H)^+$.

Example 647

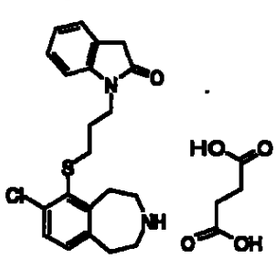
7-Chloro-6-(2,2-difluoro-2-pyridin-2-yl-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Example 647 may be prepared essentially as described in Example 646 using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 2,2-difluoro-2-pyridin-2-yl-ethyl trifluoromethanesulfonate (prepared by following the procedure described in *J. Med. Chem.* 2003, *46*, 461-473) (66% yield, MS (ES+) *m/z* 355 $(M+H)^+$).

Example 648

7-Chloro-6-[3-(2-oxo-2,3-dihydro-indol-1-yl)-propylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



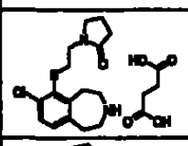
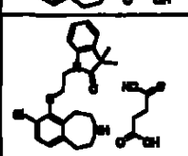
Add potassium hydroxide (899 mg, 16.64 mmol) in one portion to a solution of 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (200 mg, 0.52 mmol) in methanol (10 mL). Heat the reaction to 50 °C under nitrogen for 24 h, then cool to room temperature and add 1-(3-chloro-propyl)-1,3-dihydro-indol-2-one (217 mg, 1.04 mmol). Stir the reaction at room temperature for 4 days. Remove solvents *in vacuo*, add dichloromethane (20 mL) and water (20 mL). Remove the organic layer and dry using an ISCO® phase separator then concentrate *in vacuo* to give 3-*tert*-butoxycarbonyl-7-chloro-6-[3-(2-oxo-2,3-dihydro-indol-1-yl)-

propylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as orange powder. MS (ES+) *m/z*: 509 $(M+Na)^+$.

Dissolve 3-*tert*-butoxycarbonyl-7-chloro-6-[3-(2-oxo-2,3-dihydro-indol-1-yl)-propylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.52 mmol) in dichloromethane (10 mL), then add TFA (2 mL) dropwise and stir for 2 h. Remove solvents in vacuo, then free base using an SCX column, eluting with 7M ammonia in methanol. Purify using UV-guided reverse phase HPLC [Supelco Discovery C18 column (21.2 x 100 mm, 5µm packing), 20 mL/min flow rate, eluting with water/acetonitrile/acetic acid gradient over 15 min, fraction collection triggered using UV detector (220 and 254 nm)] followed by SCX column, eluting with 7M ammonia in methanol, then Mass-guided reverse phase HPLC [Supelco Discovery C18 column (21.2 x 100 mm, 5µm packing), 25 mL/min flow rate, eluting with water/acetonitrile/acetic acid gradient over 12 min, fraction collection triggered by Electrospray MS] and SCX column. Concentrate *in vacuo*, then use a method similar to the General Procedure 2-1 and freeze dry to give the title compound as a light pink solid (51 mg, 19%). MS (ES+) *m/z*: 387 $(M+H)^+$.

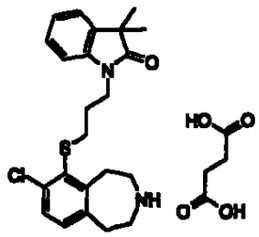
Examples 649-650

Examples 649-650 may be prepared essentially as described in Example 648 using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriately substituted alkyl chloride. Overall yields and MS (ES+) data are shown in the Table below.

Ex.	Structure	Compound	Yield (%)	MS (ES+) *m/z*
649		7-Chloro-6-[2-(2-oxo-pyrrolidin-1-yl)-ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	71	325 $(M+H)^+$
650		7-Chloro-6-[2-(3,3-dimethyl-2-oxo-2,3-dihydro-indol-1-yl)-ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	32	401 $(M+H)^+$

Example 651

7-Chloro-6-[3-(3,3-dimethyl-2-oxo-2,3-dihydro-indol-1-yl)-propylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



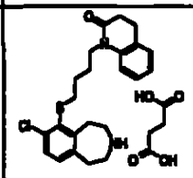
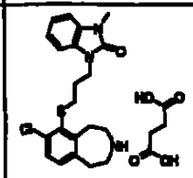
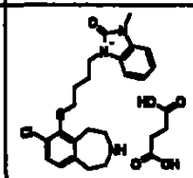
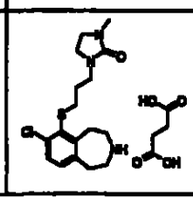
Add potassium hydroxide (170 mg, 3.03 mmol) in one portion to a solution of 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (187 mg, 0.49 mmol) in methanol (10 mL). Heat the reaction at reflux under nitrogen overnight. Then add further portion of KOH (867 mg, 15.45 mmol) and heat at reflux for 3 h. Then cool to room temperature and add 1-(3-bromo-propyl)-1,3-dihydro-3,3-dimethyl-indol-2-one (274 mg, 0.97 mmol, prepared by following the procedure described in *Perkin 1* 2000, 769-774). Stir the reaction at room temperature overnight. Remove solvents *in vacuo*, add water and extract with diethyl ether (2 x 50 mL). Combine the organic extracts, wash with water (2 x 50 mL) and brine (50 mL). Dry over $MgSO_4$ and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with isohexane/EtOAc (1:0 to 1:1 gradient over 40 min) to give 3-*tert*-butoxycarbonyl-7-chloro-6-[3-(3,3-dimethyl-2-oxo-2,3-dihydro-indol-1-yl)-propylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a colourless oil (330 mg), 50% contaminated with 1-(3-methoxypropyl)-1,3-dihydro-3,3-dimethyl-indol-2-one. MS (ES+) *m/z*: 537 $(M+Na)^+$.

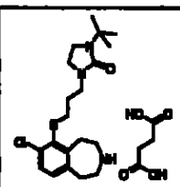
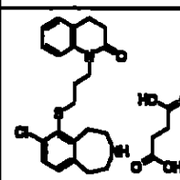
Dissolve 3-tert-butoxycarbonyl-7-chloro-6-[3-(3,3-dimethyl-2-oxo-2,3-dihydro-indol-1-yl)-propylthio]-2,3,4,5-tetrahydro-1H-benzo[d]azepine (240 mg, 0.52 mmol) in dichloromethane (10 mL), then add TFA (1 mL) dropwise and stir at room temperature overnight. Remove solvents in vacuo to give a straw coloured oil (580 mg), then free base using an SCX column, eluting with 7M ammonia in methanol. Concentrate in

vacuo, then use a method similar to the General Procedure 2-1 and freeze dry to give the title compound as a solid (196 mg, 82%). MS (ES+) m/z: 415 $(M+H)^+$.

Examples 652-654

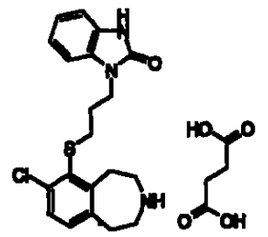
Examples 652-654 may be prepared essentially as described in Example 651 using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate alkyl bromide. Examples 655-657 may be prepared essentially as described in Example 651 using the appropriate alkyl chloride. Overall yields and MS (ES+) data are shown in the Table below.

Ex.	Structure	Compound	Yield (%)	MS (ES+) *m/z*
652		7-Chloro-6-[4-(2-oxo-3,4-dihydro-2*H*-quinolin-1-yl)-butylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	71	414 $(M+H)^+$
653		7-Chloro-6-[3-(3-methyl-2-oxo-2,3-dihydro-benzoimidazol-1-yl)-propylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	31	402 $(M+H)^+$
654		7-Chloro-6-[4-(3-methyl-2-oxo-2,3-dihydro-benzoimidazol-1-yl)-butylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	31	416 $(M+H)^+$
655		7-Chloro-6-[3-(3-methyl-2-oxo-imidazolidin-1-yl)-propylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	29	354 $(M+H)^+$

656		7-Chloro-6-[3-(3-*tert*-butyl-2-oxo-imidazolidin-1-yl)-propylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	31	396 $(M+H)^+$
657		7-Chloro-6-[3-(2-oxo-3,4-dihydro-2*H*-quinolin-1-yl)-propylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	66	400 $(M+H)^+$

Example 658

7-Chloro-6-[3-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-propylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



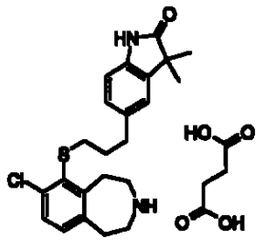
Add potassium hydroxide (933 mg, 16.6 mmol) in one portion to a solution of 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (200 mg, 0.52 mmol) in methanol (10 mL). Heat the reaction at reflux under nitrogen 4 h. Then cool to room temperature and add 1-(3-bromo-propyl)-3-isopropenyl-1,3-dihydro-benzoimidazol-2-one (142 mg, 0.52 mmol). Stir the reaction at room temperature overnight. Remove solvents *in vacuo*, extract into diethyl ether (2 x 50 mL), wash with water (2 x 50 mL) and brine (50 mL). Dry over $MgSO_4$, filtrate and concentrate *in vacuo* to give 3-*tert*-butoxycarbonyl-7-chloro-6-[3-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-propylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (209 mg, 76%). MS (ES+) *m/z*: 550 $(M+Na)^+$.

Dissolve 3-*tert*-butoxycarbonyl-7-chloro-6-[3-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-propylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (209 mg, 0.396 mmol) in

dichloromethane (10 mL), then add TFA (0.5 mL) dropwise and stir at room temperature overnight. Remove solvents *in vacuo* then free base using an SCX column, eluting with 7M ammonia in methanol. Concentrate *in vacuo*, then use a method similar to the General Procedure 2-1 and freeze dry to give the title compound as a solid (140 mg, 70%). MS (ES+) *m/z*: 388 $(M+H)^+$.

Example 659

7-Chloro-6-[3-(3,3-dimethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)-propylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



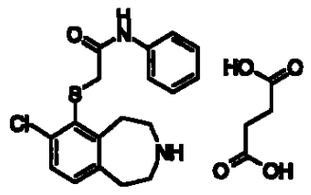
Under nitrogen atmosphere, add potassium hydroxide (138 mg, 2.46 mmol) to a stirred solution of 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (375 mg, 0.97 mmol) in methanol (10 mL). Heat under reflux for 2 h then add further potassium hydroxide (159 mg, 2.83 mmol) and continue heating under reflux for another 6 h. Cool the reaction mixture and add dropwise *via* cannula a solution of 5-(3-chloropropyl)-3,3-dimethyl-1,3-dihydro-indol-2-one (245 mg, 1.03 mmol) in methanol (10 mL). Stir at ambient temperature overnight then heat at 50 °C for 5 h. Add potassium iodide (186 mg, 1.12 mmol) to the reaction mixture and then heat under reflux for 5 h. Concentrate *in vacuo* and partition the residue between water (100 mL) and EtOAc (50 mL). Extract the aqueous phase with EtOAc (2 x 50 mL). Wash the combined extracts with brine (50 mL), dry over $MgSO_4$, filter and concentrate *in vacuo* to obtain the crude mixture as a yellow oil. Dilute this oil with dichloromethane then re-concentrate *in vacuo* and repeat until a solid remains. Dry the solid in a vacuum oven to give 3-*tert*-butoxycarbonyl-7-chloro-6-[3-(3,3-dimethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)-propylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow solid (481 mg) that was used without further purification. MS (ES+) *m/z*: 537 $(M+Na)^+$.

Add trifluoroacetic acid (0.2 mL, 2.6 mmol) to a solution of 3-*tert*-butoxycarbonyl-7-chloro-6-[3-(3,3-dimethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)-propylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (257 mg, 0.5 mmol) in dichloromethane (5 mL) then stir at ambient temperature over the weekend. Concentrate *in vacuo*. Dissolve the residue in methanol and load onto an SCX column. Elute with methanol followed by 7*M* ammonia in methanol. Collect the basic fraction and concentrate *in vacuo*. Purify the residue by prep-LCMS [Supelco Discovery C18 column (21.2 x 100 mm, 5μm packing), 25 mL/min flow rate, eluting with a water/acetonitrile gradient containing acetic acid as modifier over 12 min, fraction collection triggered by Electrospray MS] to give 7-chloro-6-[3-(3,3-dimethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)-propylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a white solid (101 mg, 25% over 2 steps). MS (ES+) *m/z*: 415 $(M+H)^+$.

Dissolve 7-chloro-6-[3-(3,3-dimethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)-propylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (101 mg, 0.24 mmol) in a mixture of diethyl ether (3 mL) and methanol (2 mL). Add succinic acid (28.7 mg, 0.24 mmol) and allow the resultant suspension to stir at ambient temperature for 2 h. Concentrate *in vacuo* and dry the residue in a vacuum oven to afford the title compound as a white solid. MS (ES+) *m/z*: 415 $(M+H)^+$.

Example 660

7-Chloro-6-(*N*-phenylcarbamoyl-methylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



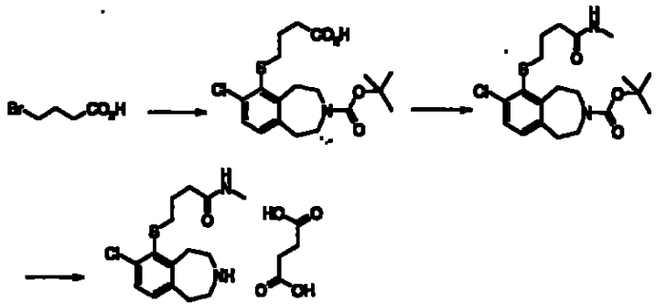
Add potassium hydroxide (890 mg, 15 mmol) in one portion to a solution of 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (180 mg, 0.47 mmol) in methanol (10 mL). Heat the reaction at reflux

under nitrogen 3 h. Then cool to room temperature, add 2-chloro-*N*-phenyl-acetamide (79 mg, 0.47 mmol) and stir overnight. Remove solvents *in vacuo*, extract into diethyl ether (2 x 50 mL), wash with water (2 x 50 mL) and brine (50 mL). Dry over $MgSO_4$, filtrate and concentrate *in vacuo* to give 3-*tert*-butoxycarbonyl-7-chloro-6-(*N*-phenylcarbamoyl-methylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a clear oil (210 mg, 100%). MS (ES+) *m/z*: 460 $(M+Na)^+$.

Dissolve 3-*tert*-butoxycarbonyl-7-chloro-6-(*N*-phenylcarbamoyl-methylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine(210 mg, 0.47 mmol) in dichloromethane (10 mL) then add TFA (0.5 mL) dropwise and stir at room temperature for 3 days. Remove solvents *in vacuo* then free base using an SCX column, eluting with 7M ammonia in methanol. Concentrate *in vacuo*, then use a method similar to the General Procedure 2-1 and freeze dry to give the title compound as a solid (150 mg, 69%). MS (ES+) *m/z*: 347 $(M+H)^+$.

Example 661

7-Chloro-6-(3-methylcarbamoyl-propylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



<u>3-*tert*-Butoxycarbonyl-7-chloro-6-(3-carboxy-propylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine</u>: Add potassium hydroxide (700 mg, 12.5 mmol) in one portion to a solution of 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (150 mg, 0.39 mmol) in methanol (10 mL). Heat the reaction at reflux under nitrogen 4 h. Then cool to room temperature, add 4-bromo-butyric acid (65 mg, 0.39 mmol) and stir for 3 days. Remove solvents *in vacuo*, neutralize with

ammonium chloride (200 mL) and extract into EtOAc (2 x 50 mL). Dry over $MgSO_4$, filtrate and concentrate *in vacuo* to give a clear oil (125 mg). Dissolve the oil in anhydrous DMF (10 mL) and add sodium hydride (30 mg, 0.78 mmol of 60% dispersion in oil) under nitrogen. Stir for 30 min. Add 4-bromo-butyric acid (65 mg, 0.39 mmol) and stir for 30 min. Pour into water (50 mL) and extract with diethyl ether (2 x 50 mL). Wash the combined organic extracts with brine (50 mL) and dry over $MgSO_4$. Concentrate the filtrate *in vacuo* to give the desired intermediate as a solid (146 mg, 94%). MS (ES+) *m/z*: 398 $(M+H)^+$.

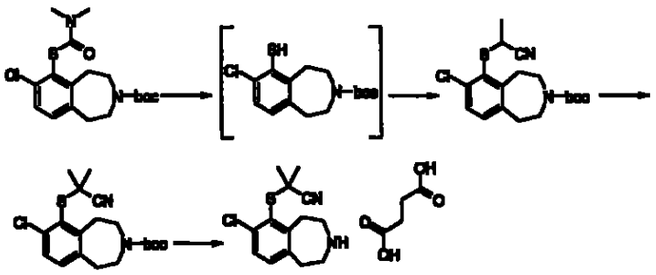
3-*tert*-Butoxycarbonyl-7-chloro-6-(3-methylcarbamoyl-propylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Add *O*-benzotriazol-1-yl-*N*,*N*,*N*',*N*'-tetramethyluronium tetrafluoroborate (123 mg, 0383 mmol) portion wise to a solution of 3-*tert*-butoxycarbonyl-7-chloro-6-(3-carboxy-propylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (146 mg, 0365 mmol) and methylamine (182 µL, 0.365 mmol) in anhydrous DMF (5 mL) under nitrogen at 0 °C. Stir for 15 min then add diisopropylethylamine (127 µL, 0.73 mmol) in anhydrous DMF (1 mL) and continue to stir at 0 °C for 1 h. Warm to room temperature and continue to stir overnight. Pour into water (50 mL) and extract with EtOAc (3 x 20 mL). Wash the combined organic extracts with saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL). Dry over $MgSO_4$, filtrate and concentrate *in vacuo* to give a pale yellow oil (74 mg). MS (ES+) *m/z*: 398 $(M+H)^+$. Purify using Mass-guided reverse phase HPLC [Supelco Discovery C18 column (21.2 x 100 mm, 5µm packing), 25 mL/min flow rate, eluting with water/acetonitrile/acetic acid gradient over 12 min, fraction collection triggered by Electrospray MS]. Concentrate *in vacuo* to give the desired intermediate as a colourless oil (30 mg, 20%). MS (ES+) *m/z*: 435 $(M+Na)^+$.

7-Chloro-6-(3-methylcarbamoyl-propylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate: Dissolve 3-*tert*-butoxycarbonyl-7-chloro-6-(3-methylcarbamoyl-propylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (30 mg, 0.07 mmol) in dichloromethane (10 mL) then add TFA (0.5 mL) dropwise and stir at room temperature for 3 days. Remove solvents *in vacuo* then free base using an SCX column, eluting with 7M ammonia in

methanol. Concentrate *in vacuo*, then use a method similar to the General Procedure 2-1 and freeze dry to give the title compound as a solid (21 mg, 72%). MS (ES+) *m/z*: 313 $(M+H)^+$.

Example 662

7-Chloro-6-(1-cyano-1-methyl-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



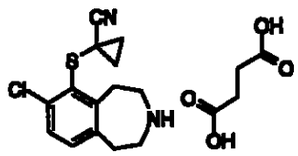
3-*tert*-Butoxycarbonyl-7-chloro-6-(1-cyano-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Add potassium hydroxide (10.8 g , 192 mmol) to a solution of 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (3 g, 7.8 mmol) in degassed methanol (150 mL) under a nitrogen atmosphere. Heat the mixture at 80 °C for 6 h. Cool the mixture to ambient temperature, then concentrate *in vacuo* to an oil. Dissolve the oil in EtOAc (50mL), wash with aqueous saturated ammonium chloride (30 mL). Separate the organic layer and extract the aqueous layer with EtOAc (3 x 50 mL). Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo* to an oil (2.4 g). Dissolve the oil in anhydrous DMF (50 mL). Slowly add sodium hydride (470 mg, 11.7 mmol) portionwise over 5 min followed by 2-bromopropionitrile (1 mL, 11.7 mmol). Stir the mixture under nitrogen at ambient temperature for 16 h. Dilute the mixture slowly with EtOAc (100 mL) and wash with cold aqueous saturated ammonium chloride (50 mL). Separate the organic layer and extract the aqueous layer with EtOAc (3 x 50 mL). Combine the organic extracts and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane/EtOAc (19:1 to 3:1 gradient) to obtain the desired intermediate (2.5 g, 89%). MS (ES+) *m/z*: 267.2 $(M\text{-}Boc)^+$.

3-*tert*-Butoxycarbonyl-7-chloro-6-(1-cyano-1-methyl-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Slowly add a solution of 3-*tert*-butoxycarbonyl-7-chloro-6-(1-cyano-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (2.5 g, 6.8 mmol) in anhydrous THF (20 mL) to a slurry of sodium hydride (1.4 g, 34 mmol) in anhydrous THF (50 mL) at 0 °C under a nitrogen atmosphere. Stir the slurry for 5 min, then add iodomethane (12.7 mL, 204 mmol) to the slurry while maintaining the temperature below 30 °C. Stir the mixture for 3 h at ambient temperature then quench with methanol (10 mL) and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane/EtOAc (19:1 to 9:1 gradient) to obtain the desired intermediate (2 g, 79%). MS (ES+) *m/z*: 281.2 $(M+H\text{-Boc})^+$.

7-Chloro-6-(1-cyano-1-methyl-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate: Use a method similar to the General Procedure 1-5 to deprotect 3-*tert*-butoxycarbonyl-7-chloro-6-(1-cyano-1-methyl-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.4 g, 3.5 mmol). Purify by chromatography on silica gel eluting with dichloromethane/2M ammonia in methanol (99:1 to 90:10 gradient) to give the free base of the title compound. Use a method similar to the General Procedure 2-1 to obtain the title compound (992 mg; 71%). MS (ES+) *m/z*: 281.2 $(M+H)^+$.

Example 663

7-Chloro-6-(1-cyano-cyclopropylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Add potassium hydroxide (5.4 g, 96.2 mmol) to a solution of 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.5 g, 4.7 mmol) in degassed methanol (75 mL) under a nitrogen atmosphere. Heat the mixture at 80 °C for 6 h. Cool the mixture to ambient temperature,

then concentrate *in vacuo* to an oil. Dissolve the oil in EtOAc (50mL) and wash with saturated aqueous ammonium chloride (30 mL). Separate the organic layer and extract the aqueous layer with EtOAc (3 x 50 mL). Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo* to an oil (1.4 g). Dissolve the oil in anhydrous DMF (25 mL), then slowly add sodium hydride (282 mg, 7.1 mmol) and bromoacetonitrile (470 µl, 7.1 mmol). Stir the mixture under nitrogen at ambient temperature for 16 h. Dilute the mixture slowly with EtOAc (100 mL) and wash with cold aqueous saturated ammonium chloride (40 mL). Separate the organic layer and extract the aqueous layer with EtOAc (3 x 50 mL). Combine the organic extracts and concentrate *in vacuo*. Purify the residue by chromatography on silica gel eluting with hexane/EtOAc (9:1 to 7:3 gradient) to obtain 3-*tert*-butoxycarbonyl-7-chloro-6-(1-cyano-methylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.34 g, 81%). MS (ES+) *m/z*: 253.2 $(M\text{-}Boc)^+$.

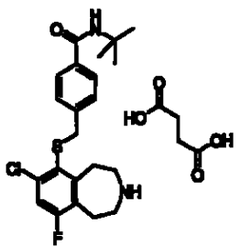
Add sodium bis(trimethylsilyl)amide (5.4 mL, 5.4 mmol, 1M solution in THF) at room temperature under nitrogen to a solution of 3-*tert*-butoxycarbonyl-7-chloro-6-(1-cyano-methylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (380 mg, 1.1 mmol) in anhydrous toluene (4 mL). Stir the solution for 10 min, then add quickly 1,2-dibromoethane (2.8 mL, 32.4 mmol) followed by anhydrous DMF (4 mL). An exothermic reaction was observed and the reaction temperature increased to 38 °C. Stir the mixture for 15 min at ambient temperature, then quench with methanol (2 mL). Concentrate *in vacuo* and purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to obtain 3-*tert*-butoxycarbonyl-7-chloro-6-(1-cyano-cyclopropylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (259 mg).

Use a method similar to the General Procedure 1-5 to deprotect 3-*tert*-butoxycarbonyl-7-chloro-6-(1-cyano-cyclopropylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Purify by reverse phase chromatography [Column: Symmetry C18, 19 x 300 mm, flow rate 30 mL/min, eluting with water with 0.1% TFA/acetonitrile (19:1 to 1:1 gradient)] followed by SCX chromatography to obtain the free base of the title

compound. Use a method similar to the General Procedure 2-1 to obtain the title compound (120 mg, 28% yield over 3 steps). MS (ES+) *m/z*: 279.2 $(M+H)^+$.

Example 664

6-(4-*tert*-Butylcarbamoyl-benzylthio)-7-chloro-9-fluoro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

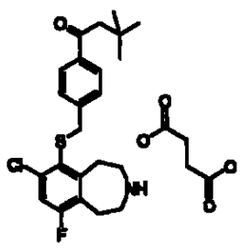


Use a method similar to Example 456 to react 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-9-fluoro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine with 4-chloromethyl-*N*-(*tert*-butyl)-benzamide.

Use methods similar to the General Procedures 1-5 and 2-1 to give the title compound as a white solid. MS (ES+) *m/z*: 421 $(M+H)^+$.

Example 665

7-Chloro-6-[4-(3,3-dimethylbutyryl)-benzylthio]-9-fluoro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

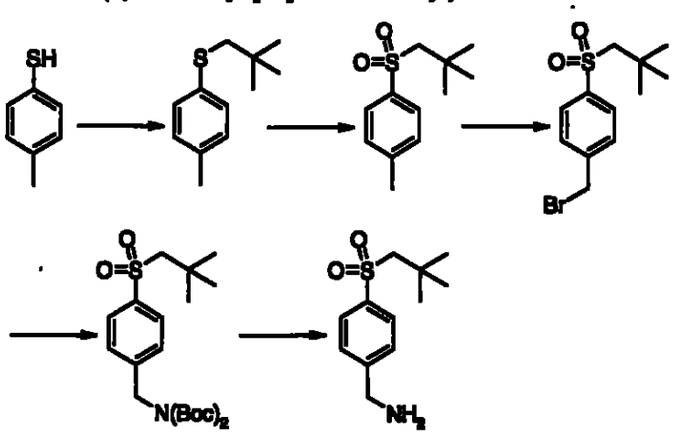


Use a method similar to Example 435 to react 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-9-fluoro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine with 1-(4-bromomethylphenyl)-3,3-dimethylbutan-1-one.

Use methods similar to the General Procedures 1-5 and 2-2 to give the title compound as a white solid. MS (ES+) *m/z*: 420 $(M+H)^+$.

Preparation 346

4-(2,2-Dimethyl-propane-1-sulfonyl)-benzylamine



1-(2,2-Dimethyl-propylthio)-4-methyl-benzene: Dissolve 4-methyl-benzenethiol (1.5 g, 12.08 mmol) in anhydrous DMF (6 mL). Cool the solution to 0°C, add sodium hydride (435 mg, 17.21 mmol, 95%) and stir the mixture under nitrogen atmosphere for 15 min. Add 1-iodo-2,2-dimethylpropane (1.93 mL, 14.5 mmol), stir the mixture for 1 h at 0°C, warm to room temperature and stir overnight. Add water and extract the aqueous phase twice with EtOAc. Wash the combined organic extracts twice with iced-water, dry over Na_2SO_4, filter and concentrate *in vacuo* to give the desired intermediate (1.476 g, 63% yield).

1-(2,2-Dimethyl-propane-1-sulfonyl)-4-methyl-benzene: Dissolve 1-(2,2-dimethyl-propylthio)-4-methyl-benzene (1.476 g, 7.6 mmol) in trifluoroacetic acid (9.5 mL). Add dropwise hydrogen peroxide (9.9 mL, 30% in water), cool the mixture to 0°C and stir 15 min at this temperature and 45 min at room temperature. Concentrate the mixture *in vacuo*, dilute with saturated aqueous $NaHCO_3$ and extract the aqueous phase twice with

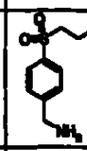
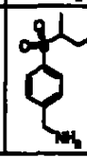
EtOAc. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo* to give the desired intermediate (1.548 g, 90%).

1-Bromomethyl-4-(2,2-dimethyl-propane-1-sulfonyl)-benzene: Use a method similar to the Preparation 213 (Step 2), using 1-(2,2-dimethyl-propane-1-sulfonyl)-4-methyl-benzene (560 mg, 2.47 mmol) to give the desired intermediate.

N-(di-*tert*-Butoxycarbonyl)-4-(2,2-dimethyl-propane-1-sulfonyl)-benzylamine: Add sodium hydride (60 mg, 2.39 mmol) to a solution of di-*tert*-butyl-iminodicarboxylate (519 mg, 2.39 mmol) in anhydrous DMF (2mL) at room temperature under nitrogen and stir for 15 min. Then add a solution of 1-bromomethyl-4-(2,2-dimethyl-propane-1-sulfonyl)-benzene (731 mg, 2.39 mmol) in anhydrous DMF (3 mL) and stir for 1.5 h. Add water and extract the aqueous phase twice with EtOAc. Wash the combined organic extracts with iced-water. Dry the organic layer over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (88:12) to obtain the desired intermediate (460 mg, 44% over 2 steps).

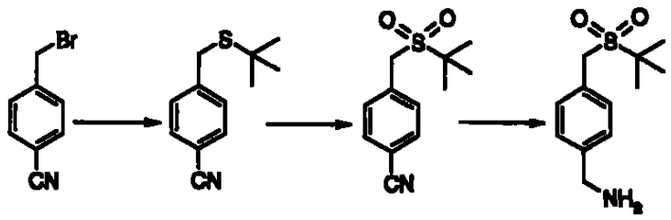
4-(2,2-Dimethyl-propane-1-sulfonyl)-benzylamine: Add 4N hydrogen chloride in dioxane (2 mL) to a solution of *N*-(di-*tert*-butoxycarbonyl)-4-(2,2-dimethyl-propane-1-sulfonyl)-benzylamine (460 mg, 1.04 mmol) in dichloromethane (20 mL) and stir overnight. Concentrate *in vacuo*, suspend the solid obtained in EtOAc, add saturated aqueous $NaHCO_3$ and stir until both phases are clear. Extract the aqueous phase three times with dichoromethane EtOAc. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo* to obtain the title compound as an oil that was used without any further purification (166 mg, 71% yield). MS (ES+) *m/z*: 242 $(M+H)^+$.

The compounds of Preparations 347-348 may be prepared essentially as described in Preparation 346 using 1-iodo-3,3,3-trifluoropropane (Preparation 347) or 1,1,1-trifluoro-3-iodobutane (Preparation 348). MS (ES+) data are shown in the Table below.

Prep.	Structure	Compound	MS (ES+) *m/z*
347		4-(3,3,3-Trifluoro-propane-1-sulfonyl)-benzylamine	268 $(M+H)^+$
348		4-(4,4,4-Trifluoro-butane-2-sulfonyl)-benzylamine	282 $(M+H)^+$

Preparation 349

4-(2-Methyl-propane-2-sulfonylmethyl)-benzylamine

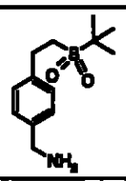


4-*tert*-Butylthiomethyl-benzonitrile: Add sodium hydride (359 mg, 14.21 mmol) to a solution of 2-methyl-2-propanethiol (900 mg, 9.98 mmol) in anhydrous DMF (15 mL) under nitrogen. Stir the mixture for 15 min, add 4-bromomethyl-benzonitrile (2.348 g, 11.97 mmol) and stir the resulting mixture overnight at room temperature. Add water and extract the aqueous phase twice with EtOAc. Wash the combined organic extracts twice with iced-water, dry over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc 92:8 to give the desired intermediate (1.42 g, 69% yield).

4-(2-Methyl-propane-2-sulfonylmethyl)-benzonitrile: Dissolve 4-*tert*-butylthiomethyl-benzonitrile (1.42 g, 6.9 mmol) in trifluoroacetic acid (9 mL). Add dropwise hydrogen peroxide (9 mL, 30% in water), cool the mixture to 0°C and stir 15 min at this temperature and 45 min at room temperature. Concentrate the mixture *in vacuo*, dilute with saturated aqueous $NaHCO_3$ and extract the aqueous phase twice with EtOAc. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo* to give the desired intermediate (1.46 g, 89%).

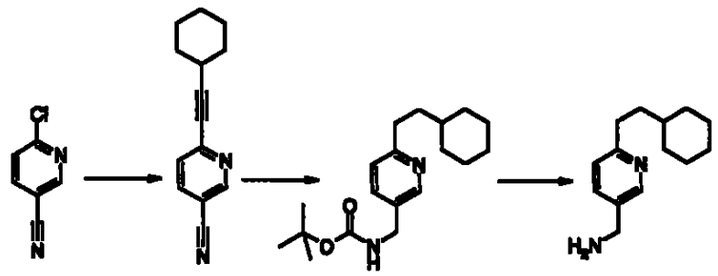
4-(2-Methyl-propane-2-sulfonylmethyl)-benzylamine: Dissolve 4-(2-methyl-propane-2-sulfonylmethyl)-benzonitrile (300 mg, 1.26 mmol) in methanol (50 mL). Add concentrated HCl (10 drops), 10% Pd/C (Degussa type E101, 60 mg) and submit the mixture to hydrogenation at atmospheric pressure for 1 h. Filter over Celite® and wash with methanol. Concentrate the filtrate *in vacuo* to give the hydrochloride salt of the title compound as a solid that was washed with diethyl ether (366 mg, 87%). Partition the solid between saturated $NaHCO_3$ and EtOAc and extract the aqueous phase twice with EtOAc. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo* to give the title compound (195 mg, 74%). MS (ES+) *m/z*: 242 $(M+H)^+$.

The compound of Preparation 350 may be prepared essentially as described in Preparation 349 using 4-(2-bromo-ethyl)-benzonitrile. MS (ES+) data are shown in the Table below.

Prep.	Structure	Compound	MS (ES+) m/z
350		4-[2-(2-Methyl-propane-2-sulfonyl)-ethyl]-benzylamine	256 $(M+H)^+$

Preparation 351

3-Aminomethyl-6-(2-cyclohexyl-ethyl)-pyridine



6-Cyclohexylethynyl-nicotinonitrile: Add cyclohexylacetylene (1.54 mL, 11.6 mmol), dichlorobis(triphenylphosphine)palladium (200 mg, 0.28 mmol), copper iodide (100 mg,

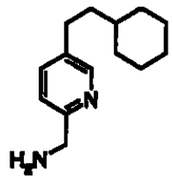
0.53 mmol), and triethylamine (2.0 mL, 14.3 mmol) to a solution of 6-chloronicotinonitrile (1.38 g, 9.9 mmol) in DMF (4 mL). Heat the mixture in a sealed flask for 3 h at 100 °C. Cool the mixture to room temperature, dilute with 1:1 hexane/EtOAc (100 mL) and wash with an aqueous 10% sodium chloride solution (3 x 30 mL). Collect the organic layer, concentrate *in vacuo*, and purify the residue by silica gel chromatography (90 g silica, hexane / EtOAc 95/5 to 85/15 gradient) to obtain the desired intermediate (1.75 g, 83%)

3-*tert*-Butoxycarbonyl-aminomethyl-6-(2-cyclohexyl-ethyl)-pyridine: Add 6-cyclohexylethynyl-nicotinonitrile (1.75 g, 8.3 mmol), 10% Pd/c (Degussa type E101, 50% water by wt) (1.0 g), methanol (100 mL), and di-*t*-butyl dicarbonate (2.3 g, 10.4 mmol) to a pressure vessel under a nitrogen atmosphere. Pressurize the vessel to 30 psi with hydrogen, and stir the mixture for 3 h (monitor the reaction by TLC). Purge the vessel with nitrogen, filter the mixture through Celite® and wash the cake with dichloromethane under a nitrogen atmosphere. Concentrate the filtrate *in vacuo*. Purify the residue by silica gel chromatography (90 g silica, hexane / EtOAc, 95/5 to 50/50 gradient) to obtain the desired intermediate (1.05 mg, 40%). MS (ES+) *m/z*: 319.2 $(M+H)^+$.

3-Aminomethyl-6-(2-cyclohexyl-ethyl)-pyridine: Add trifluoroacetic acid (2.0 mL) to a solution of 3-*tert*-butoxycarbonyl-aminomethyl-6-(2-cyclohexyl-ethyl)-pyridine (1.05 g, 3.3 mmol) in methanol (20 mL). Stir the solution for 1 h at room temperature under a nitrogen atmosphere. Concentrate the solution *in vacuo* and purify the residue via SCX chromatography to obtain the desired intermediate (670 mg, 93 %). MS (ES+) *m/z*: 219.2 $(M+H)^+$.

Preparation 352

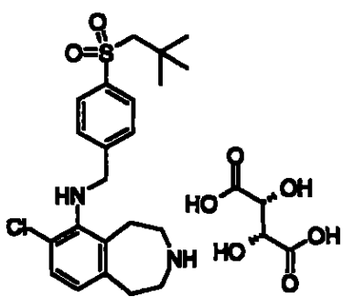
2-Aminomethyl-5-(2-cyclohexyl-ethyl)-pyridine



The title compound may be prepared essentially as described in Preparation 351 by using 5-chloro-pyridine-2-carbonitrile (24% yield, MS (ES) *m/z* 219.2 $(M+H)^+$.

Example 666

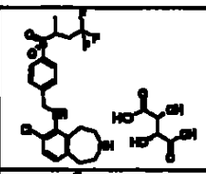
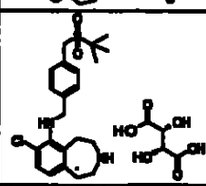
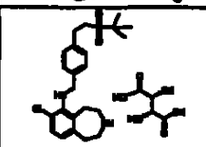
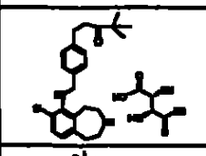
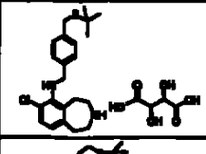
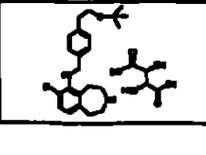
7-Chloro-6-[4-(2,2-dimethyl-propane-1-sulfonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate

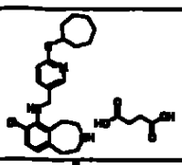
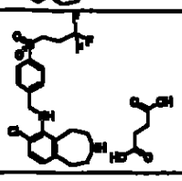


Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (158 mg, 0.37 mmol) with 4-(2,2-dimethyl-propane-1-sulfonyl)-benzylamine (166 mg, 0.73 mmol) by using tris(dibenzylideneacetone)dipalladium(0) (68 mg, 0.074 mmol), BINAP (92 mg, 0.148 mmol) and cesium carbonate (169 mg, 0.518 mmol) in anhydrous toluene (15 mL). Purify by chromatography on silica gel eluting with hexane/EtOAc (8:2) and then by reversed HPLC [Zorbax Bonus RP, 5 □M 21.2 x 100 mm, eluting with water/acetonitrile (0.05% TFA in each), UV detector (230 nm)] to give 7-chloro-6-[4-(2,2-dimethyl-propane-1-sulfonyl)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (153 mg, 80%). MS (ES+) *m/z*: 517 $(M+H)^+$.

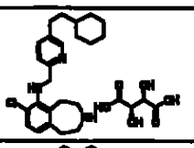
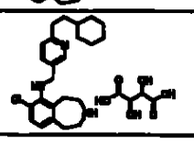
Use methods similar to the General Procedures 1-2 and 2-6 to give the title compound as a white solid. MS (ES+) *m/z*: 421 $(M+H)^+$.

Examples 667-672 may be prepared essentially as described in Example 666 using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. Examples 673-674 may be prepared essentially as described in Example 666 using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine but the succinate salt was prepared as described in General Procedure 2-1. MS (ES+) data are shown in the Table below.

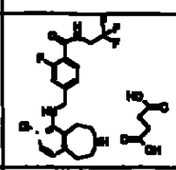
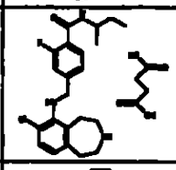
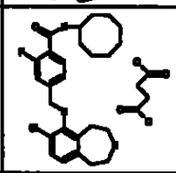
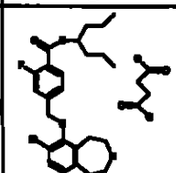
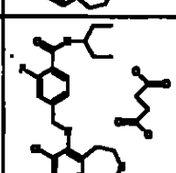
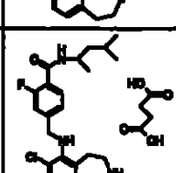
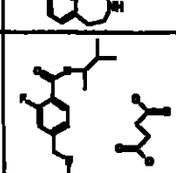
Ex.	Structure	Compound	MS (ES+) *m/z*
667		7-Chloro-6-[4-(4,4,4-trifluorobutane-2-sulfonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (L)-Tartrate	461 $(M+H)^+$
668		7-Chloro-6-[4-(2-methyl-propane-2-sulfonylmethyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (L)-Tartrate	421 $(M+H)^+$
669		7-Chloro-6-[4-(2-methyl-propane-2-sulfonylethyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (L)-Tartrate	435 $(M+H)^+$
670		7-Chloro-6-[4-(4,4-dimethyl-3-oxo-pentyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (L)-Tartrate	399 $(M+H)^+$
671		7-Chloro-6-[4-(t-butylthiomethyl-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (L)-Tartrate	389 $(M+H)^+$
672		7-Chloro-6-[4-(t-butylthioethyl-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (L)-Tartrate	403 $(M+H)^+$

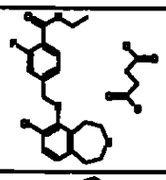
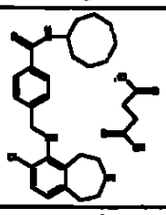
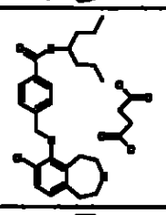
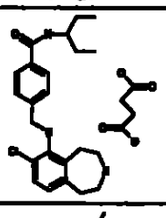
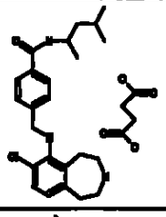
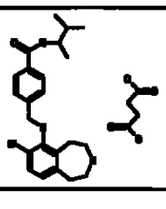
673		7-Chloro-6-[(6-cycloheptylthio-pyridin-3-ylmethyl)-amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	416 $(M+H)^+$
674		7-Chloro-6-[4-(3,3,3-trifluoropropane-1-sulfonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	447 $(M+H)^+$

Examples 675-676 may be prepared essentially as described in Example 604 using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine but the (L)-tartrate salt was prepared as described in General Procedure 2-6. MS (ES+) data are shown in the Table below.

Ex.	Structure	Compound	MS (ES+) *m/z*
675		7-Chloro-6-(5-cyclohexylethyl-pyridin-2-yl-methylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (L)-Tartrate	398 $(M+H)^+$
676		7-Chloro-6-(6-cyclohexylethyl-pyridin-3-yl-methylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (L)-Tartrate	398 $(M+H)^+$

Examples 677-684 may be prepared essentially as described in Example 563 by using 3-*tert*-butoxycarbonyl-6-(4-carboxy-3-fluoro-benzylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. Examples 685-689 may be prepared essentially as described in Example 563 by using 3-*tert*-butoxycarbonyl-6-(4-carboxy-benzylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. MS (ES+) data are shown in the Table below.

Ex.	Structure	Compound	MS (ES+) m/z
677		7-Chloro-6-[4-(2,2,2-trifluoroethylcarbamoyl)-3-fluoro-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	430 $(M+H)^+$
678		7-Chloro-6-[4-(2-butylcarbamoyl)-3-fluoro-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	404 $(M+H)^+$
679		7-Chloro-6-[4-(2-cycloheptylcarbamoyl)-3-fluoro-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	458 $(M+H)^+$
680		7-Chloro-6-[4-(4-heptylcarbamoyl)-3-fluoro-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	446 $(M+H)^+$
681		7-Chloro-6-[4-(3-pentylcarbamoyl)-3-fluoro-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	418 $(M+H)^+$
682		7-Chloro-6-[4-(4-methyl-2-pentylcarbamoyl)-3-fluoro-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	432 $(M+H)^+$
683		7-Chloro-6-[4-(3-methyl-2-butylcarbamoyl)-3-fluoro-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	418 $(M+H)^+$

684		7-Chloro-6-[4-(ethylcarbamoyl)-3-fluoro-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	376 $(M+H)^+$
685		7-Chloro-6-[4-(2-cycloheptylcarbamoyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	440 $(M+H)^+$
686		7-Chloro-6-[4-(4-heptylcarbamoyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	428 $(M+H)^+$
687		7-Chloro-6-[4-(3-pentylcarbamoyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	400 $(M+H)^+$
688		7-Chloro-6-[4-(4-methyl-2-pentylcarbamoyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	414 $(M+H)^+$
689		7-Chloro-6-[4-(3-methyl-2-butylcarbamoyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	400 $(M+H)^+$

The compounds of the present invention are relatively selective for the 5-HT_{2C} receptor. The compounds of the present invention are particularly relatively selective for the 5-HT_{2C} receptor in comparison to other 5-HT receptor subtypes and specifically the

5-HT_{2A} and 5-HT_{2B} receptors. This selectivity is demonstrated in the following agonist activity assays and receptor binding assays.

Agonist Activity Assays (G alpha q-GTPγ[^{35}S] Binding Assays)

The 5-HT_2 receptors are functionally coupled to specific G-proteins. Agonist activation of 5-HT_2 G-protein-coupled receptors results in the release of GDP from the α-subunit (G alpha q or G alpha i) of the G-protein and the subsequent binding of GTP. The binding of the stable analog GTPγ[^{35}S] is an indicator of receptor activation (i.e. agonist activity).

The G alpha q-GTPγ[^{35}S] binding assay is used to determine the in vitro potency (EC_{50}) and maximal efficacy (E_{max}, normalized to the 5-HT response) of a test compound at the 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptors. The area under the dose response curve (AUC) is also determined for each receptor subtype and used to measure the test compound's selectivity for the 5-HT_{2C} receptor over the 5-HT_{2A} and 5-HT_{2B} receptors, expressed as Selectivity Ratios (AUC 2C/2A and AUC 2C/2B, respectively). The Selectivity Ratios allow the assessment of selectivity based on both potency and efficacy. A selectivity measure that incorporates both potency and efficacy at the 5-HT_{2C} receptor, as compared to the 5-HT_{2A} and 5-HT_{2B} receptors, is considered important due to the adverse events associated with 5-HT_{2A} and 5-HT_{2B} agonist activity (see introduction).

Membrane Preparation: Grow AV12 cells stably transfected with the human 5-HT_{2A}, 5-HT_{2B}, or 5-HT_{2C} receptors in suspension, harvest by centrifugation, wash the cell pellet with phosphate buffered saline, pH 7.4, pellet the cells again, remove the supernatant, freeze the cell pellet on dry ice and store at -70°C. Thaw stock cell pellet and resuspend in 50mM Tris, pH 7.4, aliquot into 1-2 mL volumes and refreeze at -70°C for subsequent assays. (As is appreciated in the art, optimal cell quantities used per aliquot will vary with the individual transfected cell line used. In one embodiment, 5-HT_{2A} and 5-HT_{2C} transfected cells are typically used at about 6×10^5 cells per aliquot, while 5-HT_{2B} cells are typically used at about 7.5×10^6 cells per aliquot).

On the day of assay, thaw membranes, wash the membranes with assay buffer (50 mM Tris-HCl (pH 7.4), 10 mM $MgCl_2$, 100 mM NaCl, and 0.2 mM EDTA), resuspend in assay buffer and incubate for 10 min. at 37°C to hydrolyze any residual endogenous 5-HT. Wash the membranes again with assay buffer, and resuspend in assay buffer at a concentration to provide aliquots of about 1-4x10^6 cell equivalents per well (typically about 1-2 x 10^6 cell equivalents for assays with 5-HT_{2A} or 5-HT_{2C} receptor assays, and about 3-4 x 10^6 cell equivalents for assays with 5-HT_{2B} receptor assays). Homogenize the cells with a tissue grinder and use the homogenate directly in the assay as described below.

G alpha q-GTPγ[^{35}S] Binding Assays: The immunoadsorption scintillation proximity assay (ISPA) of [^{35}S]-GTPγS binding to G alpha q is modified from published conditions (DeLapp et al, JPET 289 (1999) 946-955). Dissolve test compounds in DMSO and dilute in assay buffer to provide a range of concentrations to generate a concentration response curve. In wells of a 96 well microtiter plate, mix diluted test compound, GDP (0.1 μM final concentration), and [^{35}S]-GTPγS (between 0.5 and 1.0 nM final concentration). Add an aliquot of membranes to the incubation mixture and mix the plates to initiate agonist stimulation of the nucleotide exchange (200 μl final volume). Incubate the microtiter plates for 30 min. at room temperature. Quench the incubation with IGEPAL® CA-630 detergent (0.27% final concentration). Add affinity purified polyclonal rabbit anti-G alpha q antibody (about 1-2 μg per well), and anti-rabbit Ig scintillation proximity assay beads (Amersham; about 1.25 mg per well; 300 μl final volume). Seal the plates and incubate the mixture for 3 h at room temperature. Centrifuge the microtiter plates briefly to pellet beads. Quantitate the GTPγ[^{35}S] binding by microtiter plate scintillation spectrometry (Wallac Trilux MicroBeta™ scintillation counter).

Data Analysis: For each concentration response curve for a test compound at a given receptor, analyze the data with GraphPad Prism™ software (v3.02; GraphPad Software, San Diego, CA) running on a personal computer with MicroSoft Windows

OS®, using nonlinear regression analysis curve fitting to determine the EC_{50} and E_{max} (normalized to 5-HT control curves). Determine the Area Under the agonist concentration-response Curve (AUC) with GraphPad Prism™ by the trapezoidal method.

To calculate the Selectivity Ratios, first, determine the AUC for the test compound for each receptor subtype as described above. Second, normalize the AUC's at each receptor subtype relative to the AUC determined for 5-HT at that receptor. The normalized AUC for a test compound at a given receptor is therefore expressed as a percentage of the AUC determined for 5-HT at that receptor. For example:

$$5HT_{2A}\text{ Normalized AUC} = a = \frac{(AUC_{\text{test compound}}\text{ at }5HT_{2A}\text{ receptor})}{(AUC_{5\text{-HT}}\text{ at }5HT_{2A}\text{ receptor})} \times 100\%$$

$$5HT_{2B}\text{ Normalized AUC} = b = \frac{(AUC_{\text{test compound}}\text{ at }5HT_{2B}\text{ receptor})}{(AUC_{5\text{-HT}}\text{ at }5HT_{2B}\text{ receptor})} \times 100\%$$

$$5HT_{2C}\text{ Normalized AUC} = c = \frac{(AUC_{\text{test compound}}\text{ at }5HT_{2C}\text{ receptor})}{(AUC_{5\text{-HT}}\text{ at }5HT_{2C}\text{ receptor})} \times 100\%$$

Third, calculate the Selectivity Ratios for the test compound as follows:

Selectivity Ratio for 5-HT_{2C} receptor/5-HT_{2A} receptor (AUC 2C/2A) = c/a

Selectivity Ratio for 5-HT_{2C} receptor/5-HT_{2B} receptor (AUC 2C/2B) = c/b

For reference purposes, the AUC 2C/2A and AUC 2C/2B for 5-HT are each 1.0. Likewise, the ratios for mCPP (*meta*-chlorophenylpiperazine) are tested and are found to be 2.1 and 2.1 respectively.

Representative compounds of the present invention are tested in the G alpha q-GTPγ[^{35}S] assays for the 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptors essentially as described above and are found to be a highly potent and selective agonists of the 5-HT_{2C} receptor, with EC_{50}'s typically less than or equal to 200 nM, and AUC 2C/2A and AUC 2C/2B ratios greater than 1.5. Preferred compounds are those with EC50's less than or equal to 100 nM, and AUC 2C/2A and AUC 2C/2B ratios greater than or equal to 2.0. More preferred are those with EC50's less than or equal to 50 nM, and AUC 2C/2A and AUC 2C/2B ratios greater than or equal to 3.0.

Ligand Binding Assays

The ligand binding affinity of the compounds of the present invention to the 5-HT_{2C} receptor subtype is measured essentially as described by Wainscott (Wainscott, *et al.*, *Journal of Pharmacology and Experimental Therapeutics*, 276:720-727 (1996)). Data is analyzed by nonlinear regression analysis on the concentration response curves using the four parameter logistic equation described by DeLean (DeLean, et al., Molecular Pharmacology, 21, 5-16 (1982)). IC_{50} values are converted to K_i values using the Cheng-Prusoff equation (Cheng, et al., Biochem. Pharmacol., 22, 3099-3108 (1973)).

Representative compounds of the present invention are tested essentially as described above and are found to have excellent affinity for the 5-HT_{2C} receptor, with K_i's typically less than or equal to about 200 nM. Preferred compounds are those with K_i's of less than or equal to about 100 nM. More preferred are those with K_i's less than or equal to 50 nM.

Affinities for other receptor subtypes can readily be determined by slight modification of the above described radioligand receptor binding assay using cells transfected with the desired receptor in place of cells transfected with the 5-HT_{2C} receptor subtype and using an appropriate radioligand. The binding affinities for representative compounds of the present invention for a variety of receptors are determined in such assays and the compounds are found to have surprisingly higher affinity for the 5-HT_{2C} receptor. Affinity for the 5-HT_{2C} receptor is found to be significantly higher than for other 5-HT receptor subtypes, and notably higher than the 5-HT_{2A} and 5-HT_{2B} receptor subtypes. Preferred compounds are those with IC_{50}'s equal to or greater than 300 nM for the alpha 1 and alpha 2 adrenergic receptors and equal to or greater than 500 nM for D_1 and D_2 dopaminergic receptors. More preferred compounds are those with IC_{50}'s equal to or greater than 1000 nM for the alpha 1 and alpha 2 adrenergic receptors and the D_1 and D_2 dopaminergic receptors. Still more preferred are those compounds with IC_{50}'s equal to or greater than 3000 nM for the alpha 1 and alpha 2 adrenergic receptors and the D_1 and D_2 dopaminergic receptors.

For the above in vitro assays, exemplified compounds are assayed and found to have either an EC_{50} or a K_i value of equal to or less than 50 nM, and to have AUC 2C/2A and AUC 2C/2B ratios of greater than or equal to 2.0. Exemplified compounds are assayed and found to have alpha 1 and alpha 2 adrenergic receptor IC_{50}'s equal to or greater than 300 nM, and D_1 and D_2 dopaminergic receptor IC_{50}'s equal to or greater than 500 nM.

Rat feeding assays

The ability of the compounds of the present invention to treat obesity is demonstrated by testing in acute and chronic rat feeding assays.

Animals: Obtain male Long-Evans rats (Harlan Sprague-Dawley, Indianapolis, IN) that are approximately one hundred-days old and have been maintained on a calorie rich diet since weaning (TD 95217, 40% calories from fat; Teklad, Madison, WI). House the rats individually with a 12 h:12 h light:dark cycle (lights on from about 22:00 h to about 10:00 h) and maintain rats on the same diet (TD 95217) with free access to water, for about 1-2 weeks to acclimate the rats to the environment. Dose rats orally with vehicle (10% acacia with 0.15% saccharin in water) once daily for at least 1 day (typically 1-2 days) to acclimate the rats to the procedures. Randomize the rats into groups so each group has similar mean body weights.

Calorimetric Acute Feeding Assay: At approximately 8:00 h on the day of assay, weigh each rat and transfer to individual chambers of an open circuit calorimetry system (Oxymax, Columbus Instruments International Corporation; Columbus, OH), with free access to food (pre-weighed) and water, and begin measuring VO_2 and VCO_2. At approximately 10:00 h, dose rats orally with vehicle or test compound, return them to their calorimetry chambers, and continue measuring VO_2 and VCO_2 at regular time intervals (approximately hourly). At approximately 8:00 h the following day, measure rat body weight and the remaining food, assuming the difference in weight of food is equal to the mass of food consumed. Calculate the 24 h energy expenditure (EE) and respiratory

quotient (RQ) essentially as described in Chen, Y. and Heiman, M. L., Regulatory Peptide, 92:113-119 (2000). EE during light photoperiod is indicative of the resting metabolic rate and RQ is indicative of the fuel source the animal utilizes (pure carbohydrate metabolism gives an RQ of about 1.0, pure fat metabolism gives an RQ of about 0.7, mixed carbohydrate and fat metabolism gives intermediate values for RQ). Calculate EE as the product of calorific value (CV) and VO_2 per body weight (kg); where CV = 3.815 + 1.232*RQ, and RQ is the ratio of CO_2 produced (VCO_2) to O_2 consumed (VO_2). Caloric intake is calculated as (mass of 24 h food intake in grams) x (physiological fuel value of the diet in kilocalorie/g) per kg of body weight.

Acute Feeding Assay with a selective 5-HT_{2C} receptor antagonist: The above calorimetric acute feeding assay is conducted with the following modifications. Open circuit calorimetry systems are not used and only the 24 h periodic food intake and body weight are measured. Three groups of rats are used with the first group receiving a subcutaneous dose of saline (0.5 mL) about 15 minutes prior to the oral dose of vehicle, the second group receiving a subcutaneous dose of saline (0.5 mL) about 15 minutes prior to the oral dose of test compound in vehicle, and the third group receiving a subcutaneous injection of a selective 5-HT_{2C} receptor antagonist, 6-chloro-5-methyl-N-{2-[(2-methylpyridin-3-yl-oxy)pyridin-5-yl]aminocarbonyl}-2,3-dihydroindole (3 mg/Kg, in 35% cyclodextrin, 0.5 mL), about 15 min. prior to the oral dose of test compound in vehicle.

Chronic Feeding Assay: At between approximately 8:00 h and 10:00 h on day one of the assay, weigh and orally dose each rat with vehicle or test compound and return the animal to its home cage, with free access to food (pre-weighed) and water. For each of days 2-15, at between approximately 8:00 h and 10:00 h, measure rat body weight and the weight of food consumed in the last 24 h period, and administer daily oral dose of test compound or vehicle. On days –2 and 15 measure total fat mass and lean mass by nuclear magnetic resonance (NMR) using an EchoMRI™ system (Echo Medical Systems, Houston Texas). (See Frank C. Tinsley, Gersh Z. Taicher, and Mark L. Heiman, "Evaluation of a New

Quantitative Magnetic Resonance (QMR) Method for Mouse Whole Body Composition Analysis", Obesity Research, submitted May 1, 2003.)

Representative compounds of the present invention are tested in acute and chronic feeding assays essentially as described above. In the acute assays, the compounds are found to significantly reduce 24 h food intake, which effect is blocked by pre-administration of the 5-HT_{2C} receptor antagonist. The compounds also are found to dose-dependently reduce RQ without significantly changing the energy expenditure during the light photo-period. Thus the compounds are found to reduce caloric intake and increase the proportion of fuel deriving from fat utilization, without significantly changing the resting metabolic rate. In the chronic assay, the compounds are found to significantly decrease cumulative food intake and cumulative body weight change in a dose-dependent manner compared to control animals. The decrease in body weight is found to be due to loss of adipose tissue while lean body mass is not changed.

The ability of the 5-HT_{2C} receptor agonists of the present invention to treat obsessive/compulsive disorder is demonstrated by testing in a variety of in vivo assays as follows:

<u>Marble burying assay</u>

Marble burying in mice has been used to model anxiety disorders including obsessive-compulsive disorders (OCD) due to ethological study of the behavior (e.g. Gyertyan I. "Analysis of the marble burying response: Marbles serve to measure digging rather than evoke burying", *Behavioural Pharmacology* 6: 24-31, (1995)) and due to the pharmacological effects of clinical standards (e.g., Njung'E K. Handley SL. "Evaluation of marble-burying behavior as a model of anxiety", *Pharmacology, Biochemistry & Behavior*. 38: 63-67, (1991)); Borsini F., Podhorna J., and Marazziti, D. "Do animal models of anxiety predict anxiolytic effects of antidepressants?", *Psychopharmacology* 163: 121-141, (2002)). Thus, drugs used in the treatment of generalized anxiety in humans (e.g. benzodiazepines) as well as compounds used to treat OCD (e.g. SSRIs like fluoxetine) decrease burying.

House experimentally-naïve male, NIH Swiss mice (Harlan Sprague-Dawley, Indianapolis, IN) weighing between 28-35 g in groups of 12 for at least three days prior to testing in a vivarium with 12 h light and dark cycles. Conduct experiments during the light cycle in a dimly lit experimental testing room. Dose mice with vehicle or test compound and, after a specified pretreatment interval (generally 30 min.), place each mouse individually on a rotorod (Ugo Basile 7650) operating at a speed of 6 revolutions/min. and observe for falling. After 2 min. on the rotorod, place the mice individually in a 17 x 28 x 12 cm high plastic tub with 5 mm sawdust shavings on the floor that are covered with 20 blue marbles (1.5 cm diameter) placed in the center. After 30 min., count the number of marbles buried (2/3 covered with sawdust). Assess the test compound's effect on marble burying with Dunnett's test and the effect on rotorod performance by Fisher's exact test.

Clinically effective standard compounds suppress marble burying at doses that are devoid of motor-impairing effects as measured on the rotorod. The *in vivo* efficacy of $5HT_{2C}$ compounds at the $5HT_{2C}$ receptor is confirmed by the prevention of effects of the $5HT_{2C}$ agonists on marble burying by co-administration of the $5HT_{2C}$ receptor antagonist, 6-chloro-5-methyl-N-{2-[(2-methylpyridin-3-yl-oxy)pyridin-5-yl]aminocarbonyl}-2,3-dihydroindole.

Representative compounds of the present invention are assayed in the marble burying assay essentially as described and are surprisingly found to reduce burying behavior in the test mice. The reduction of burying behavior is found to be blocked by co-administration of the $5\text{-}HT_{2C}$ antagonist. In contrast to the compounds of the present invention, the anxiolytic compound chlordiazepoxide and the antipsychotic compound chlorpromazine decrease marble burying only at doses that also disrupt rotorod performance.

Nestlet Shredding

Mice naturally will construct nests of material available in their living environment. Since this behavior is obsessive in nature, it has been used to model OCD (Xia Li, Denise Morrow and Jeffrey M. Witkin, "Decreases in nestlet shredding of mice by serotonin uptake inhibitors: comparison with marble burying", Psychopharmacology, submitted July 14, 2003). House experimentally-naïve male, NIH Swiss mice (Harlam Sprague-Dawley, Indianapolis, IN) weighing between 28-35 g in groups of 12 for at least three days prior to testing in a vivarium with a 12 h light/dark cycle. Conduct experiments during the light cycle in an experimental room with normal overhead fluorescent lighting. Dose mice with vehicle or test compound and after a specified pretreatment interval (generally 30 min.), place the mice individually in a 17 x 28 x 12 cm high plastic tub with about 5 mm sawdust shavings on the floor along with a pre-weighed multi-ply gauze pad (51 mm square). After 30 min., weigh the remainder of the gauze pad not removed by the mouse. Determine the weight of the gauze used for nestlet construction by subtraction. Compare the results for test compound treated mice to the results for vehicle control treated mice with Dunnett's test.

Clinically effective OCD treatment standard compounds suppress nestlet shredding at doses that are devoid of motor-impairing effects as measured by the rotorod test. The *in vivo* efficacy of $5HT_{2C}$ compounds at the $5HT_{2C}$ receptor is confirmed by the prevention of effects of the $5HT_{2C}$ agonists on nestlet shredding by co-administration of the $5HT_{2C}$ receptor antagonist, 6-chloro-5-methyl-N-{2-[(2-methylpyridin-3-yl-oxy)pyridin-5-yl]aminocarbonyl}-2,3-dihydroindole.

Representative compounds of the present invention are assayed essentially as described above and are surprisingly found to suppress nestlet shredding at doses that are devoid of motor-impairing effects as measured by the rotorod test.

In contrast to the compounds of the present invention, the anxiolytic chlordiazepoxide and the psychomotor stimulant d-amphetamine decreases nestlet shredding only at doses that produce motoric side effects (depression or stimulation, respectively).

Schedule-Induced Polydipsia

Food-deprived rats exposed to intermittent presentations of food will drink amounts of water that are far in excess of their normal daily intake and in excess of their intake when given all of their food at one time (Falk JL. "Production of polydipsia in normal rats by an intermittent food schedule", *Science* 133: 195-196, (1961)). This excessive behavior is persistent and has been used to model OCD.

Maintain Wistar rats on a food restricted diet (to maintain 85% free feeding weight), but with free access to water. Train the rats in a behavioral testing chamber to press a lever to receive a food pellet under a fixed interval schedule, such that the rats are rewarded with a 45 mg food pellet the first time they press a lever after a 120 second interval has elapsed. The fixed interval is then reset to 120 seconds and the process repeated. Thus, during a 90 min. test session, the rats can earn a maximum of 45 pellets. The behavioral chamber is also equipped with a water bottle that is weighed before and after the session to determine the amount of water consumed.

Administer test compounds on Tuesdays and Fridays. Determine control day performances on Thursdays. Administer compounds either orally at 60 min. before the beginning of a test session, or subcutaneously at 20 min. before the beginning of a test session. Compare the rates of lever pressing and water consumption for each animal's performance during sessions after test compound treatment with that animal's performance during control sessions, expressed as a percent of the control rate. Average the individual percent of control rates for each dose and calculate the standard error of the mean.

Clinically effective OCD treatment standard compounds (e.g. chlomipramine, fluoxetine) suppress schedule-induced polydipsia without producing notable changes in motor patterns, food intake, or behavior the following day. The *in vivo* efficacy of $5HT_{2C}$ compounds at the $5HT_{2C}$ receptor is confirmed by the prevention of effects of the $5HT_{2C}$ agonists on excessive drinking by co-administration of the $5HT_{2C}$ receptor antagonist, 6-

chloro-5-methyl-N-{2-[(2-methylpyridin-3-yl-oxy)pyridin-5-yl]aminocarbonyl}-2,3-dihydroindole.

Representative compounds of the present invention are assayed in the schedule-induced polydipsia assay essentially as described above and are surprisingly found to suppress schedule-induced polydipsia without producing notable changes in motor patterns, food intake, or behavior the following day. The behavior suppression is blocked by co-administration of the 5-HT_{2C} antagonist.

In contrast to the compounds of the present invention, the psychomotor stimulant d-amphetamine decreases excessive drinking only at behaviorally stimulating doses and these effects are not prevented by the $5HT_{2C}$ receptor antagonist.

While it is possible to administer compounds employed in the methods of this invention directly without any formulation, the compounds are usually administered in the form of pharmaceutical compositions comprising a pharmaceutically acceptable excipient and at least one compound of Formula I or a pharmaceutically acceptable salt thereof. These compositions can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal. The compounds employed in the methods of this invention are effective as both injectable and oral compositions. Such compositions are prepared in a manner well known in the pharmaceutical art. *See, e.g.* REMINGTON'S PHARMACEUTICAL SCIENCES, (16th ed. 1980).

In making the compositions employed in the present invention the active ingredient is usually mixed with at least one excipient, diluted by at least one excipient, or enclosed within such a carrier which can be in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing for example up to 10% by weight of the active compound,

soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

In preparing a formulation, it may be necessary to mill the compound to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it ordinarily is milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size is normally adjusted by milling to provide a substantially uniform distribution in the formulation, e.g. about 40 mesh.

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxybenzoates; sweetening agents; and flavoring agents. The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 0.05 to about 100 mg, more usually about 1.0 to about 30 mg, of the active ingredient. The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

The compounds are generally effective over a wide dosage range. For examples, dosages per day normally fall within the range of about 0.01 to about 30 mg/kg. In the treatment of adult humans, the range of about 0.1 to about 15 mg/kg/day, in single or divided dose, is especially preferred. However, it will be understood that the amount of

the compound actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound or compounds administered, the age, weight, and response of the individual patient, and the severity of the patient's symptoms, and therefore the above dosage ranges are not intended to limit the scope of the invention in any way. In some instances dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed.

Another preferred formulation employed in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. See, e.g., U.S. Patent 5,023,252, issued June 11, 1991, herein incorporated by reference. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

Under some circumstances, it will be desirable or necessary to introduce the pharmaceutical composition to the brain, either directly or indirectly. Direct techniques usually involve placement of a drug delivery catheter into the host's ventricular system to bypass the blood-brain barrier. One such implantable delivery system, used for the transport of biological factors to specific anatomical regions of the body, is described in U.S. Patent 5,011,472, issued April 30, 1991, which is herein incorporated by reference.

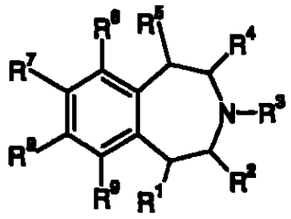
Indirect techniques, which are generally preferred, usually involve formulating the compositions to provide for drug latentiation by the conversion of hydrophilic drugs into lipid-soluble drugs or prodrugs. Latentiation is generally achieved through blocking of the hydroxy, carbonyl, sulfate, and primary amine groups present on the drug to render the drug more lipid soluble and amenable to transportation across the blood-brain barrier. Alternatively, the delivery of hydrophilic drugs may be enhanced

by intra-arterial infusion of hypertonic solutions which can transiently open the blood-brain barrier.

The type of formulation employed for the administration of the compounds employed in the methods of the present invention may be dictated by the particular compound employed, the type of pharmacokinetic profile desired from the route of administration, and the state of the patient.

WE CLAIM:

1. A compound of Formula I:



I

where:

R^1 is hydrogen, fluoro, or (C_1-C_3)alkyl;

R^2, R^3, and R^4 are each independently hydrogen, methyl, or ethyl;

R^5 is hydrogen, fluoro, methyl, or ethyl;

R^6 is $-C\equiv C-R^{10}$, $-O-R^{12}$, $-S-R^{14}$, or $-NR^{24}R^{25}$;

R^7 is hydrogen, halo, cyano, (C_1-C_6)alkyl optionally substituted with 1 to 6 fluoro substituents, (C_2-C_6)alkenyl optionally substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl, (C_1-C_6)alkoxy optionally substituted with 1 to 6 fluoro substituents, (C_1-C_6)alkylthio optionally substituted with 1 to 6 fluoro substituents, $Ph^1-(C_0-C_3)$alkyl, $Ph^1-(C_0-C_3)$alkyl-O-, or $Ph^1-(C_0-C_3)$alkyl-S-;

R^8 is hydrogen, halo, cyano, or $-SCF_3$;

R^9 is hydrogen, halo, cyano, $-CF_3$, $-SCF_3$, or (C_1-C_3)alkoxy optionally substituted with 1 to 6 fluoro substituents;

R^{10} is $-CF_3$, ethyl substituted with 1 to 5 fluoro substituents, (C_3-C_6) alkyl optionally substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, $Ar^1-(C_0-C_3)$alkyl, $Ph^1-(C_0-C_3)$alkyl, or 3-(C_1-C_4)alkyl-2-oxo-imidazolidin-1-yl-(C_1-C_3)alkyl;

R^{12} is $Ph^2-(C_1-C_3)$alkyl, $Ar^2-(C_1-C_3)$alkyl, (C_1-C_6)alkyl-S-(C_2-C_6)alkyl, (C_3-C_7)cycloalkyl-S-(C_2-C_6)alkyl, phenyl-S-(C_2-C_6)alkyl, Ph^2-S-(C_2-C_6)alkyl, phenylcarbonyl-(C_1-C_3)alkyl, Ph^2-C(O)-(C_1-C_3)alkyl, (C_1-C_6)alkoxycarbonyl(C_3-C_6)alkyl, (C_3-C_7)cycloalkyl-OC(O)-(C_3-C_6)alkyl,

phenyloxycarbonyl-(C_3-C_6)alkyl, Ph^2-OC(O)-(C_3-C_6)alkyl, Ar^2-OC(O)-(C_3-C_6)alkyl, (C_3-C_7)cycloalkyl-NH-C(O)-(C_2-C_4)alkyl-, Ph^1-NH-C(O)-(C_2-C_4)alkyl-, Ar^2-NH-C(O)-(C_2-C_4)alkyl-, or R^{13}-C(O)NH-(C_2-C_4)alkyl;

R^{13} is (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, Ph^1, Ar^2, or (C_1-C_3)alkoxy optionally substituted with 1 to 6 fluoro substituents, Ph^1-NH- or N-linked Het^1;

R^{14} is Ar^2 which is not N-linked to the sulfur atom, Ph^2, R^{15}-L-, tetrahydrofuranyl, tetrahydropyranyl, or phenyl-methyl substituted on the methyl moiety with a substituent selected from the group consisting of (C_1-C_3)-*n*-alkyl substituted with hydroxy, (C_1-C_3)alkyl-O-(C_1-C_2)-*n*-alkyl, (C_1-C_3)alkyl-C(O)-(C_0-C_2)-*n*-alkyl, and (C_1-C_3)alkyl-O-C(O)-(C_0-C_2)-*n*-alkyl,

wherein when R^{14} is Ph^2 or Ar^2, wherein Ar^2 is pyridyl, then R^{14} may also, optionally be substituted with phenyl-CH=CH- or phenyl-C≡C-, said phenyl-CH=CH- or phenyl-C≡C- being optionally further substituted with 1 to 3 substituents independently selected from the group consisting of halo, cyano, $-SCF_3$, (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, and (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents, and

wherein when Ar^2 is pyridyl, the pyridyl may alternatively, optionally be substituted with $R^{28}R^{29}N$-C(O)-, and optionally further substituted with one methyl, $-CF_3$, cyano, or $-SCF_3$ substituent, or with 1 to 2 halo substituents, and

wherein the tetrahydrofuranyl and tetrahydropyranyl may optionally be substituted with an oxo substituent, or with one or two groups independently selected from methyl and $-CF_3$;

R^{15} is $-OR^{16}$, cyano, $-SCF_3$, Ph^2, Ar^2, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, phthalimido, benzothiophenyl optionally substituted at the 2-position with phenyl or benzyl, benzothiazolyl optionally substituted at the 2-position with phenyl or benzyl, benzothiadiazolyl optionally substituted with phenyl or benzyl, 2-oxo-dihydroindol-1-yl optionally substituted at the 3 position with gem dimethyl or (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, 2-oxo-dihydroindol-5-yl

optionally substituted at the 3 position with gem dimethyl or (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, 2-oxo-imidazolidin-1-yl optionally substituted at the 3 position with gem dimethyl or (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, 2-oxo-tetrahydropyrimidinyl optionally substituted at the 3 or 4 position with gem dimethyl or (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, 2-oxo-tetrahydroquinolin-1-yl optionally substituted at the 3 position with gem dimethyl or (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, 2-oxo- dihydrobenzimidazol-1-yl optionally substituted at the 3 position with gem dimethyl or (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, $-NR^{17}R^{18}$, $-C(O)R^{22}$, or a saturated heterocycle selected from the group consisting of pyrrolidinyl, piperidinyl, morpholinyl, and thiomorpholinyl, tetrahydrofuranyl, and tetrahydropyranyl,

wherein Ph^2 and Ar^2 when Ar^2 is pyridyl, may also optionally be substituted with phenyl-CH=CH- or phenyl-C≡C-,

said phenyl-CH=CH- and phenyl-C≡C- being optionally further substituted on the phenyl moiety with 1 to 3 substituents independently selected from the group consisting of halo, cyano, $-SCF_3$, (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, and (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents, and

wherein Ar^2 may alternatively, optionally be substituted with a substituent selected from the group consisting of (C_3-C_7)cycloalkyl-(C_0-C_3)alkyl, Het^1-(C_0-C_3)alkyl, pyridyl-(C_0-C_3)alkyl, and phenyl-(C_0-C_3)alkyl, and optionally further substituted with one methyl, $-CF_3$, cyano, or $-SCF_3$ substituent, or with 1 to 2 halo substituents,

said pyridyl-(C_0-C_3)alkyl and phenyl-(C_0-C_3)alkyl optionally being further substituted with 1-3 substituents independently selected from halo, $-CH_3$, $-OCH_3$, $-CF_3$, $-OCF_3$, -CN, and $-SCF_3$, and

wherein when Ar^2 is pyridyl, the pyridyl may alternatively, optionally be substituted with $R^{28}R^{29}N$-C(O)-, or (C_1-C_4)alkyl-C(O)- optionally substituted with 1 to 6 fluoro substituents, and may be optionally further

substituted with one methyl, $-CF_3$, cyano, or $-SCF_3$ substituent, or with 1 to 2 halo substituents, and

wherein when Ar^2 is thiazolyl, the thiazolyl may alternatively, optionally be substituted with (C_3-C_7)cycloalkyl-(C_0-C_3)alkyl-NH-, and

wherein the pyrrolidinyl, piperidinyl, morpholinyl, and thiomorpholinyl is substituted with oxo- on a carbon atom adjacent to the ring nitrogen atom, or is N-substituted with a substituent selected from the group consisting of

(C_1-C_6)alkylcarbonyl, (C_1-C_6)alkylsulfonyl,

(C_3-C_7)cycloalkyl(C_0-C_3)alkyl-C(O)-,

(C_3-C_7)cycloalkyl(C_0-C_3)alkyl-$S(O)_2$-, Ph^1-(C_0-C_3)alkyl-C(O)-, and

Ph^1-(C_0-C_3)alkyl-$S(O)_2$-, and

may optionally be further substituted with 1 or 2 methyl or $-CF_3$ substituents, and when oxo-substituted, may optionally be further N-substituted with a substituent selected from the group consisting of

(C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, and Ph^1-(C_0-C_3)alkyl, and

wherein tetrahydrofuranyl and tetrahydropyranyl may optionally be substituted with an oxo substituent, and/or with one or two groups independently selected from methyl and $-CF_3$;

L is branched or unbranched (C_1-C_6)alkylene, except when R^{15} is $-NR^{17}R^{18}$ or Ar^2-N-linked to L, in which case L is branched or unbranched (C_2-C_6)alkylene, and when L is methylene or ethylene, L may optionally be substituted with gem-ethano or with 1 to 2 fluoro substituents, and when R^{15} is Ph^2, Ar^2, or a saturated heterocycle, L may alternatively, optionally be substituted with a substituent selected from the group consisting of hydroxy, cyano, $-SCF_3$, (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents, (C_1-C_6)alkoxycarbonyl optionally further substituted with 1 to 6 fluoro substituents, (C_1-C_6)alkylcarbonyloxy optionally further substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl-(C_0-C_3)alkyl-O-, (C_3-C_7)cycloalkyl-(C_0-C_3)alkyl-O-C(O)-, and (C_3-C_7)cycloalkyl-(C_0-C_3)alkyl-C(O)-O-;

R^{16} is hydrogen, (C_1-C_6)alkyl optionally substituted with 1 to 6 fluoro substituents, (C_1-C_6)alkylcarbonyl, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-C(O)-, Ph^1-(C_0-C_3)alkyl, Ph^1-(C_0-C_3)alkyl-C(O)-, Ar^2-(C_0-C_3)alkyl, or Ar^2-(C_0-C_3)alkyl-C(O)-,

R^{17} is (C_1-C_4)alkyl optionally substituted with 1 to 6 fluoro substituents, *t*-butylsulfonyl, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-C(O)-, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-sulfonyl, Ph^1-(C_0-C_3)alkyl, Ph^1-(C_0-C_3)alkyl-C(O)-, Ph^1-(C_0-C_3)alkylsulfonyl, Ar^2-(C_0-C_3)alkyl, Ar^2-(C_0-C_3)alkyl-C(O)-, Ar^2-(C_0-C_3)alkylsulfonyl, $R^{19}OC(O)$-, or $R^{20}R^{21}NC(O)$-;

R^{18} is hydrogen or (C_1-C_4)alkyl optionally substituted with 1 to 6 fluoro substituents, or R^{17} and R^{18}, taken together with the nitrogen atom to which they are attached form Het^1 where Het^1 is substituted with oxo- on a carbon atom adjacent to the ring nitrogen atom, or

R^{17} and R^{18}, taken together with the nitrogen atom to which they are attached, form an aromatic heterocycle selected from the group consisting of pyrolyl, pyrazolyl, imidazolyl, 1,2,3-triazolyl, and 1,2,4-triazolyl,

said aromatic heterocycle optionally being substituted with 1 to 2 halo substituents, or substituted with 1 to 2 (C_1-C_4)alkyl substituents optionally further substituted with 1 to 3 fluoro substituents, or mono-substituted with fluoro, nitro, cyano, $-SCF_3$, or (C_1-C_4)alkoxy optionally further substituted with 1 to 3 fluoro substituents, and optionally further substituted with a (C_1-C_4)alkyl substituent optionally further substituted with 1 to 3 fluoro substituents;

R^{19} is (C_1-C_6)alkyl optionally substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, Ar^2-(C_0-C_3)alkyl, or Ph^1-(C_0-C_3)alkyl,

R^{20} is (C_1-C_6)alkyl optionally substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, Ar^2-(C_0-C_3)alkyl, or Ph^1-(C_0-C_3)alkyl,

R^{21} is hydrogen or (C_1-C_4)alkyl optionally substituted with 1 to 6 fluoro substituents, or R^{20} and R^{21}, taken together with the nitrogen atom to which they are attached, form Het^1;

R^{22} is (C_1-C_6)alkyl optionally substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, R^{23}-O-, Ph^1-(C_0-C_3)alkyl, Ar^2-(C_0-C_3)alkyl, or $R^{32}R^{33}N$-;

R^{23} is (C_1-C_6)alkyl optionally substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, Ph^1-(C_0-C_3)alkyl, or Ar^2-(C_0-C_3)alkyl;

R^{24} is (C_1-C_6)alkoxy(C_2-C_5)alkyl optionally substituted with 1 to 6 fluoro substituents, (C_1-C_6)alkylthio(C_2-C_5)alkyl optionally substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl(C_0-C_1)alkyl-O-(C_1-C_3)alkyl, (C_3-C_7)cycloalkyl(C_0-C_1)alkyl-S-(C_1-C_3)alkyl, phenyl(C_1-C_3) *n*-alkyl, Ph^2-(C_1-C_3)-*n*-alkyl, $Ar^2(C_0-C_3)$ *n*-alkyl, phenyl(C_0-C_1)alkyl-O-(C_1-C_3)alkyl, phenyl(C_0-C_1)alkyl-S-(C_1-C_3)alkyl, Ph^1-(C_0-C_1)alkyl-C(O)NH-(C_2-C_4)alkyl, Ph^1-(C_0-C_1)alkyl-NH-C(O)NH-(C_2-C_4)alkyl, pyridyl-(C_0-C_1)alkyl-C(O)NH-(C_2-C_4)alkyl, pyridyl-(C_0-C_1)alkyl-NH-C(O)NH-(C_2-C_4)alkyl, or $Ar^3(C_1-C_2)$alkyl,

where Ar^3 is a bi-cyclic moiety selected from a group consisting of indanyl, indolyl, dihydrobenzofuranyl, benzofuranyl, benzothiophenyl, benzoxazolyl, benzothiazolyl, benzo[1,3]dioxolyl, naphthyl, dihydrobenzopyranyl, quinolinyl, isoquinolinyl, and benzo[1,2,3]thiadiazolyl,

said Ar^3 optionally being substituted with (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, phenyl(C_0-C_1)alkyl optionally further substituted with 1 to 6 fluoro substituents, or substituted with (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, or substituted with 1-3 substituents independently selected from the group consisting of halo, oxo, methyl, and $-CF_3$,

said phenyl(C_1-C_3) *n*-alkyl, Ph^2-(C_1-C_3) *n*-alkyl, or $Ar^2(C_0-C_3)$ *n*-alkyl optionally being substituted on the *n*-alkyl moiety when present with (C_1-C_3)alkyl, dimethyl, gem-ethano, 1 to 2 fluoro substituents, or (C_1-C_6)alkyl-C(O)-,

said $Ar^2(C_0-C_3)$ *n*-alkyl being alternatively optionally substituted with a substituent selected from the group consisting of (C_3-C_7)cycloalkyl-(C_0-C_3)alkyl, Het^1-(C_0-C_3)alkyl, pyridyl-(C_0-C_3)alkyl, phenyl-

(C_0-C_3)alkyl, pyridyl-(C_0-C_3)alkyl-NH-, phenyl-(C_0-C_3)alkyl-NH-, (C_1-C_6)alkyl-S-, and (C_3-C_7)cycloalkyl-(C_0-C_3)alkyl-S-, and optionally further substituted with one methyl, -CF_3, cyano, or -SCF_3 substituent, or with 1 to 2 halo substituents,

said pyridyl-(C_0-C_3)alkyl and phenyl-(C_0-C_3)alkyl optionally being further substituted with 1-3 substituents independently selected from halo, -CH_3, -OCH_3, -CF_3, -OCF_3, -CN, and -SCF_3, and

said Ph^2-(C_1-C_3) *n*-alkyl and Ar^2(C_0-C_3) *n*-alkyl where Ar^2 is pyridyl, also optionally being substituted on the phenyl or Ar^2 moiety, respectively, with phenyl-CH=CH- or phenyl-C≡C-,

said phenyl-CH=CH- or phenyl-C≡C- being optionally further substituted with 1 to 3 substituents independently selected from the group consisting of halo, cyano, -SCF_3, (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, and (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents, and

said Ar^2(C_0-C_3) *n*-alkyl where Ar^2 is pyridyl, alternatively, optionally being substituted with (C_1-C_6)alkyl-C(O)- or $R^{28}R^{29}N$-C(O)-, and optionally further substituted with one methyl, -CF_3, cyano, or -SCF_3 substituent, or with 1 to 2 halo substituents,

said phenyl(C_0-C_1)alkyl-O-(C_1-C_3)alkyl, or phenyl(C_0-C_1)alkyl-S-(C_1-C_3)alkyl optionally being substituted on the phenyl moiety with (C_1-C_2)-$S(O)_2$-, or with 1 to 5 independently selected halo substituents, or with 1 to 3 substituents independently selected from the group consisting of halo, cyano, –SCF_3, (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, and (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents, and

said pyridyl-(C_0-C_1)alkyl-C(O)NH-(C_2-C_4)alkyl and pyridyl-(C_0-C_1)alkyl-NH-C(O)NH-(C_2-C_4)alkyl optionally being substituted on the pyridyl moiety with methyl, -CF_3, or 1 to 3 halo substituents;

R^{25} is hydrogen, (C_1-C_3)alkyl optionally substituted with 1 to 6 fluoro substituents, or allyl;

R^{26} is hydrogen, (C_1-C_6)alkyl optionally substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl;

R^{27} is hydrogen or (C_1-C_4)alkyl optionally substituted with 1 to 6 fluoro substituents, or R^{26} and R^{27}, taken together with the nitrogen atom to which they are attached, form Het^1;

R^{28} is (C_1-C_6)alkyl optionally substituted with 1 to 6 fluoro substituents, (C_3-C_8)cycloalkyl(C_0-C_3)alkyl, tetrahydropyran-3-yl(C_0-C_3)alkyl, tetrahydropyran-4-yl(C_0-C_3)alkyl, tetrahydrofuranyl(C_0-C_3)alkyl, Ph^1-(C_0-C_2) *n*-alkyl, or Ar^2-(C_0-C_2) *n*-alkyl,

said Ph^1-(C_0-C_2) *n*-alkyl and Ar^2-(C_0-C_2) *n*-alkyl optionally being substituted on the alkyl moiety when present with (C_1-C_3)alkyl, dimethyl, or gem-ethano;

R^{29} is hydrogen or (C_1-C_3)alkyl;

R^{30} is hydrogen, (C_1-C_6)alkyl optionally substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, Ph^1-(C_0-C_3)alkyl, or $Ar^2(C_0-C_3)$alkyl,

R^{31} is hydrogen or (C_1-C_6)alkyl optionally substituted with 1 to 6 fluoro substituents, or R^{30} and R^{31}, taken together with the nitrogen atom to which they are attached, form Het^1,

said Het^1 also optionally being substituted with phenyl optionally further substituted with 1 to 3 halo substituents;

R^{32} and R^{33} are each independently hydrogen or (C_1-C_6)alkyl optionally substituted with 1 to 6 fluoro substituents, or R^{32} and R^{33}, taken together with the nitrogen atom to which they are attached, form Het^1, or R^{32} is $Ph^1(C_0-C_1)$alkyl provided that R^{33} is hydrogen;

Ar^1 is an aromatic heterocycle substituent selected from the group consisting of furanyl, thiophenyl, thiazolyl, oxazolyl, isoxazolyl, pyridyl, and pyridazinyl, any of which may optionally be substituted with 1 to 3 substituents independently selected from the group consisting of halo, (C_1-C_3)alkyl, (C_1-C_3)alkoxy, $-CF_3$, $-O-CF_3$, nitro, cyano, and trifluoromethylthio;

Ar^2 is an aromatic heterocycle substituent selected from the group consisting of pyrrolyl, pyrazolyl, imidazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, furanyl, oxazolyl, isoxazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, thiophenyl, thiazolyl, isothiazolyl, 1,2,3-thiadiazolyl, 1,3,4-thiadiazolyl, pyridyl, pyridazinyl, and benzimidazolyl, any of which may optionally be substituted with 1 to 3 substituents independently selected from the group consisting of halo, cyano, $-SCF_3$, (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, and (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents, and wherein pyridyl and pyridazinyl may also optionally be substituted with (C_1-C_6)alkylamino optionally further substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, or (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-amino;

Het^1 is a saturated, nitrogen-containing heterocycle substituent selected from the group consisting of azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl, morpholinyl, thiomorpholinyl, homomorpholinyl, and homothiomorpholinyl, any of which may optionally be substituted with (C_1-C_6)alkyl or with 2 methyl substituents;

Het^2 is a saturated, oxygen-containing heterocycle substituent selected from the group consisting of tetrahydrofuranyl and tetrahydropyranyl, any of which may optionally be substituted with (C_1-C_6)alkyl or with 2 methyl substituents; .

Ph^1 is phenyl optionally substituted with 1 to 5 independently selected halo substituents, or with 1 to 3 substituents independently selected from the group consisting of halo, cyano, $-SCF_3$, (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, and (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents;

Ph^2 is phenyl substituted with:

a) 1 to 5 independently selected halo substituents; or

b) 1 to 3 substituents independently selected from the group consisting of halo, cyano, $-SCF_3$, nitro, hydroxy, (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, and (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents; or

c) 0, 1, or 2 substituents independently selected from the group consisting of halo, cyano, -SCF_3, methyl, -CF_3, methoxy, -OCF_3, nitro, and hydroxy, together with one substituent selected from the group consisting of

i) (C_1-C_{10})alkyl optionally further substituted with 1 to 6 fluoro substituents or mono-substituted with hydroxy, (C_1-C_6)alkoxy, (C_3-C_7)cycloalkyl(C_0-C_3)alkyloxy, Het^2-(C_0-C_3)alkyloxy, Ph^1-(C_0-C_3)alkyloxy,

ii) (C_1-C_{10})alkoxy-(C_0-C_3)alkyl optionally further substituted with 1 to 6 fluoro substituents, and optionally further substituted with hydroxy,

iii) (C_1-C_6)alkyl-C(O)-(C_0-C_3)alkyl optionally further substituted with 1 to 6 fluoro substituents,

iv) carboxy,

v) (C_1-C_6)alkoxycarbonyl optionally further substituted with 1 to 6 fluoro substituents,

vi) (C_1-C_6)alkyl-C(O)-(C_0-C_3)-O- optionally further substituted with 1 to 6 fluoro substituents,

vii) (C_1-C_6)alkylthio-(C_0-C_3)alkyl optionally further substituted with 1 to 6 fluoro substituents,

viii) (C_1-C_6)alkylsulfinyl-(C_0-C_3)alkyl optionally further substituted with 1 to 6 fluoro substituents,

ix) (C_1-C_6)alkylsulfonyl-(C_0-C_3)alkyl optionally further substituted with 1 to 6 fluoro substituents,

x) (C_1-C_6)alkylsulfonyl-(C_0-C_3)alkyl-O- optionally further substituted with 1 to 6 fluoro substituents,

xi) (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, optionally further substituted on the cycloalkyl with 1 to 4 substituents selected from methyl and fluoro,

xii) (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-O-, optionally further substituted on the cycloalkyl with 1 to 4 substituents selected from methyl and fluoro,

xiii) (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-C(O)-,

xiv) (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-O-C(O)-,

xv) (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-S-,

xvi) (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-S(O)-,

xvii) (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-S$(O)_2$-,

xviii) Ph^1-(C_0-C_3)alkyl, optionally substituted on the alkyl moisty with 1 to 2 fluoro substituents,

xix) Ph^1-(C_0-C_3)alkyl-O-, optionally substituted on the alkyl moiety with 1 to 2 fluoro substituents

xx) Ph^1-(C_0-C_3)alkyl-C(O)-,

xxi) Ph^1-(C_0-C_3)alkyl-O-C(O)-,

xxii) Ph^1-(C_0-C_3)alkyl-C(O)-(C_0-C_3)alkyl-O-,

xxiii) Ph^1-(C_0-C_3)alkylthio,

xxiv) Ph^1-(C_0-C_3)alkylsulfinyl,

xxv) Ph^1-(C_0-C_3)alkylsulfonyl,

xxvi) $Ar^2(C_0-C_3)$alkyl,

xxvii) $Ar^2(C_0-C_3)$alkyl-O-

xxviii) Ar^2-(C_0-C_3)alkyl-S-,

xxix) $Ar^2(C_0-C_3)$alkyl-C(O)-,

xxx) $Ar^2(C_0-C_3)$alkyl-C(S)-,

xxxi) Ar^2-(C_0-C_3)alkylsulfinyl,

xxxii) Ar^2-(C_0-C_3)alkylsulfonyl,

xxxiii) $Het^1(C_0-C_3)$alkyl-C(O)- optionally substituted on the Het^1 moiety with Ph^1,

xxxiv) $Het^1(C_0-C_3)$alkyl-C(S)- optionally substituted on the Het^1 moiety with Ph^1,

xxxv) N-linked Het^1-C(O)-(C_0-C_3)alkyl-O-,

xxxvi) Het^2-(C_0-C_3)alkyloxy,

xxxvii) $R^{26}R^{27}N$-,

xxxviii) $R^{28}R^{29}$-N-(C_1-C_3)alkoxy,

xxxix) $R^{28}R^{29}N$-C(O)-,

xl) $R^{28}R^{29}N$-C(O)-(C_1-C_3)alkyl-O-,

xli) $R^{28}R^{29}N$-C(S)-,

xiii) $R^{30}R^{31}N\text{-}S(O)_2\text{-}$,

xiiii) HON=C(CH_3)-, and

xiv) HON=C(Ph^1)-,

or a pharmaceutically acceptable salt thereof, subject to the following provisos:

a) no more than two of R^1, R^2, R^3, R^4, and R^5 may be other than hydrogen;

b) when R^2 is methyl, then R^1, R^3, R^4, and R^5 are each hydrogen;

c) when R^3 is methyl, then R^2 and R^4 are each hydrogen;

d) when R^3 is methyl, R^7 and R^8 are each –OH, and R^1, R^2, R^4, R^5, and R^9 are each hydrogen, then R^6 is other than cyclohexylthio, furanylthio, or phenylthio; and

e) When R^{12} is Ar^2-(C_1-C_3)alkyl, then R^7 is other than hydrogen or R^9 is other than chloro.

2. A compound according to Claim 1 wherein R^7 is selected from halo, -CN, and CF_3.

3. A compound according to either Claim 1 or Claim 2 wherein R^7 is chloro.

4. A compound according to any one of Claims 1 to 3 wherein R^6 is -C≡C-R^{10}.

5. A compound according to any one of Claims 1 to 3 wherein R^6 is -O-R^{12}.

6. A compound according to any one of Claims 1 to 3 wherein R^6 is -S-R^{14}.

7. A compound according to Claim 6 wherein R^6 is -S-L-R^{15}.

8. A compound according to Claim 7 wherein R^{15} is Ph^2 or Ar^2.

9. A compound according to any one of Claims 1 to 3 wherein R^6 is -$NR^{24}R^{25}$.

10. A compound according to Claim 9 wherein R^{24} is Ph^2-(C_1-C_3) *n*-alkyl-.

11. A compound according to Claim 9 wherein R^{24} is Ar^2-(C_1-C_3) *n*-alkyl-.

12. A Compound according to any one of Claims 9 to 11 wherein R^{25} is hydrogen.

13. A compound according to any one of Claims 1 to 12 wherein R^9 is hydrogen, halo or (C_1-C_3)alkoxy.

14. A compound according to any one of Claims 1 to 12 wherein R^9 is hydrogen.

15. A compound according to any one of Claims 1 to 14 wherein R^1, R^2, R^3, R^4, R^5, and R^6, are each hydrogen.

16. A pharmaceutical composition comprising a compound according to any one of Claims 1 to 15 as an active ingredient in association with a pharmaceutically acceptable carrier, diluent or excipient.

17. A compound according to any one of Claims 1 to 15 for use in therapy.

18. A method for the treatment of obesity in mammals, comprising administering to a mammal in need of such treatment an effective amount of a compound according to Claim 1.

19. The method of Claim 18, where the mammal is human.

20. A method for the treatment of obsessive compulsive disorder in mammals, comprising administering to a mammal in need of such treatment an effective amount of a compound according to Claim 1.

21. The method of Claim 20, where the mammal is human.

22. A method for the treatment of depression in mammals, comprising administering to a mammal in need of such treatment an effective amount of a compound according to Claim 1.

23. The method of Claim 22, where the mammal is human.

24. A method for the treatment of anxiety in mammals, comprising administering to a mammal in need of such treatment an effective amount of a compound according to Claim 1.

25. The method of Claim 24, where the mammal is human.

26. A compound according to any one of Claims 1 to 15 for use as a pharmaceutical.

27. A compound according to any one of Claims 1 to 15 for use in the treatment of obesity in mammals.

28. A compound according to any one of Claims 1 to 15 for use in the treatment of obsessive/compulsive disorder in mammals.

29. A compound according to any one of Claims 1 to 15 for use in the treatment of depression in mammals.

30. A compound according to any one of Claims 1 to 15 for use in the treatment of anxiety in mammals.

31. A compound according to any one of Claims 27-30, where the mammal is a human.

32. The use of a compound according to any one of Claims 1 to 15 in the manufacture of a medicament for the treatment of a disorder selected from obesity, hyperphagia, obsessive/compulsive disorder, depression, anxiety, substance abuse, sleep disorder, hot flashes, and/or hypogonadism.

33. The use of a compound according to any one of Claims 1 to 15 in the manufacture of a medicament for the treatment of a disorder selected from obesity, obsessive/compulsive disorders, anxiety, or depression.

34. A pharmaceutical composition adapted for the treatment of obesity comprising a compound according to any one of Claims 1 to 15 in combination with one or more pharmaceutically acceptable excipients, carriers, or diluents therefore.

35. A pharmaceutical composition adapted for the treatment of obsessive/compulsive disorders comprising a compound according to any one of Claims 1 to 15 in combination with one or more pharmaceutically acceptable excipients, carriers, or diluents therefore.

36. A pharmaceutical composition adapted for the treatment of depression comprising a compound according to any one of Claims 1 to 15 in combination with one or more pharmaceutically acceptable excipients, carriers, or diluents therefore.

37. A pharmaceutical composition adapted for the treatment of anxiety comprising a compound according to any one of Claims 1 to 15 in combination with one or more pharmaceutically acceptable excipients, carriers, or diluents therefore.

INTERNATIONAL SEARCH REPORT

Interna tl Application No
PCT/US2005/005418

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D223/16 C07D401/12 C07D417/12 C07D413/12 C07D403/12
C07D409/12 C07D405/12 C07D413/14 C07D417/06 C07D403/06
A61K31/55 A61P25/22 A61P25/24 A61P25/30 A61P3/04

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)
IPC 7 C07D A61K A61P

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, PAJ, 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.
X	WO 93/04686 A (SMITHKLINE BEECHAM CORPORATION) 18 March 1993 (1993-03-18) cited in the application page 11, line 3 - line 18 claim 6	1-37
X	US 4 265 890 A (HOLDEN ET AL) 5 May 1981 (1981-05-05) cited in the application example 19	1-15
Y	WO 93/03015 A (SMITHKLINE BEECHAM CORPORATION) 18 February 1993 (1993-02-18) cited in the application page 11, line 3 - line 18 claim 7	1-37
	-/—	

[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

* Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
18 May 2005	02/06/2005

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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	KILPATRICK, ANDREW T. ET AL: "The .alpha.2-adrenoceptor antagonist SK & F 104078 has high affinity for 5-HT1A and 5-HT2 receptors" EUROPEAN JOURNAL OF PHARMACOLOGY , 166(2), 315-18 CODEN: EJPHAZ; ISSN: 0014-2999, 1989, XP002328505 cited in the application abstract	1-37
A	DATABASE WPI Section Ch, Week 200274 Derwent Publications Ltd., London, GB; Class B02, AN 2002-691852 XP002328506 -& WO 02/074746 A1 (YAMANOUCHI PHARM CO LTD) 26 September 2002 (2002-09-26) cited in the application page 32; examples 75,76	1-37

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/005418

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

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

1. [X] Claims Nos.: 18-25
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 18-25 are directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. al Application No
PCT/US2005/005418

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
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2,3,4,5-TETRAHIDRO-1H-BENZO[d]AZEPINAS 6-SUBSTITUIDAS COMO AGONISTAS DEL RECEPTOR 5-HT_{2C}

El neurotransmisor de serotonina (5-hidroxitriptamina, 5-HT) tiene una farmacología rica que resulta de una población heterogénea de al menos siete clases de receptores. La serotonina clase 5-HT_{2C} se subdivide además en al menos tres subtipos, designados 5-HT_{2A}, 5-HT_{2B}, y 5-HT_{2C}. El receptor 5-HT_{2C} se ha aislado y caracterizado (JuliUs, et al., Patente E.U.A. No. 4,985,352), y ratones transgénicos que carecen del receptor 5-HT_{2C} se han reportado por mostrar ataques y un trastorno alimenticio que resulta en un consumo creciente de alimento (Julius et al., Patente E.U.A. No. 5,698,766). El receptor 5-HT_{2C} también se ha ligado a varios otros trastornos neurológicos que incluyen obesidad (Vickers et al., Psychopharmacology, 167:274-280 (2003)), hiperfagia (Tecott et al., Nature, 374: 542-546 (1995)), trastorno obsesivo compulsivo (Martin et al., Pharmacol. Biochem. Beba., 71:615 (2002); Chou-Green et al., Physiology & Behavior, 78:641-649 (2003)), depresión (Leysen, Kelder, Trends in Drug Research II, 29: 49-61 (1998)), ansiedad (Curr. Opin, Invest. Drugs 2(4), p. 317 (1993)), abuso de substancias, trastornos del dormir (Frank et al., Neuropsychopharmacology 27: 869-873 (2002)), bochornos (EP 1213017 A2), epilepsia (Upton et al., Eur. J. Pharmacol., 359:33 (1998); Fitzgerald, Ennis, Annual

Reports in Medicinal Chemistry, 37:21-30 (2002)), e hipogonadismo (Curr. Opin, Invest. Drugs 2(4), p. 317 (1993)).

Ciertos compuestos de 2,3,4,5-tetrahidro-1H-benzo[d]azepina substituidos se han descrito como terapéuticos útiles como por ejemplo:

La patente de E.U.A. 4,265,890 describe ciertos compuestos de 2,3,4,5-tetrahidro-1H-benzo[d]azepina substituidos como antagonistas del receptor dopaminérgico para usarse como antipsicóticos y antieméticos, entre otros.

La EP 0 285 287 describe ciertos compuestos de 2,3,4,5-tetrahidro-1H-benzo[d]azepina substituidos para usarse como agentes para tratar trastornos de movilidad gastrointestinal, entre otros.

La WO 93/03015 y WO 93/04686 describen ciertos compuestos de 2,3,4,5-tetrahidro-1H-benzo[d]azepina substituidos como agonistas del receptor alfa-adrenérgico para usarse como agentes para tratar la hipertensión y enfermedades cardiovasculares en los cuales los cambios en la resistencia vascular son deseables, entre otros.

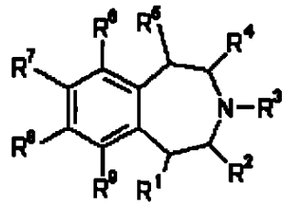
La WO 02/074746 A1 describe ciertos compuestos de 2,3,4,5-tetrahidro-1H-benzo[d]azepina substituidos como agonistas de 5-HT_{2C} para el tratamiento de hipogonadismo, obesidad, hiperfagia, ansiedad, depresión, trastornos del dormir, entre otros.

La WO 03/006466 A1 describe ciertos compuestos de hexahidroazepinoindol e indolina tricíclicos substituidos como ligandos 5-HT y consecuentemente su utilidad para tratar enfermedades donde la modulación de la actividad 5-HT se desea.

Los agonistas del receptor 5-HT_{2C} de alta afinidad proporcionarán terapéuticos útiles para el tratamiento de los trastornos asociados con el receptor 5-HT_{2C} arriba mencionado que incluyen obesidad, hiperfagia, trastorno obsesivo/compulsivo, depresión, ansiedad, abuso de substancias, trastorno del dormir, bochornos, e hipogonadismo. Los antagonistas del receptor 5-HT_{2C} de alta afinidad que también son selectivos para el receptor 5-HT_{2C}, proporcionarán tal beneficio terapéutico sin los eventos adversos indeseables asociados con las terapias actuales. La selectividad alcanzada por el receptor 5-HT_{2C}, particularmente como contra los receptores 5-HT_{2A} y 5-HT_{2B}, proporciona una dificultad en el diseño de agonistas 5-HT_{2C}. Los agonistas del receptor 5-HT_{2A} se han asociado con eventos adversos alucinógenos problemáticos. (Nelson et al., Naunyn-Schmiedeberg's Arch. Pharm., 359: 1-6 (1999)). Los agonistas del receptor 5-HT_{2B} se han asociado con los eventos adversos relacionados cardiovasculares, tales como valvulopatía. (V. Setola et al., Mol. Pharmacology, 63: 1223-1229 (2003), y referencias citadas en la presente).

Las referencias previas para compuestos de 2,3,4,5-tetrahidro-1H-benzo[d]azepina substituidos como terapéuticos potenciales han mencionado predominantemente sus usos como moduladores alfa adrenérgicos y/o dopaminérgicos. Los moduladores adrenérgicos se asocian frecuentemente con el tratamiento de enfermedades cardiovasculares (Frishman, Kotob, Journal of Clinical Pharmacology, 39: 7-16 (1999)). Los receptores dopaminérgicos son objetivos primarios en el tratamiento de esquizofrenia y enfermedad de Parkinson (Seeman, Van Tol, Trends in Pharmacological Sciences, 15: 264-270 (1994)). Se apreciará por aquellos expertos en la técnica que la selectividad, como contra estos y otros receptores fisiológicamente importantes, serán generalmente también características preferidas para terapéuticos para el tratamiento específico de trastornos asociados con 5-HT_{2C} como se describe arriba.

La presente invención proporciona compuestos agonistas 5-HT_{2C} selectivos de la Fórmula I:



I

donde:

R^1 es hidrógeno, fluoro, o alquilo (C_1-C_3);

R^2, R^3, y R^4 son cada uno independientemente hidrógeno, metilo, o etilo;

R^5 es hidrógeno, fluoro, metilo, o etilo;

R^6 es $-C\equiv C-R^{10}$, $-O-R^{12}$, $-S-R^{14}$, o $-NR^{24}R^{25}$;

R^7 es hidrógeno, halo, ciano, alquilo (C_1-C_6) opcionalmente substituido con 1 hasta 6 substituyentes de fluoro, alquenilo (C_2-C_6) opcionalmente substituido con 1 hasta 6 substituyentes de fluoro, cicloalquilo (C_3-C_7), alcoxi (C_1-C_6) opcionalmente substituido con 1 hasta 6 substituyentes de fluoro, alquiltio (C_1-C_6) opcionalmente substituido con 1 hasta 6 substituyentes de fluoro, Ph^1-alquilo (C_0-C_3), Ph^1-alquilo (C_0-C_3)-O-, o Ph^1-alquilo (C_0-C_3)-S-;

R^8 es hidrógeno, halo, ciano, o $-SCF_3$;

R^9 es hidrógeno, halo, ciano, $-CF_3$, $-SCF_3$, o alcoxi (C_1-C_3) opcionalmente substituido con 1 hasta 6 substituyentes de fluoro;

R^{10} es $-CF_3$, etilo substituido con 1 hasta 5 substituyentes de fluoro, alquilo (C_3-C_6) opcionalmente substituido con 1 hasta 6 substituyentes de fluoro, cicloalquilo (C_3-C_7)alquilo (C_0-C_3), Ar^1-alquilo (C_0-C_3), Ph^1-alquilo (C_0-C_3), o 3-alquilo (C_1-C_4)-2-oxo-imidazolidin-1-il-alquilo (C_1-C_3);

R^{12} es Ph^2-alquilo (C_1-C_3), Ar^2-alquilo (C_1-C_3), alquilo (C_1-C_6)-S-alquilo (C_2-C_6), cicloalquilo (C_3-C_7)-S-alquilo (C_2-C_6), fenil-S-alquilo (C_2-C_6), Ph^2-S-alquilo (C_2-C_6),

fenilcarbonil-alquilo (C_1-C_3), Ph^2-C(O)-alquilo (C_1-C_3), alcoxicarbonilo (C_1-C_6)alquilo (C_3-C_6), cicloalquilo (C_3-C_7)-OC(O)-alquilo (C_3-C_6), feniloxicarbonil-alquilo (C_3-C_6), Ph^2-OC(O)-alquilo (C_3-C_6), Ar^2-OC(O)-alquilo (C_3-C_6), cicloalquilo (C_3-C_7)-NH-C(O)-alquilo (C_2-C_4)-, Ph^1-NH-C(O)-alquilo (C_2-C_4)-, Ar^2-NH-C(O)-alquilo (C_2-C_4)-, o R^{13}-C(O)NH-alquilo (C_2-C_4);

R^{13} es cicloalquilo (C_3-C_7)alquilo (C_0-C_3), Ph^1, Ar^2, o alcoxi (C_1-C_3) opcionalmente substituido con 1 hasta 6 substituyentes de fluoro, Ph^1-NH- o Het^1 ligado a N;

R^{14} es Ar^2 el cual no se liga a N al átomo de azufre, Ph^2, R^{15}-L-, tetrahidrofuranilo, tetrahidropiranilo, o fenil-metilo substituido en la porción metilo con un substituyente seleccionado del grupo que consiste de alquilo (C_1-C_3)-n-substituido con hidroxi, alquilo (C_1-C_3)-O-alquilo (C_1-C_2)-n-, alquilo (C_1-C_3)-C(O)-alquilo (C_0-C_2)-n-, y alquilo (C_1-C_3)-O-C(O)-alquilo (C_0-C_2)-n-,

en donde cuando R^{14} es Ph^2 o Ar^2, en donde Ar^2 es piridilo, entonces R^{14} también puede, opcionalmente substituirse con fenil-CH=CH- o fenil-C≡C-,

el fenil-CH=CH- o fenil-C≡C- son además opcionalmente substituidos con 1 hasta 3 substituyentes independientemente seleccionados del grupo que consiste de halo, ciano, $-SCF_3$, alquilo (C_1-C_6) opcionalmente además substituido con 1 hasta 6 substituyentes de fluoro, y alcoxi (C_1-C_6) opcionalmente además substituido con 1 hasta 6 substituyentes de fluoro, y

en donde cuando Ar^2 es piridilo, el piridilo puede alternativamente, opcionalmente substituirse con $R^{28}R^{29}N-C(O)-$, y opcionalmente además substituido con un metilo, $-CF_3$, ciano, o substituyente $-SCF_3$, o con 1 hasta 2 substituyentes halo, y

en donde el tetrahidrofuranilo y tetrahidropiranilo pueden opcionalmente substituirse con un substituyente oxo, o con uno o 2 grupos independientemente seleccionados de metilo y $-CF_3$;

R^{15} es $-OR^{16}$, ciano, $-SCF_3$, Ph^2, Ar^2, quinolinilo, isoquinolinilo, cinolinilo, quinazolinilo, ftalimido, benzotiofenilo opcionalmente substituido en la posición 2 con fenilo o bencilo, benzotiazolilo opcionalmente substituido en la posición 2 con fenilo o bencilo, benzotiadiazolilo opcionalmente substituido con fenilo o bencilo, 2-oxo-dihidroindol-1-ilo opcionalmente substituido en la posición 3 con dimetilo gem o alquilo (C_1-C_6) opcionalmente además substituido con 1 hasta 6 substituyentes de fluoro, 2-oxo-dihidroindol-5-ilo opcionalmente substituido en la posición 3 con dimetilo gem o alquilo (C_1-C_6) opcionalmente además substituido con 1 hasta 6 substituyentes de fluoro, 2-oxo-imidazolidin-1-ilo opcionalmente substituido en la posición 3 con dimetilo gem o alquilo (C_1-C_6), opcionalmente además substituido con 1 hasta 6 substituyentes de fluoro, 2-oxo-tetrahidropirimidinilo opcionalmente substituido en la

posición 3 ó 4 con dimetilo gem o alquilo (C_1-C_6) opcionalmente además substituido con 1 hasta 6 substituyentes de fluoro, 2-oxo-tetrahidroquinolin-1-ilo opcionalmente substituido en la posición 3 con dimetilo gem o alquilo (C_1-C_6) opcionalmente además substituido con 1 hasta 6 substituyentes de fluoro, 2-oxo-dihidrobenzimidazol-1-ilo opcionalmente substituido en la posición 3 con dimetilo gem o alquilo (C_1-C_6) opcionalmente además substituido con 1 hasta 6 substituyentes de fluoro, $-NR^{17}R^{18}$, $-C(O)R^{22}$, o un heterocilo saturado seleccionado del grupo que consiste de pirrolidinilo, piperidinilo, morfolinilo, y tiomorfolinilo, tetrahidrofuranilo, y tetrahidropiranilo,

en donde Ph^2 y Ar^2 cuando Ar^2 es piridilo, también puede opcionalmente substituirse con fenil-CH=CH- o fenil-C≡C-,

el fenil-CH=CH- y fenil-C≡C- son además opcionalmente substituidos en la porción fenilo con 1 hasta 3 substituyentes independientemente seleccionados del grupo que consiste de halo, ciano, $-SCF_3$, alquilo (C_1-C_6) opcionalmente además substituido con 1 hasta 6 substituyentes de fluoro, y alcoxi (C_1-C_6) opcionalmente además substituido con 1 hasta 6 substituyentes de fluoro, y

en donde Ar^2 puede alternativamente, opcionalmente substituirse con un substituyente seleccionado del grupo que consiste de cicloalquilo (C_3-C_7)-alquilo (C_0-C_3), Het^1-alquilo (C_0-C_3), piridil-alquilo (C_0-C_3), y fenil-alquilo (C_0-C_3), y

opcionalmente además substituido con un substituyente metilo, $-CF_3$, ciano, o $-SCF_3$, o con 1 hasta 2 substituyentes halo,

el piridil-alquilo (C_0-C_3) y fenil-alquilo (C_0-C_3) opcionalmente son además substituidos con 1-3 substituyentes independientemente seleccionados de halo, $-CH_3$, $-OCH_3$, $-CF_3$, $-OCF_3$, -CN, y $-SCF_3$, y

en donde cuando Ar^2 es piridilo, el piridilo puede alternativamente, opcionalmente substituirse con $R^{28}R^{29}N$-C(O)-, o alquilo (C_1-C_6)-C(O)- opcionalmente substituido con 1 hasta 6 substituyentes de fluoro, y puede ser opcionalmente además substituido con un substituyente metilo, $-CF_3$, ciano, o $-SCF_3$, o con 1 hasta 2 substituyentes halo, y

en donde cuando Ar^2 es tiazolilo, el tiazolilo puede alternativamente, opcionalmente substituirse con cicloalquilo (C_3-C_7)-alquilo (C_0-C_3)-NH-, y

en donde el pirrolidinilo, piperidinilo, morfolinilo, y tiomorfolinilo es substituido con oxo- en un átomo de carbono adyacennte al átomo de nitrógeno en el anillo, o es N-substituido con un substituyente seleccionado del grupo que consiste de

alquilcarbonilo (C_1-C_6), alquilsulfonilo (C_1-C_6), cicloalquilo (C_3-C_7)alquilo (C_0-C_3)-C(O)-, cicloalquilo (C_3-C_7)alquilo (C_0-C_3)-$S(O)_2$-, Ph^1-alquilo (C_0-C_3)-C(O)-, y Ph^1-alquilo (C_0-C_3)-$S(O)_2$-, y

puede opcionalmente ser además substituido con 1 ó 2 substituyentes metilo o $-CF_3$, y cuando oxo substituido, puede opcionalmente ser además N substituido con un substituyente seleccionado del grupo que consiste de

alquilo (C_1-C_6) opcionalmente además substituido con 1 hasta 6 substituyentes de fluoro, cicloalquilo (C_3-C_7)alquilo (C_0-C_3), y Ph^1- alquilo (C_0-C_3), y

en donde tetrahidrofuranilo y tetrahidropiranilo pueden opcionalmente substituirse con un substituyente oxo, y/o con uno o 2 grupos independientemente seleccionados de metilo y $-CF_3$;

L es alquileno (C_1-C_6) ramificado o no ramificado, excepto cuando R^{15} es $-NR^{17}R^{18}$ o Ar^2-N-ligado a L, en tal caso L es alquileno (C_2-C_6) ramificado o no ramificado, y cuando L es metileno o etileno, L puede opcionalmente substituirse con etano gem o con 1 hasta 2 substituyentes de fluoro, y cuando R^{15} es Ph^2, Ar^2, o un heterocilo saturado, L puede alternativamente, opcionalmente substituirse con un substituyente seleccionado del grupo que consiste de hidroxi ciano, $-SCF_3$, alcoxi (C_1-C_6) opcionalmente además substituido con 1 hasta 6 substituyentes de fluoro, alcoxicarbonilo (C_1-C_6) opcionalmente además substituido con 1 hasta 6 substituyentes de fluoro, alquilcarboniloxi (C_1-C_6) opcionalmente además substituido con 1 hasta 6 substituyentes de fluoro, cicloalquilo (C_3-C_7)-alquilo (C_0-C_3)-O-,

cicloalquilo (C_3-C_7)-alquilo (C_0-C_3)-O-C(O)-, y cicloalquilo (C_3-C_7)-alquilo (C_0-C_3)-C(O)-O-;

R^{16} es hidrógeno, alquilo (C_1-C_6) opcionalmente substituido con 1 hasta 6. substituyentes de fluoro, alquilcarbonilo (C_1-C_6), cicloalquilo (C_3-C_7)alquilo (C_0-C_3), cicloalquilo (C_3-C_7)alquilo (C_0-C_3)-C(O)-, Ph^1-alquilo (C_0-C_3), Ph^1-alquilo (C_0-C_3)-C(O)-, Ar^2-alquilo (C_0-C_3), o Ar^2-alquilo (C_0-C_3)-C(O)-,

R^{17} es alquilo (C_1-C_4) opcionalmente substituido con 1 hasta 6 substituyentes de fluoro, t-butilsulfonilo, cicloalquilo (C_3-C_7)alquilo (C_0-C_3)-C(O)-, cicloalquilo (C_3-C_7)alquilo (C_0-C_3)-sulfonilo, Ph^1-alquilo (C_0-C_3), Ph^1-alquilo (C_0-C_3)-C(O)-, Ph^1-alquilsulfornilo (C_0-C_3), Ar^2-alquilo (C_0-C_3), Ar^2-alquilo (C_0-C_3)-C(O)-, Ar^2-alquilsulfornilo (C_0-C_3), $R^{19}OC(O)$-, o $R^{20}R^{21}NC(O)$-;

R^{18} es hidrógeno o alquilo (C_1-C_4) opcionalmente substituido con 1 hasta 6 substituyentes de fluoro, o R^{17} y R^{18}, tomados juntos con el átomo de nitrógeno al cual se enlazan forman Het^1 donde Het^1 es substituido con oxo- en un átomo de carbono adyacente al átomo de nitrógeno en el anillo, o

R^{17} y R^{18}, tomados juntos con el átomo de nitrógeno al cual se enlazan, forman un heterociclo aromático seleccionado del grupo que consiste de pirolilo, pirazolilo, imidazolilo, 1,2,3-triazolilo, y 1,2,4-triazolilo,

el heterociclo aromático opcionalmente es substituido con 1 hasta 2 substituyentes halo, o substituido con 1 hasta 2 substituyentes alquilo (C_1-C_4) opcionalmente además substituido con 1 hasta 3 substituyentes fluoro, o mono-substituido con fluoro, nitro, ciano, $-SCF_3$, o alcoxi (C_1-C_4) opcionalmente además substituido con 1 hasta 3 substituyentes fluoro, y opcionalmente además substituido con un substituyente alquilo (C_1-C_4) opcionalmente además substituido con 1 hasta 3 substituyentes fluoro;

R^{19} es alquilo (C_1-C_6) opcionalmente substituido con 1 hasta 6 substituyentes de fluoro, cicloalquilo (C_3-C_7)alquilo (C_0-C_3), Ar^2-alquilo (C_0-C_3), o Ph^1-alquilo (C_0-C_3),

R^{20} es alquilo (C_1-C_6) opcionalmente substituido con 1 hasta 6 substituyentes de fluoro, cicloalquilo (C_3-C_7)alquilo (C_0-C_3), Ar^2-alquilo (C_0-C_3), o Ph^1-alquilo (C_0-C_3),

R^{21} es hidrógeno o alquilo (C_1-C_4) opcionalmente substituido con 1 hasta 6 substituyentes de fluoro, o R^{20} y R^{21}, tomados juntos con el átomo de nitrógeno al cual se enlazan, forman Het^1;

R^{22} es alquilo (C_1-C_6) opcionalmente substituido con 1 hasta 6 substituyentes de fluoro, cicloalquilo (C_3-C_7)alquilo (C_0-C_3), R^{23}-O-, Ph^1-alquilo (C_0-C_3), Ar^2-alquilo (C_0-C_3), o $R^{32}R^{33}N$-;

R^{23} is (C_1-C_6)alquilo opcionalmente substituido con 1 hasta 6 substituyentes de fluoro, cicloalquilo (C_3-C_7)alquilo (C_0-C_3), Ph^1-alquilo (C_0-C_3), o Ar^2-alquilo (C_0-C_3);

R^{24} es alcoxi (C_1-C_6)alquilo (C_2-C_5) opcionalmente substituido con 1 hasta 6 substituyentes de fluoro, alquiltio (C_1-C_6)alquilo (C_2-C_5) opcionalmente substituido con 1 hasta 6 substituyentes de fluoro, cicloalquilo (C_3-C_7)alquilo (C_0-C_1)-O-alquilo (C_1-C_5), cicloalquilo (C_3-C_7)alquilo (C_0-C_1)-S-alquilo (C_1-C_5), fenilalquilo (C_1-C_3) n-, Ph^2-alquilo (C_1-C_3)-n-, Ar^2alquilo (C_0-C_3) n-, fenilalquilo (C_0-C_1)-O-alquilo (C_1-C_5), fenilalquilo (C_0-C_1)-S-alquilo (C_1-C_5), Ph^1-alquilo (C_0-C_1)-C(O)NH-alquilo (C_2-C_4), Ph^1-alquilo (C_0-C_1)-NH-C(O)NH-alquilo (C_2-C_4), piridil-alquilo (C_0-C_1)-C(O)NH-alquilo (C_2-C_4), piridil-alquilo (C_0-C_1)-NH-C(O)NH-alquilo (C_2-C_4), o Ar^3alquilo (C_1-C_2),

donde Ar^3 es una porción bíciclica seleccionada de un grupo que consiste de indanilo, indolilo, dihidrobenzofuranilo, benzofuranilo, benzotiofenilo, benzoxazolilo, benzotiazolilo, benzo[1,3]dioxolilo, naftilo, dihidrobenzopiranilo, quinolinilo, isoquinolinilo, y benzo[1,2,3]tiadiazolilo,

el Ar^3 opcionalmente es substituido con alquilo (C_1-C_6) opcionalmente además substituido con 1 hasta 6 substituyentes de fluoro, fenilalquilo (C_0-C_1) opcionalmente además substituido con 1 hasta 6 substituyentes de fluoro, o

substituido con cicloalquilo (C_3-C_7)alquilo (C_0-C_3), o substituido con 1-3 substituyentes independientemente seleccionado del grupo que consiste de halo, oxo, metilo, y $-CF_3$,

el fenil n-alquilo (C_1-C_3), Ph^2- n-alquilo (C_1-C_3), o Ar^2 n-alquilo (C_0-C_3) opcionalmente son substituidos en la porción n-alquilo cuando se presenta con alquilo (C_1-C_3), dimetilo, etano gem, 1 hasta 2 substituyentes fluoro, o alquilo (C_1-C_6)-C(O)-,

el Ar^2 n-alquilo (C_0-C_3) es alternativamente opcionalmente substituido con un substituyente seleccionado del grupo que consiste de cicloalquilo (C_3-C_7)-alquilo (C_0-C_3), Het^1-alquilo (C_0-C_3), piridil-alquilo (C_0-C_3), fenil-alquilo (C_0-C_3), piridil-alquilo (C_0-C_3)-NH-, fenil-alquilo (C_0-C_3)-NH-, alquilo (C_1-C_6)-S-, y cicloalquilo (C_3-C_7)-alquilo (C_0-C_3)-S-, y opcionalmente además substituido con un substituyente metilo, $-CF_3$, ciano, o $-SCF_3$, o con 1 hasta 2 substituyentes halo,

el piridil-alquilo (C_0-C_3) y fenil-alquilo (C_0-C_3) opcionalmente son además substituidos con 1-3 substituyentes independientemente seleccionados de halo, $-CH_3$, $-OCH_3$, $-CF_3$, $-OCF_3$, -CN, y $-SCF_3$, y

el Ph^2-n-alquilo (C_1-C_3) y Ar^2 n-alquilo (C_0-C_3) donde Ar^2 es piridilo, opcionalmente también son substituidos en la

porción fenilo o Ar^2, respectivamente, con fenil-CH=CH- o fenil-C≡C-,

el fenil-CH=CH- o fenil-C≡C- son además opcionalmente substituidos con 1 hasta 3 substituyentes independientemente seleccionado del grupo que consiste de halo, ciano, $-SCF_3$, alquilo (C_1-C_6) opcionalmente además substituido con 1 hasta 6 substituyentes de fluoro, y alcoxi (C_1-C_6) opcionalmente además substituido con 1 hasta 6 substituyentes de fluoro, y

el Ar^2 n-alquilo (C_0-C_3) donde Ar^2 es piridilo, alternativamente, opcionalmente es substituido con alquilo (C_1-C_6)-C(O)- o $R^{28}R^{29}N$-C(O)-, y opcionalmente además substituido con un substituyente metilo, $-CF_3$, ciano, o $-SCF_3$, o con 1 hasta 2 substituyentes halo,

el fenilalquilo (C_0-C_1)-O-alquilo (C_1-C_5), o fenilalquilo (C_0-C_1)-S-alquilo (C_1-C_5) opcionalmente son substituidos en la porción fenilo con (C_1-C_2)-$S(O)_2$-, o con 1 hasta 5 independientemente seleccionados de substituyentes halo, o con 1 hasta 3 substituyentes independientemente seleccionado del grupo que consiste de halo, ciano, $-SCF_3$, alquilo (C_1-C_6) opcionalmente además substituido con 1 hasta 6 substituyentes de fluoro, y alcoxi (C_1-C_6) opcionalmente además substituido con 1 hasta 6 substituyentes de fluoro, y

el piridil-alquilo (C_0-C_1)-C(O)NH-alquilo (C_2-C_4) y piridil-alquilo (C_0-C_1)-NH-C(O)NH-alquilo (C_2-C_4)

opcionalmente son substituidos en la porción piridilo con metilo, $-CF_3$, o 1 hasta 3 substituyentes halo;

R^{25} es hidrógeno, alquilo (C_1-C_3) opcionalmente substituido con 1 hasta 6 substituyentes de fluoro, o alilo;

R^{26} es hidrógeno, alquilo (C_1-C_6) opcionalmente substituido con 1 hasta 6 substituyentes de fluoro, cicloalquilo (C_3-C_7)alquilo (C_0-C_3);

R^{27} es hidrógeno o alquilo (C_1-C_4) opcionalmente substituido con 1 hasta 6 substituyentes de fluoro, o R^{26} y R^{27}, tomados juntos con el átomo de nitrógeno al cual se enlazan, forman Het^1;

R^{28} es alquilo (C_1-C_8) opcionalmente substituido con 1 hasta 6 substituyentes de fluoro, cicloalquilo (C_3-C_8)alquilo (C_0-C_3), tetrahidropiran-3-il alquilo (C_0-C_3), tetrahidropiran-4-il alquilo (C_0-C_3), tetrahidrofuranil alquilo (C_0-C_3), Ph^1- n-alquilo (C_0-C_2), o Ar^2-n-alquilo (C_0-C_2),

el Ph^1-n-alquilo (C_0-C_2) y Ar^2-n-alquilo (C_0-C_2) opcionalmente son substituidos en la porción alquilo cuando se presenta con alquilo (C_1-C_3), dimetilo, o etano gem;

R^{29} es hidrógeno o alquilo (C_1-C_3);

R^{30} es hidrógeno, alquilo (C_1-C_6) opcionalmente substituido con 1 hasta 6 substituyentes de fluoro, cicloalquilo (C_3-C_7)alquilo (C_0-C_3), Ph^1-alquilo (C_0-C_3), o Ar^2alquilo (C_0-C_3),

R^{31} es hidrógeno o alquilo (C_1-C_6) opcionalmente substituido con 1 hasta 6 substituyentes de fluoro, o R^{30} y R^{31}, tomados juntos con el átomo de nitrógeno al cual se enlazan, forman Het^1,

el Het^1 opcionalmente también es substituido con fenilo opcionalmente además substituido con 1 hasta 3 substituyentes halo;

R^{32} y R^{33} son cada uno independientemente hidrógeno o alquilo (C_1-C_6) opcionalmente substituido con 1 hasta 6 substituyentes de fluoro, o R^{32} y R^{33}, tomados juntos con el átomo de nitrógeno al cual se enlazan, forman Het^1, o R^{32} es Ph^1alquilo (C_0-C_1) con la condición de que R^{33} es hidrógeno;

Ar^1 es un substituyente heterociclo aromático seleccionado del grupo que consiste de furanilo, tiofenilo, tiazolilo, oxazolilo, isoxazolilo, piridilo, y piridazinilo, cualquiera de los cuales puede opcionalmente substituirse con 1 hasta 3 substituyentes independientemente seleccionado del grupo que consiste de halo, alquilo (C_1-C_3), alcoxi (C_1-C_3), -CF_3, -O-CF_3, nitro, ciano, y trifluorometiltio;

Ar^2 es un substituyente heterociclo aromático seleccionado del grupo que consiste de pirrolilo, pirazolilo, imidazolilo, 1,2,3-triazolilo, 1,2,4-triazolilo, furanilo, oxazolilo, isoxazolilo, 1,2,3-oxadiazolilo, 1,2,4-oxadiazolilo, 1,3,4-oxadiazolilo, tiofenilo, tiazolilo, isotiazolilo, 1,2,3-tiadiazolilo, 1,3,4-tiadiazolilo,

piridilo, piridazinilo, y benzimidazolilo, cualquiera de los cuales puede opcionalmente substituirse con 1 hasta 3 substituyentes independientemente seleccionado del grupo que consiste de halo, ciano, $-SCF_3$, alquilo (C_1-C_6) opcionalmente además substituido con 1 hasta 6 substituyentes de fluoro, y alcoxi (C_1-C_6) opcionalmente además substituido con 1 hasta 6 substituyentes de fluoro, y en donde piridilo y piridazinilo también puede opcionalmente substituirse con alquilamino (C_1-C_6) opcionalmente además substituido con 1 hasta 6 substituyentes de fluoro, cicloalquilo (C_3-C_7)alquilo (C_0-C_3), o cicloalquilo (C_3-C_7)alquilo (C_0-C_3)-amino;

Het^1 es un substituyente heterociclo que contiene nitrógeno saturado seleccionado del grupo que consiste de azetidinilo, pirrolidinilo, piperidinilo, homopiperidinilo, morfolinilo, tiomorfolinilo, homomorfolinilo, y homotiomorfolinilo, cualquiera de los cuales puede opcionalmente substituirse con alquilo (C_1-C_6) o con 2 substituyentes metilo;

Het^2 es un substituyente heterociclo que contiene oxígeno saturado, seleccionado del grupo que consiste de tetrahidrofuranilo y tetrahidropiranilo, cualquiera de los cuales puede opcionalmente substituirse con alquilo (C_1-C_6) o con 2 substituyentes metilo;

Ph^1 es fenilo opcionalmente substituido con 1 hasta 5 independientemente seleccionado de substituyentes halo, o con

1 hasta 3 substituyentes independientemente seleccionado del grupo que consiste de halo, ciano, $-SCF_3$, alquilo (C_1-C_6) opcionalmente además substituido con 1 hasta 6 substituyentes de fluoro, y alcoxi (C_1-C_6) opcionalmente además substituido con 1 hasta 6 substituyentes de fluoro;

Ph^2 es fenilo substituido con:

a) 1 hasta 5 independientemente seleccionados de substituyentes halo; o

b) 1 hasta 3 substituyentes independientemente seleccionado del grupo que consiste de halo, ciano, $-SCF_3$, nitro, hidroxi, alquilo (C_1-C_6) opcionalmente además substituido con 1 hasta 6 substituyentes de fluoro, y alcoxi (C_1-C_6) opcionalmente además substituido con 1 hasta 6 substituyentes de fluoro; o

c) 0, 1, 6 2 substituyentes independientemente seleccionado del grupo que consiste de halo, ciano, $-SCF_3$, metilo, $-CF_3$, metoxi, $-OCF_3$, nitro, e hidroxi junto con un substituyente seleccionado del grupo que consiste de

i) alquilo (C_1-C_{10}) opcionalmente además substituido con 1 hasta 6 substituyentes de fluoro o mono-substituido con hidroxi, alcoxi (C_1-C_6), cicloalquilo (C_3-C_7)alquiloxi (C_0-C_3), Het^2-alquiloxi (C_0-C_3), Ph^1-alquiloxi (C_0-C_3),

ii) alcoxi (C_1-C_{10})-alquilo (C_0-C_3) opcionalmente además substituido con 1 hasta 6 substituyentes de fluoro, y opcionalmente además substituido con hidroxi,

iii) alquilo (C_1-C_6)-C(O)-alquilo (C_0-C_5) opcionalmente además substituido con 1 hasta 6 substituyentes de fluoro,

iv) carboxi,

v) alcoxicarbonilo (C_1-C_6) opcionalmente además substituido con 1 hasta 6 substituyentes de fluoro,

vi) alquilo (C_1-C_6)-C(O)-(C_0-C_3)-O- opcionalmente además substituido con 1 hasta 6 substituyentes de fluoro,

vii) alquiltio (C_1-C_6)-alquilo (C_0-C_5) opcionalmente además substituido con 1 hasta 6 substituyentes de fluoro,

viii) alquilsulfinilo (C_1-C_6)-alquilo (C_0-C_5) opcionalmente además substituido con 1 hasta 6 substituyentes de fluoro,

ix) alquilsulfonilo (C_1-C_6)-alquilo (C_0-C_5) opcionalmente además substituido con 1 hasta 6 substituyentes de fluoro,

x) alquilsulfonilo (C_1-C_6)-alquilo (C_0-C_3)-O- opcionalmente además substituido con 1 hasta 6 substituyentes de fluoro,

xi) cicloalquilo (C_3-C_7)alquilo (C_0-C_3), opcionalmente además substituido en el cicloalquilo con 1 hasta 4 substituyentes seleccionados de metilo y fluoro,

xii) cicloalquilo (C_3-C_7) alquilo (C_0-C_3)-O-, opcionalmente además substituido en el cicloalquilo con 1 hasta 4 substituyentes seleccionados de metilo y fluoro,

xiii) cicloalquilo (C_3-C_7) alquilo (C_0-C_3)-C(O)-,

xiv) cicloalquilo (C_3-C_7) alquilo (C_0-C_3)-O-C(O)-,

xv) cicloalquilo (C_3-C_7) alquilo (C_0-C_3)-S-,

xvi) cicloalquilo (C_3-C_7) alquilo (C_0-C_3)-S(O)-,

xvii) cicloalquilo (C_3-C_7) alquilo (C_0-C_3)-$S(O)_2$-,

xviii) Ph^1-alquilo (C_0-C_3), opcionalmente substituido en la porción alquilo con 1 hasta 2 substituyentes de fluoro,

xix) Ph^1-alquilo (C_0-C_3)-O-, opcionalmente substituido en la porción alquilo con 1 hasta 2 substituyentes de fluoro

xx) Ph^1-alquilo (C_0-C_3)-C(O)-,

xxi) Ph^1-alquilo (C_0-C_3)-O-C(O)-,

xxii) Ph^1-alquilo (C_0-C_3)-C(O)-alquilo (C_0-C_3)-O-,

xxiii) Ph^1-alquiltio (C_0-C_3),

xxiv) Ph^1-alquilsulfinilo (C_0-C_3),

xxv) Ph^1-alquilsulfonilo (C_0-C_3),

xxvi) Ar^2 alquilo (C_0-C_3),

xxvii) Ar^2 alquilo (C_0-C_3)-O-

xxviii) Ar^2-alquilo (C_0-C_3)-S-,

xxix) Ar^2 alquilo (C_0-C_3)-C(O)-,

xxx) Ar^2 alquilo (C_0-C_3)-C(S)-,

xxxi) Ar^2-alquilsulfinilo (C_0-C_3),

xxxii) Ar^2-(C_0-C_3)alquilsulfonilo,

xxxiii) Het^1 alquilo (C_0-C_3)-C(O)- opcionalmente substituido en la porción Het^1 con Ph^1,

xxxiv) Het^1 alquilo (C_0-C_3)-C(S)- opcionalmente substituido en la porción Het^1 con Ph^1,

xxxv) N ligado a Het^1-C(O)-alquilo (C_0-C_3)-O-,

xxxvi) Het^2-alquiloxi (C_0-C_3),

xxxvii) $R^{26}R^{27}N$-,

xxxviii) $R^{28}R^{29}$-N-alcoxi (C_1-C_3),

xxxix) $R^{28}R^{29}N$-C(O)-,

xl) $R^{28}R^{29}N$-C(O)-alquilo (C_1-C_3)-O-,

xli) $R^{28}R^{29}N$-C(S)-,

xlii) $R^{30}R^{31}N$-$S(O)_2$-,

xliii) $HON=C(CH_3)$-, y

xliv) $HON=C(Ph^1)$-,

o una sal farmacéuticamente aceptable del mismo, se somete a las siguientes condiciones:

a) no más que 2 de R^1, R^2, R^3, R^4, y R^5 pueden ser diferente a hidrógeno;

b) cuando R^2 es metilo, entonces R^1, R^3, R^4, y R^5 son cada uno hidrógeno;

c) cuando R^3 es metilo, entonces R^2 y R^4 son cada uno hidrógeno;

d) cuando R^3 es metilo, R^7 y R^8 son cada uno -OH, y R^1, R^2, R^4, R^5, y R^9 son cada uno hidrógeno, entonces R^6 es diferente a ciclohexiltio, furaniltio, o feniltio; y

e) cuando R^{12} es Ar^2-alquilo (C_1-C_3), entonces R^7 es diferente a hidrógeno o R^9 es diferente a cloro.

Esta invención tambien proporciona composiciones farmacéuticas que comprenden un compuesto de la Fórmula I, o una sal farmacéuticamente aceptable del mismo, en asociación con un portador, diluyente o excipiente farmacéuticamente aceptable.

En otro aspecto de la presente invención, se proporciona un método para incrementar la activación del receptor 5-HT_{2c} en mamífero que comprende administrar a un mamífero que necesita de tal activación una cantidad efectiva de un compuesto de la Fórmula I, o una sal farmacéuticamente aceptable del mismo.

La presente invención también proporciona un método para tratar la obesidad en mamíferos que comprende administrar a un mamífero que necesita de tal tratamiento una cantidad efectiva de un compuesto de la Fórmula I, o una sal farmacéuticamente aceptable del mismo.

La presente invención tambien proporciona un método para tratar el trastorno obsesivo/compulsivo en mamíferos que comprende administrar a un mamifero que necesite de tal tratamiento una cantidad efectiva de un compuesto de la Fórmula I, o una sal farmacéuticamente aceptable del mismo.

Adicionalmente, la presente invención proporciona un método para tratar depresión en mamíferos que comprende administrar a un mamífero que necesite de tal tratamiento una cantidad efectiva de un compuesto de la Fórmula I, o una sal farmacéuticamente aceptable del mismo.

Adicionalmente, la presente invención proporciona un método para tratar ansiedad en mamíferos que comprende administrar a un mamífero que necesite de tal tratamiento una cantidad efectiva de un compuesto de la Fórmula I, o una sal farmacéuticamente aceptable del mismo.

En modalidades preferidas de los métodos anteriores para el tratamiento utilizando un compuesto de la Fórmula, o una sal farmacéuticamente aceptable del mismo, el mamífero es un humano.

En otro aspecto de la presente invención, se proporciona un compuesto de la Fórmula I para uso en selectivamente para incrementar la activación del receptor 5-HT_{2C} y/o para uso en el tratamiento de una variedad de trastornos asociados con reducción de la activación de los receptores 5-HT_{2C}. Las modalidades preferidas de este aspecto de la invención

incluyen un compuesto de la Fórmula I para uso en el tratamiento de obesidad, hiperfagia, trastorno obsesivo/compulsivo, depresión, ansiedad, abuso de substancias, trastorno del dormir, bochornos, y/o hipogonadismo. Particularmente las modalides preferidas de este aspecto de la invención incluye el tratamiento de obesidad, trastorno obsesivo/compulsivo, depresión, y/o ansiedad.

En otro aspecto de la presente invención, se proporciona el uso de uno o más compuestos de la Fórmula I en la manufactura de un medicamento para la activación de los receptores $5\text{-}HT_{2C}$ en un mamífero. En modalidades preferidas de este aspecto de la invención, se proporciona el uso de uno o más compuestos de la Fórmula I en la manufactura de un medicamento para el tratamiento de obesidad, hiperfagia, trastorno obsesivo/compulsivo, depresión, ansiedad, abuso de sustancia, trastorno del dormir, bochornos, y/o hipogonadismo. Particularmente las modalidades preferidas de este aspecto de la invención incluyen el uso de uno o más compuestos de la Fórmula I en la manufactura de medicamentos para el tratamiento de obesidad, trastorno obsesivo/compulsivo, depresión, y/o ansiedad.

Adicionalmente, la presente invención proporciona una formulación farmacéutica adaptada para el tratamiento de

obesidad, o para el tratamiento de trastorno obsesivo/compulsivo, o para el tratamiento de depresión, o para el tratamiento de ansiedad, cada uno de los cuales comprende un compuesto de la Fórmula I en asociación con un portador, diluyente o excipiente farmacéuticamente aceptable.

En aquellos casos donde los trastornos que pueden tratarse por agonistas $5\text{-}HT_{2c}$ son conocidos por clasificaciones establecidas y aceptadas, sus clasificaciones se pueden encontrar en diversas fuentes. Por ejemplo, en la actualidad, la cuarta edición del Diagnostic and Statistical Manual of Mental Disorders (DSM-IV™) (1994, American Psychiatric Association, Washington, D.C.), proporciona una herramienta de diagnóstico para identificar muchos de los trastornos descritos en la presente. También, la Clasificación Internacional de Enfermedades, décima revisión (ICD-10), proporciona clasificaciones para muchos de los trastornos descritos en la presente. El técnico experimentado reconocerá que son nomenclaturas, nosologías y sistemas de clasificación para trastornos descritos en la presente, incluyendo aquellos como se describen en la DSM-IV y ICD-10, y que la terminología y sistemas de clasificación se desarrolla con progresos científicos médicos.

Los términos químicos generales usados a lo largo tienen sus significados usuales. Por ejemplo, el término

"alquilo" e refiere a un grupo hidrocarburo ramificado o no ramificado saturado. El término "n-alquilo" se refiere a un grupo alquilo no ramificado. A modo de ilustración, pero sin limitación, el término "alquilo (C_1-C_2)" se refiere a metilo y etilo. El término "alquilo n-(C_1-C_3)" se refiere a metilo, etilo, y propilo. El término "alquilo (C_1-C_3)" se refiere a metilo, etilo, propilo, e isopropilo. El término "alquilo (C_1-C_4) n-" se refiere a metilo, etilo, n-propilo, y n-butilo. El término "alquilo (C_1-C_4)" se refiere a metilo, etilo, propilo, isopropilo, n-butilo, isobutilo, sec-butilo, y tert-butilo. El término "alquilo (C_1-C_6)" se refiere a todos los grupos ramificados y no ramificados que tiene desde uno hasta 6 átomos de carbono. El término "alquilo (C_3-C_6)" se refiere a todos los grupos alquilo ramificados y no ramificados tiene desde 3 hasta 6 átomos de carbono. El término "alquilo (C_2-C_6)" se refiere a todos los grupos alquilo ramificados y no ramificados que tienen desde 2 hasta 6 átomos de carbono.

Alquilo (C_x-C_y) también puede usarse en conjunto con otros substituyentes para indicar un ligador hidrocarburo ramificado o no ramificado saturado para el substituyente, donde x e y indican el rango de átomos de carbono permitidos en la porción ligadora. A modo de ilustración, pero sin limitación, -alquilo (C_0-C_1) se refiere a un enlace sencillo o una porción ligadora metileno; -alquilo (C_0-C_2) se refiere a

un enlace sencillo, porción ligadora de metileno, metil-metileno, o etileno; alquilo -(C_0-C_3) además incluye trimetileno, alfa- o beta-metil etileno, o etil metileno. -alquilo (C_1-C_2), -alquilo (C_1-C_3), -alquilo (C_1-C_4), y -alquilo (C_1-C_6) se refiere a ligadores alquileno ramificados o no ramificados que tienen desde 1 hasta 2, 3, 4, ó 6 carbonos, respectivamente.

El término "alquenilo" se refiere a un grupo hidrocarburo ramificado o no ramificado insaturado. A modo de ilustración, pero sin limitación, el término "alquenilo (C_2-C_6)" se refiere a un grupo hidrocarburo ramificado o no ramificado que tiene desde 2 hasta 6 átomos de carbono y 1 o más enlaces dobles carbono-carbono. Alilo significa una porción propil-2-en-1-ilo (CH_2=CH-CH_2-).

El término "cicloalquilo (C_3-C_7)" se refiere a ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo y cicloheptilo. Cicloalquilalquilo se refiere a una porción cicloalquilo ligada a través de un ligador alquileno ramificado o no ramificado, como por ejemplo, pero sin limitación, -CH_2-, -CH_2CH_2-, -CH(CH_3)-, -$CH_2CH_2CH_2$-, -CH_2CH(CH_3)-, -CH(CH_3)CH_2-, -CH(CH_2CH_3)-, y similares. Cicloalquilo (C_3-C_7) alquilo (C_0-$C_{1,\ 2\ o\ 3}$), se refiere a ligadroes cicloalquilos a través de un enlace sencillo (esto es alquilo C_0-) o un ligador alquileno. Cada grupo alquilo,

cicloalquilo, y cicloalquilalquilo puede ser opcionalmente substituido como se proporciona para la presente.

Los términos "alcoxi", "feniloxi", "sulfoniloxi", y "carboniloxi" se refiere a un grupo alquilo, grupo fenilo, grupo sulfonilo, o grupo carbonilo, respectivamente, esto es enlazado a través de un átomo de oxígeno.

Los términos "alquiltio", "trifluorometiltio", "cicloalquiltio" ("ciclohexiltio"), "feniltio", y "furaniltio" se refiere a un grupo alquilo, grupo trifluorometilo, grupo cicloalquilo (ciclohexilo), grupo fenilo, o grupo furanilo, respectivamente, esto es enlazado a través de un átomo de azufre.

Los términos "alquilcarbonilo", "alcoxicarbonilo", "fenilcarbonilo", y "feniloxicarbonilo", se refiere a un grupo alquilo, alcoxi, fenilo, o feniloxi enlazado a través de una porción carbonilo.

El término "alquilcarboniloxi" se refiere a un grupo alquilcarbonilo enlazado a través de un átomo de oxígeno.

Los términos "alquilsulfinilo (C_1-C_6)", "Ph^1-alquilsulfinilo (C_0-C_3)", y "Ar^2-alquilsulfinilo (C_0-C_3)", se refiere a un alquilo, Ph^1-alquilo (C_0-C_3), o Ar^2-alquilo (C_0-C_3), respectivamente, un grupo enlazado a través de una porción sulfinilo (-SO-).

Los términos "alquilsulfonilo" (t-butilsulfonilo), "cicloalquilsulfonilo (C_3-C_7)", "fenilsulfonilo",

"Ph^1-alquilsulfonilo (C_0-C_3)", y "Ar^2-alquilsulfonilo (C_0-C_3)", se refiere a un grupo alquilo (t-butilo), cicloalquilo (C_3-C_7), fenilo, Ph^1-alquilo (C_0-C_3), o Ar^2-alquilo (C_0-C_3) enlazado a través de una porción sulfonilo (-SO_2-).

El término "fenilamino" se refiere a un grupo fenilo enlazado a través de un átomo de nitrógeno.

El término "ligado a N" significa que la porción referida se liga a través de su átomo de nitrógeno, a modo de ilustración, pero sin limitación, Het^1 ligado a N significa la porción Het^1 se liga a través de un átomo de nitrógeno en el anillo de la porción Het^1, y Ar^2 ligado a N significa la porción Ar^2 se liga a través de un átomo de nitrógeno en el anillo de la porción Ar^2.

El término "halo" se refiere a fluoro, cloro, bromo, o yodo. Los grupos halo preferidos son fluoro, cloro, y bromo. Los grupos halo más preferidos son fluoro y cloro.

El término "heterociclo" se toma para significar un anillo de 4 hasta 7 miembros saturado o insaturado que contiene desde 1 hasta 3 heteroátomos seleccionados de nitrógeno, oxígeno, y azufre, el anillo opcionalmente es benzofusionado. Los heterociclos saturados ejemplares, para los proporsiots de la presente invención, incluyen azetidinilo, pirrolidinilo, piperidinilo, homopiperidinilo, tetrahidrofuranilo, tetrahidropiranilo, morfolinilo, tiomorfolinilo, piperazinilo, y similares. Los heterociclos

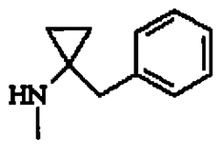
insatruados ejemplares incluyen, pero no se limitan a, pirrolilo, pirazolilo, imidazolilo, 1,2,3-triazolilo, 1,2,4-triazolilo, furanilo, oxazolilo, isoxazolilo, 1,2,3-oxadiazolilo, 1,2,4-oxadiazolilo, 1,3,4-oxadiazolilo, tiofenilo, tiazolilo, isotiazolilo, 1,2,3-tiadiazolilo, 1,2,4-tiadiazolilo, 1,3,4-tiadiazolilo, piridilo, piridazinilo, y similares. Los anillos heterocíclicos benzofusionados ejemplares incluyen, pero no se limitan a, indolilo, dihidroindolilo, indazolilo, benzisoxazolilo, benzimidazolilo, benzofuranilo, dihidrobenzofuranilo, benzoxazolilo, benzo[1,3]dioxolilo, benzotiofenilo, benzotiazolilo, quinolinilo, isoquinolinilo, benzopiranilo, dihidrobenzopiranilo, cinolinilo, quinazolinilo y similares, todos los cuales pueden ser opcionalmente substituidos como se proporciona para la presente, los cuales también incluye opcionalmente substituido en el anillo benceno cuando el heterociclo es benzofusionado.

En una modalidad, los heterociclos preferidos incluyen pirrolidinilo, piperidinilo, homopiperidinilo, tetrahidrofuranilo, tetrahidropiranilo, pirrolilo, pirazolilo, imidazolilo, furanilo, isoxazolilo, 1,2,4-oxadiazolilo, tiofenilo, tiazolilo, 1,2,3-tiadiazolilo, piridilo, piridazinilo, indolilo, dihidroindolilo, benzimidazolilo, benzofuranilo, dihidrobenzofuranilo, benzoxazolilo, benzo[1,3]dioxolilo, benzotiofenilo,

benzotiazolilo, quinolinilo, isoquinolinilo, y benzopiranilo, todos los cuales pueden ser opcionalmente substituidos como se proporciona para la presente.

Todavía en otra modalidad, los heterociclos preferidos incluyen piridilo, piridazinilo, y tiofenilo.

Los términos "gem", "geminal", o "geminato" se refiere a 2 substituyentes identicos enlazados a un átomo de carbono común, como por ejemplo, pero sin limitación, metilo gem, significa 2 grupos metilo enlazados a un átomo de carbono común, como para cada caso en un grupo 3,3-dimetiltetrahidrobenzofuranilo. Para los propósitos de esta solicitud, etano gem significa un substituyente etileno en donde ambos carbonos se enlazan al átomo de carbono del grupo substituido para formar una porción ciclopropilo, como por ejemplo, pero sin limitación, el substituyente etano en el grupo 2-fenil-(1,1-etano)etilamino a continuación:



Se entenderá que cuando una definición básica de substituyentes opcionalmente permitidos listados del grupo, y en lugar de otro grupo que también es opcionalmente substituido con otros substituyentes mencionados, luego aquellos otros substituyentes mencionados se pretende para

que se agreguen a la lista de substituyentes opcionalmente permitidos listados en la definición básica del grupo. Inversamente, si en lugar de que otro grupo es para ser alternativamente, opcionalmente substituido con otros substituyentes mencionados, entonces aquellos otros substituyentes mencionados se pretenden para reemplazar la lista de substituyentes opcionalmente permitidos mencionados de la definición básica del substituyente. Por ejemplo, pero sin limitación, Ar^2 tiene una definición básica que menciona que cualquiera de los grupos heteroaromáticos listados pueden "opcionalmente substituirse con 1 hasta 3 substituyentes independientemente seleccionado del grupo que consiste de halo, ciano, $-SCF_3$, alquilo (C_1-C_6) opcionalmente además substituido con 1 hasta 6 substituyentes de fluoro, y alcoxi (C_1-C_6) opcionalmente además substituido con 1 hasta 6 substituyentes de fluoro, y en donde piridilo y piridazinilo también puede opcionalmente substituirse con alquiloamino (C_1-C_6) opcionalmente además substituido con 1 hasta 6 substituyentes de fluoro, cicloalquilo (C_3-C_7) alquilo (C_0-C_3), o cicloalquilo (C_3-C_7) alquilo (C_0-C_3)-amino." Esto se entenderá que significa que cualquiera de los grupos heteroaromáticos listados puede opcionalmente substituirse con [1 hasta 3 substituyentes independientemente seleccionado del grupo que consiste de

halo, ciano, $-SCF_3$, alquilo (C_1-C_6) opcionalmente además substituido con 1 hasta 6 substituyentes de fluoro, y alcoxi (C_1-C_6) opcionalmente además substituido con 1 hasta 6 substituyentes de fluoro], y que cuando Ar^2 se seleccionan para ser piridilo o piridazinilo, la lista de substituyentes se seleccionan para los 1 hasta 3 substituyentes se expanden también para incluir [alquilamino (C_1-C_6) opcionalmente además substituido con 1 hasta 6 substituyentes de fluoro, cicloalquilo (C_3-C_7) alquilo (C_0-C_3), y cicloalquilo (C_3-C_7) alquilo (C_0-C_3)-amino]. Similarmente, en la definición de R^{14}, la terminología "en donde . . . Ar^2, en donde Ar^2 es piridilo, entonde R^{14} también puede, opcionalmente substituirse con fenil-CH=CH- o fenil-C≡C- . . ." se entenderá que significa que la lista de substituyentes se seleccionan para los 1 hasta 3 substituyentes opcionalmente permitidos en Ar^2 = piridilo de nuevo se expanden también para que se incluyan [fenil-CH=CH- o fenil-C≡C- . . .]. Inversamente, después en la definición de R^{14}, la terminología "en donde cuando Ar^2 es piridilo, el piridilo puede alternativamente, opcionalmente substituirse con $R^{28}R^{29}N$-C(O)- y opcionalmente además substituido con un substituyente metilo, $-CF_3$, ciano, o $-SCF_3$, o con 1 hasta 2 substituyentes halo", se entenderá que significa que cuando R^{14} se selecciona para ser Ar^2 = piridilo, luego la lista de 1 hasta 3 independientemente

seleccionados de substituyentes opcionalmente permitidos en la definición básica de Ar^2 puede ser antecedido por "$R^{28}R^{29}N$-C(O)- y opcionalmente además substituido con un substituyente metilo, $-CF_3$, ciano, o $-SCF_3$, o con 1 hasta 2 substituyentes halo."

El término "grupo protector amino" como se usa en esta especificación se refiere a un substituyente comúnmente empleado para bloquear o proteger la funcionalidad amino mientras reacciona con otros grupos funcionales en el compuesto. Ejemplos de tales grupos protectores amino incluyen el grupo formilo, el grupo tritilo, el grupo acetilo, el grupo tricloroacetilo, el grupo trifluoroacetilo, los grupos cloroacetilo, bromoacetilo, y yodoacetilo, grupos bloqueadores de tipo carbamoilo tales como benciloxicarbonilo, 9-fluorenilmetoxicarbonilo ("FMOC"), t-butoxicarbonilo (t-BOC), y grupos protectores amino similares. Las especies de grupo protector amino empleados no son críticos de manera que como el grupo amino derivado es estable a las condiciones de reacciones posteriores en otras posiciones de la molécula y puede eliminarse en el punto apropiado sin disrupción del resto de la molécula. La selección y uso (adición y eliminación posterior) de grupos protectores amino es bien conocido dentro de la experiencia ordinaria dla técnica. Ejemplos adicionales de grupos referidos por los términos descritos por T. W. Greene and P.

G. M. Wuts, "Protective Groups in Organic Synthesis", 3rd edición, John Wiley and Sons, New York, NY, 1999, capítulo 7, referido de aquí en adelante como "Greene".

El término "farmacéutico" o "farmacéuticamente aceptable" cuando se usan en la presente como un adjetivo, significa substancialmente no tóxico y substancialmente no perjudiciales para el receptor.

Por "composición farmacéutica" significa además que el portador, solvente, excipientes y/o sales deben ser compatibles con el ingrediente activo de la composición (por ejemplo un compuesto de la Fórmula I). Se entenderá por aquellos de experiencia ordinaria en este arte que los términos "formulación farmacéutica" y "composición farmacéutica" son generalmente intercambiables, y que son usados para los propósitos de esta solicitud.

El término "cantidad efectiva" significa una cantidad de un compuesto de la Fórmula I la cual es capaz de activar los receptores 5-HT_{2c} y/o externos da un efecto farmacológico.

El término "solvente adecuado" se refiere a cualquier solvente, o mezcla de solventes, inertes a la reacción siguiente que suficientemente solubiliza los reactivos para proporcionar un medio dentro el cual para efecto e la reacción deseada.

Se entenderá que los compuestos de la presente invención pueden existir como estereoisómeros. Como tal, todos los

enantiómeros, diastereómeros, y mezclas de los mismos, se incluyen dentro del alcance de la presente invención. Donde las estereoquímicas específicas se identifican en esta solicitud, las designaciones Cahn-Prelog-Ingold de (R)- y (S)- y la designación cis y trans de la estereoquímica relativa se usan para referir a los isómeros específicos y la estereoquímica relativa. Las rotaciones ópticas conocidas se designan por (+) y (-) para dextrorotatorio y levorotatorio, respectivamente. Donde un compuesto químico se resuelve en sus isómeros, pero con configuraciones absolutas o rotaciones ópticas que no se determinan, los isómeros son arbitrariamente designados como isómero 1, isómero 2, etc. Mientras todos los enantiómeros, diastereómeros, y mezclas de los mismos, se contemplan dentro de la presente invención, en modalidades preferidas son enenatiómeros sencillos y diastereómeros sencillos.

Generalmente se entenderá por aquellos de experiencia en este arte, que los compuetos pretendidos para uso en composiciones farmacéuticas son rutinalmente, aunque no necesariamente, convertido a una forma de sal en esfuerzos para optimizar tales características como las propiedades de manejo, estabilidad, farmacocinéticas, y/o biodisponibilidad, etc. Los métodos para convertir un compuesto para dar una forma de sal son bien conocidos en la técnica (ver por ejemplo, Berge, S.M, Bighley, L.D., and

Monkhouse, D.C., J. Pharm. Sci., 66:1, (1977)). En que los compuestos de la presente invención son aminas y por lo tanto con base en lo natural, fácilmente reaccionan con una amplia variedad de ácidos orgánicos e inorgánicos farmacéuticamente aceptable para formar sales de adición ácida farmacéuticamente aceptables con ello. Tales sales también son modalidades de esta invención.

Los ácidos inorgánicos típicos usados para formar tales sales incluyen ácido clorhídrico, bromhídrico, yodhídrico, nítrico, sulfúrico, fosfórico, hipofosfórico, metafosfórico, pirofosfórico, y similares. Las sales derivadas de ácidos orgánicos, tales como ácidos alifáticos mono y dicarboxílicos, ácidos alcanoicos substituidos con fenilo, ácidos hidroxialcanoico e hidroxialcandioico, ácidos aromáticos, ácidos alifáticos y sulfónicos aromáticos, también pueden usarse. Tales sales farmacéuticamente aceptable así incluyen cloruro, bromuro, yoduro, nitrato, acetato, fenilacetato, trifluoroacetato, acrilato, ascorbato, benzoato, clorobenzoato, dinitrobenzoato, hidroxibenzoato, metoxibenzoato, metilbenzoato, o-acetoxibenzoato, isobutirato, fenilbutirato, α-hidroxibutirato, butino-1,4-dicarboxilato, hexino-1,4-dicarboxilato, caprato, caprilato, cinamato, citrato, formiato, fumarato, glicolato, heptanoato, hipurato, lactato, malato, maleato, hidroximaleato, malonato,

mandelato, nicotinato, isonicotinato, oxalato, ftalato, tereftalato, propiolato, propionato, fenilpropionato, salicilato, sebacato, succinato, suberato, bencensulfonato, p-bromobencensulfonato, clorobencensulfonato, etilsulfonato, 2-hidroxietilsulfonato, metilsulfonato (mesilato), naftalen-1-sulfonato, naftalen-2-sulfonato, naftalen-1,5-sulfonato, p-toluensulfonato, xilensulfonato, tartrato, y similares.

Es bien conocido que tales compuestos pueden formar sales en varias relaciones molares con el ácido para proporcionar, por ejemplo, la sal del hemi-ácido, mono-ácido, di-ácido, etc. En donde el procedimiento de la formación de sal, el ácido se agrega en una relación estequiométrica especifica, a menos que se analice de otra manera para confirmar, la sal se presume, pero no se conoce, para formar su relación molar. Los términos tales como "(ácido)$_x$" se entenderá que signifique que la relación molar de la sal formada no se conoce y no se puede presumir, como por ejemplo, pero sin limitación, $(HCl)_x$ y (ácido metansulfónico)$_x$.

Abreviaturas usadas en la presente se definen como sigue:

"2B-3 etanol" significa etanol desnaturalizado con tolueno.

"AIBN" significa 2,2'-azobisisobutironitrilo.

"Análisis calculado" o "Anal. Calcd" significa analisis elemental calculado.

"APCI" significa ionización química de presión atmosférica.

"p.e." significa punto de ebullición.

"BINAP" significa rac-2,2'-bis(difenilfosfino)-1,1'binaftilo.

"Boc" o "t-Boc" significa tert-butoxicarbonilo.

"salmuera" significa una solución de cloruro de sodio saturado.

"CV" significa valor calorífico de oxígeno.

"DBU" significa 1,8-diazabiciclo[5.4.0]undec-7-eno.

"DCE" significa 1,2-dicloroetano.

"DCM" significa diclorometano (esto es cloruro de metileno, CH_2Cl_2).

"DIBAL-H" significa hidruro de diisobutilaluminio.

"DIEA" significa N,N-diisopropiletilamina.

"DMAP" significa 4-(dimetilamino)piridina.

"DME" significa 1,2-dimetoxietano.

"DMEA" significa N,N-dimetiletilamina.

"DMF" significa N,N-dimetilformamida.

"DMSO" significa dimetilsulfoxido.

"DOI" significa (±)-1-(2,5-dimetoxi-4-[^{125}I]-yodofenil)-2-aminopropano.

"EDC" significa clorohidrato 1-[3-(dimetilamino)propil]-3-etilcarbodiimida.

"EDTA" significa ácido etilendiamintetraacético.

"EE" significa expeditura de energía.

"EtOAc" significa acetato de etilo.

"CG-EM" significa cromatografía en gas-espectrometría de masas.

"GDP" significa difosfato de guanosina.

"GTP" significa trifosfato de guanosina.

"GTPγ[^{35}S]" significa trifosfato de guanosina que tiene la terminal de fosfato substituida con ^{35}S en lugar de un oxígeno.

"HATU" significa O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio hexafluorofosfato.

"HMPA" significa hexametilfosforamida.

"HOBT" significa hidrato de 1-hidroxibenzotriazol.

"CLAR" significa cromatografía líquida de alta presión.

"EMAR" significa espectrometría de masas de alta resolución.

"ISPA" significa ensayo de proximidad de escintilación por inmunoadsorción.

"m-CPBA" significa ácido meta-cloroperoxibenzoico.

"pf" significa punto de fusión.

"Ms" en una estructura química que significa la porción metansulfonilo ($-SO_2CH_3$).

"EM (ES+)" significa espectroscopía de masas usando ionización por electrorocío.

"MTBE" significa éter metil t-butilo.

"NBS" significa N-bromosuccinimida.

"NMP" significa 1-metil-2-pirrolidinona.

"RMN" significa resonancia magnética nuclear.

"Pd/C" significa paladio en carbono activado.

"RQ" significa cociente respiratorio.

"cromatografía SCX" significa cromatografía en una columna o cartucho SCX.

"columna SCX" o "cartucho SCX", como se usa en la presente, se refiere a una columna de resina de intercambio de catión fuerte basado en sílice Varian Bond Elute o cartucho o equivalente desechable.

"Sudan III" significa 1-[(4-fenilazo)fenilazo]-2-naftalenol.

"Tf" en una estructura química significa la porción trifluorometansulfonilo ($-SO_2CF_3$).

"TFA" significa ácido trifluoroacético.

"THF" significa tetrahidrofurano.

"CCD" significa cromatografía de capa delgada.

Aunque todos los compuestos de la presente invención son úiltes como agonistas 5-HT_{2C}, ciertas clases se prefieren, como por ejemplo, compuestos que tienen cualquiera de las

siguientes selecciones enumeradas de substituyentes: compuestos en donde

1) R^7 es halo;

2) R^7 es cloro;

3) R^7 es alquilo (C_1-C_6) opcionalmente substituido con 1 hasta 6 substituyentes de fluoro;

4) R^7 es alquilo (C_1-C_3) opcionalmente substituido con 1 hasta 6 substituyentes de fluoro;

5) R^7 es $-CF_3$;

6) R^7 es alquenilo (C_3-C_6) opcionalmente substituido con 1 hasta 6 substituyentes de fluoro;

7) R^7 es alquenilo (C_3-C_6);

8) R^7 es ciano;

9) R^{1-5} son cada uno hidrógeno;

10) R^4 es metilo o etilo;

11) R^4 es metilo;

12) R^3 es metilo;

13) R^8 es hidrógeno;

14) R^9 is alcoxi (C_1-C_3);

15) R^9 es metoxi;

16) R^9 es halo;

17) R^9 es cloro;

18) R^6 es $-C\equiv C-R^{10}$;

19) R^{10} es Ph^1-alquilo (C_0-C_3);

20) R^{10} es Ph^1-alquilo (C_1-C_2);

21) R^{10} es Fenil alquilo (C_0-C_3);

22) R^{10} es cicloalquilo (C_3-C_7) alquilo (C_0-C_3);

23) R^{10} es cicloalquilmetilo (C_3-C_7);

24) R^{10} es alquilo (C_4-C_6);

25) R^{10} es alquilo (C_4-C_6) ramificado;

26) R^{10} es alquilo (C_1-C_6) substituido con 2-6 substituyentes fluoro;

27) R^{10} es Ar^1-alquilo (C_0-C_3);

28) R^{10} es Ar^1-alquilo (C_1-C_2);

29) R^6 es -O-R^{12};

30) R^{12} es Ph^2-alquilo (C_0-C_3);

31) R^{12} es Ph^2-alquilo (C_1-C_2);

32) R^{12} es Ph^2-alquilo (C_1-C_2) y Ph^2 es substituido con 1-3 substituyentes halo;

33) R^{12} es Ph^2-alquilo (C_1-C_2) y Ph^2 es substituido con 1-3 fluoro substituyentes;

34) R^{12} es Ph^2-alquilo (C_1-C_2) y Ph^2 es substituido con ciano;

35) R^{12} es Ph^2-alquilo (C_1-C_2) y Ph^2 es substituido con $R^{30}R^{31}N$-$S(O)_2$-;

36) R^{12} es Ph^2-alquilo (C_1-C_2), Ph^2 es substituido con $R^{30}R^{31}N$-$S(O)_2$-, R^{30} es alquilo (C_1-C_3) opcionalmente además substituido con 1-3 fluoro substituyentes y R^{31} es hidrógeno;

37) R^{12} es Ar^2-alquilo (C_0-C_3);

38) R^{12} es Ar^2-alquilo (C_1-C_2);

39) R^{12} es Ar^2-alquilo (C_1-C_2) y Ar^2 es piridilo, tiazolilo, oxazolilo, o pirazolilo, cada uno opcionalmente substituido con metilo;

40) R^{12} es benzazolil-alquilo (C_1-C_3);

41) R^{12} es Ph^2-C(O)-alquilo (C_1-C_3),

42) R^{12} es Ph^2-C(O)-alquilo (C_1-C_3) y Ph^2 es substituido con 1 a 3 substituyentes halo;

43) R^{12} es Ph^2-C(O)-alquilo (C_1-C_3) y Ph^2 es substituido con 1 hasta 3 substituyentes halofluoro;

44) R^{12} es Ph^1-$S(O)_2$-;

45) R^{12} es alquilo (C_1-C_6)-O-C(O)-alquilo (C_3-C_6);

46) R^{12} es alquilo (C_1-C_3)-O-C(O)-alquilo (C_3-C_6);

47) R^{12} es R^{13}-C(O)NH-alquilo (C_2-C_4);

48) R^{12} es R^{13}-C(O)NH-alquilo (C_2-C_4) y R^{13} es Ph^1;

49) R^{12} es R^{13}-C(O)NH-alquilo (C_2-C_4), R^{13} es Ph^1; substituido con 1 hasta 3 substituyentes halo;

50) R^{12} es R^{13}-C(O)NH-alquilo (C_2-C_4) y R^{13} es cicloalquilo (C_3-C_7);

51) R^{12} es R^{13}-C(O)NH-alquilo (C_2-C_4) y R^{13} es piridilo;

52) R^{12} es R^{13}-C(O)NH-alquilo (C_2-C_4) y R^{13} es alcoxi (C_1-C_3);

53) R^{12} es R^{13}-C(O)NH-alquilo (C_2-C_4) y R^{13} es cicloalquilo (C_3-C_7);

54) R^6 es -S-R^{14};

55) R^6 es -S-R^{14} y R^{14} es Ph^2;

56) R^6 es $-S-R^{14}$, R^{14} es Ph^2 substituido con 1 hasta 3 substituyentes halo;

57) R^6 es $-S-R^{14}$, R^{14} es Ph^2 substituido con ciano;

58) R^6 es $-S-R^{14}$, R^{14} es Ph^2; substituido con ciano y 1 hasta 2 substituyentes halo;

59) R^6 es $-S-R^{14}$ y R^{14} es Ar^2;

60) R^6 es $-S-R^{14}$, R^{14} es Ar^2, y Ar^2 es piridilo o piridazinilo opcionalmente substituido;

61) R^6 es $-S-R^{14}$, R^{14} es Ar^2, y Ar^2 es tiofenilo, tiazolilo, isotiazolilo, 1,2,3-tiadiazolilo, 1,3,4-tiadiazolilo opcionalmente substituido;

62) R^6 es $-S-R^{14}$ y R^{14} es tetrahidrofuranilo o tetrahidropiranilo;

63) R^6 es $-S-R^{14}$ y R^{14} es tetrahidrofuranilo o tetrahidropiranilo y el tetrahidrofuranilo o tetrahidropiranilo es substituido con oxo en un carbono adyacente al anillo de oxígeno;

64) R^6 es $-S-R^{14}$ y R^{14} es $R^{15}-L-$;

65) L es alquileno (C_1-C_2);

66) L es alquileno (C_2-C_3) ramificado;

67) L es metilo-metileno;

68) L es di-metil-metileno;

69) L es metil-etileno;

70) L es -di-metil-etileno gem ;

71) L es -etano-etileno gem;

72) R^{15} es Ph^2;

73) R^{15} es Ph^2 substituido con 1 hasta 3 substituyentes halo;

74) R^{15} es Ph^2 substituido con ciano;

75) R^{15} es Ph^2 substituido con alcoxi (C_1-C_6);

76) R^{15} es Ph^2 substituido con alcoxi (C_1-C_6) opcionalmente además substituido con 1 hasta 3 substituyentes fluoro;

77) R^{15} es Ph^2 substituido con alcoxi (C_1-C_6) alquilo (C_1-C_1);

78) R^{15} es Ph^2 substituido con alcoxi (C_1-C_6) alquilo (C_1-C_1) además substituido con 1 hasta 3 substituyentes fluoro;

79) R^{15} es Ph^2 substituido con alquiltio (C_1-C_6);

80) R^{15} es Ph^2 substituido con alquiltio (C_1-C_6) opcionalmente además substituido con 1 hasta 3 substituyentes fluoro;

81) R^{15} es Ph^2 substituido con alquiltio (C_1-C_6) alquilo (C_1-C_1);

82) R^{15} es Ph^2 substituido con alquiltio (C_1-C_6) alquilo (C_1-C_1) además substituido con 1 hasta 3 substituyentes fluoro;

83) R^{15} es Ph^2 substituido con cicloalquilo (C_3-C_7) alquilo (C_0-C_1);

84) R^{15} es Ph^2 substituido con alquilsulfonilo (C_1-C_6) alquilo (C_0-C_1) opcionalmente además substituido con 1 hasta 3 substituyentes fluoro;

85) R^{15} es Ph^2 substituido con alquilsulfinilo (C_1-C_6) alquilo (C_0-C_1) opcionalmente además substituido con 1 hasta 3 substituyentes fluoro;

86) R^{15} es Ph^2 substituido con Ph^1-alquilo (C_0-C_1)-sulfonilo;

87) R^{15} es Ph^2 substituido con Ph^1-alquilo (C_0-C_1);

88) R^{15} es Ph^2 substituido con $R^{26}R^{27}N$-;

89) R^{15} es Ph^2 substituido con Het^1;

90) R^{15} es Ph^2 substituido con alquilo (C_1-C_6)-C(O)- opcionalmente además substituido con 1 hasta 3 substituyentes fluoro;

91) R^{15} es Ph^2 substituido con alquilo (C_1-C_6)-O-C(O)- opcionalmente además substituido con 1 hasta 3 substituyentes fluoro;

92) R^{15} es Ph^2 substituido con Ph^1;

93) R^{15} es Ph^2 substituido con Ph^1 alquilo (C_0-C_3)-O-;

94) R^{15} es Ph^2 substituido con Ph^1 alquilo (C_0-C_3)-C(O)-;

95) R^{15} es Ph^2 substituido con Ph^1 alquilo (C_0-C_3)-C(O)-;

96) R^{15} es Ph^2 substituido con Ar^2 alquilo (C_0-C_3)-C(O)-;

97) R^{15} es Ph^2 substituido con Ar^2 alquilo (C_0-C_3)-C(O)- y Ar^2 es pirazolilo opcionalmente además substituido como se proporciona para Ar^2;

98) R^{15} es Ph^2 substituido con $R^{28}R^{29}N$-C(O)-;

99) R^{15} es Ph^2 substituido con $R^{28}R^{29}N$-C(O)- y R^{28} es alquilo (C_1-C_6);

100) R^{15} es Ph^2 substituido con $R^{28}R^{29}N$-C(O)- y R^{28} es cicloalquilo (C_3-C_7) alquilo (C_0-C_3);

101) R^{15} es Ph^2 substituido con $R^{28}R^{29}N$-C(O)- y R^{28} es Ph^1-alquilo (C_0-C_2)-n- opcionalmente substituido en la porción

alquilo cuando se presenta con alquilo (C_1-C_3), dimetilo, o -etano gem;

102) R^{15} es Ph^2 substituido con $R^{28}R^{29}N$-C(O)- y R^{28} es Ar^2-alquilo (C_0-C_2)-n- opcionalmente substituido en la porción alquilo cuando se presenta con alquilo (C_1-C_3), dimetilo, o -etano gem;

103) R^{15} es Ph^2 substituido con Het^1-C(O)-;

104) R^{15} es Ph^2 substituido con Het^1-C(O)- además substituido con Ph^1;

105) R^{15} es Ar^2;

106) R^{15} es Ar^2 además substituido con metilo;

107) R^{15} es Ar^2 además substituido con cicloalquilo (C_3-C_7) alquilo (C_0-C_2), Het^1, piridilo, o fenilo opcionalmente además substituido con metilo, $-CF_3$, ciano, $-SCF_3$, o con 1 hasta 3 substituyentes halo;

108) R^{15} es pirrolilo, pirazolilo, imidazolilo, 1,2,3-triazolilo, 1,2,4-triazolilo, furanilo, oxazolilo, isoxazolilo, 1,2,3-oxadiazolilo, 1,2,4-oxadiazolilo, 1,3,4-oxadiazolilo, tiofenilo, tiazolilo, isotiazolilo, 1,2,3-tiadiazolilo, o 1,3,4-tiadiazolilo, cualquiera de los cuales puede opcionalmente substituirse con 1 hasta 3 substituyentes seleccionado del grupo que consiste de halo, ciano, $-SCF_3$, alquilo (C_1-C_6) opcionalmente además substituido con 1 hasta 6 fluoro, y alcoxi (C_1-C_6) opcionalmente además substituido con 1 hasta 6 fluoro.

109) R^{15} es piridilo opcionalmente además substituido como se proporciona para Ar^2;

110) R^{15} es tetrahidrofuranilo o tetrahidropiranilo, ya sea opcionalmente son substituidos con un substituyente oxo, o con uno o 2 grupos seleccionados independientemente de metilo y $-CF_3$;

111) R^{15} es tetrahidrofuranilo o tetrahidropiranilo, son substituidos con un substituyente oxo, y opcionalmente son además substituidos con uno o 2 grupos seleccionados independientemente de metilo y $-CF_3$;

112) R^{15}-L- es pirid-2-il-metilo;

113) R^{15}-L- es pirid-3-il-metilo;

114) R^{15}-L- es pirid-2-il-$CH(CH_3)$-;

115) R^{15}-L- es pirid-3-il-$CH(CH_3)$-;

116) R^{15} es piridazinilo opcionalmente además substituido como se proporciona para Ar^2;

117) R^{15}-L- es piridazin-2-il-metilo;

118) R^{15}-L- es piridazin-3-il-metilo;

119) R^{15}-L- es piridazin-2-il-$CH(CH_3)$-;

120) R^{15}-L- es piridazin-3-il-$CH(CH_3)$-;

121) R^{15} es piridilo además substituido con cicloalquilo (C_3-C_7) alquilo (C_0-C_2), Het^1, piridilo, o fenilo opcionalmente además substituido con metilo, $-CF_3$, ciano, $-SCF_3$, o con 1 hasta 3 substituyentes halo;

122) R^{15} es piridazinilo además substituido con cicloalquilo (C_3-C_7) alquilo (C_0-C_2), Het^1, piridilo, o fenilo opcionalmente además substituido con metilo, $-CF_3$, ciano, $-SCF_3$, o con 1 hasta 3 substituyentes halo;

123) R^{15} es R^{22}-C(O)-;

124) R^{15} es R^{22}-C(O)- y R^{22} es alquilo (C_1-C_6) opcionalmente substituido con 1 hasta 6 substituyentes de fluoro;

125) R^{15} es R^{22}-C(O)- y R^{22} es alcoxi (C_1-C_6) opcionalmente substituido con 1 hasta 6 substituyentes de fluoro;

126) R^{15} es R^{22}-C(O)- y R^{22} es cicloalquilo (C_3-C_7) alquilo (C_0-C_3);

127) R^{15} es R^{22}-C(O)- y R^{22} es cicloalquilo (C_3-C_7) alquilo (C_0-C_3)-O-;

128) R^{15} es R^{22}-C(O)- y R^{22} es Ph^1-alquilo (C_0-C_3);

129) R^{15} es R^{22}-C(O)- y R^{22} es Ph^1-alquilo (C_0-C_3)-O-;

130) R^{15} es R^{22}-C(O)- y R^{22} es Ar^2-alquilo (C_0-C_3);

131) R^{15} es R^{22}-C(O)- y R^{22} es Ar^2-alquilo (C_0-C_3)-O-;

132) R^{15} es R^{22}-C(O)- y R^{22} es $R^{32}R^{33}N$-;

133) R^{15} es ftalimido;

134) R^{15} es $R^{17}R^{18}N$-;

135) R^{15} es $R^{17}R^{18}N$- y R^{17} es alcoxi (C_1-C_3)-C(O)-;

136) R^{15} es $R^{17}R^{18}N$- y R^{17} es cicloalquilo (C_3-C_7) (C_0-C_2)-C(O)-;

137) R^{15} es $R^{17}R^{18}N$- y R^{17} es Ph^1-(C_0-C_2)-C(O)-;

138) R^{15} es $R^{17}R^{18}N$- y R^{17} es Ar^2-(C_0-C_2)-C(O)-;

139) R^{15} es $R^{16}O$-;

140) R^{15} es $R^{16}O$- y R^{16} es oalquilo (C_1-C_6)-C(O)-;

141) R^{15} es $R^{16}O$- y R^{16} es cicloalquilo (C_3-C_7) (C_0-C_2)-C(O)-;

142) R^6 es $R^{24}R^{25}N$- y R^{24} es alcoxi (C_1-C_6) alquilo (C_2-C_5) opcionalmente substituido con 1 hasta 6 substituyentes de fluoro;

143) R^6 es $R^{24}R^{25}N$- y R^{24} es alquiltio (C_1-C_6) alquilo (C_2-C_5) opcionalmente substituido con 1 hasta 6 substituyentes de fluoro;

144) R^6 es $R^{24}R^{25}N$- y R^{24} es cicloalquilo (C_3-C_7) alquilo (C_0-C_1)-O-alquilo (C_1-C_5);

145) R^6 es $R^{24}R^{25}N$- y R^{24} es cicloalquilo (C_3-C_7) alquilo (C_0-C_1)-S-alquilo (C_1-C_5);

146) R^6 es $R^{24}R^{25}N$- y R^{24} es fenil alquilo (C_1-C_3) n- opcionalmente substituido en la porción n-alquilo cuando se presenta con alquilo (C_1-C_3), dimetilo, o -etano gem;

147) R^6 es $R^{24}R^{25}N$- y R^{24} es Ph^2-n-alquilo (C_1-C_3) opcionalmente substituido en la porción n-alquilo cuando se presenta con alquilo (C_1-C_3), dimetilo, o -etano gem;

148) R^6 es $R^{24}R^{25}N$- y R^{24} es Ar^2 n-alquilo (C_0-C_3) opcionalmente substituido en la porción n-alquilo cuando se presenta con alquilo (C_1-C_3), dimetilo, o -etano gem;

149) R^6 es $R^{24}R^{25}N$- y R^{24} es Ar^2 n-alquilo (C_0-C_3) opcionalmente substituido en la porción n-alquilo cuando se presenta con alquilo (C_1-C_3), dimetilo, o -etano gem, en donde Ar^2 contiene un átomo de nitrógeno, y Ar^2 es substituido;

150) R^6 es $R^{24}R^{25}N$- y R^{24} es Ar^2 n-alquilo (C_0-C_3) opcionalmente substituido en la porción n-alquilo cuando se presenta con alquilo (C_1-C_3), dimetilo, o -etano gem, en donde Ar^2 contiene un átomo de nitrógeno, y Ar^2 es substituido con alcoxi (C_1-C_6) opcionalmente además substituido con 1 hasta 6 fluoro, alquilamino (C_1-C_6) opcionalmente además substituido con 1 hasta 6 fluoro, o cicloalquilo (C_3-C_7) alquilo (C_0-C_2) opcionalmente además substituido con 1 hasta 6 fluoro;

151) R^6 es $R^{24}R^{25}N$- y R^{24} es Ar^2 n-alquilo (C_0-C_3) opcionalmente substituido en la porción n-alquilo cuando se presenta con alquilo (C_1-C_3), dimetilo, o -etano gem, y en donde Ar^2 es piridilo o piridazinilo y es substituido con alcoxi (C_1-C_6) opcionalmente además substituido con 1 hasta 6 fluoro, alquilamino (C_1-C_6) opcionalmente además substituido con 1 hasta 6 fluoro, o cicloalquilo (C_3-C_7) alquilo (C_0-C_2) opcionalmente además substituido con 1 hasta 6 fluoro;

152) R^6 es $R^{24}R^{25}N$- y R^{24} es Ar^2 n-alquilo (C_0-C_3) opcionalmente substituido en la porción n-alquilo cuando se presenta con alquilo (C_1-C_3), dimetilo, o -etano gem, y en donde Ar^2 es piridilo substituido con $R^{28}R^{29}N$-C(O)- y R^{28} es cicloalquilo (C_3-C_7) alquilo (C_0-C_2) o Ph^1 y R^{29} es hidrógeno;

153) R^6 es $R^{24}R^{25}N$- y R^{24} es Ar^2 n-alquilo (C_0-C_3), en donde Ar^2 es piridilo substituido con $R^{28}R^{29}N$-C(O)- y R^{28} es cicloalquilo (C_3-C_7) o fenilo opcionalmente substituido con 1 hasta 3 halo, preferiblemente fluoro, y R^{29} es hidrógeno;

154) R^6 es $R^{24}R^{25}N$- y R^{24} es Ph^1-alquilo (C_0-C_1)-O-alquilo (C_1-C_5);

155) R^6 es $R^{24}R^{25}N$- y R^{24} es Ph^1-alquilo (C_0-C_1)-S-alquilo (C_1-C_5);

156) R^6 es $R^{24}R^{25}N$- y R^{24} es Ph^1-alquilo (C_0-C_1)-C(O)NH-alquilo (C_2-C_4);

157) R^6 es $R^{24}R^{25}N$- y R^{24} es Ph^1-alquilo (C_0-C_1)-NH-C(O)NH-alquilo (C_2-C_4);

158) R^6 es $R^{24}R^{25}N$- y R^{24} es piridil-alquilo (C_0-C_1)-C(O)NH-alquilo (C_2-C_4) opcionalmente substituido en la porción piridilo con metilo, $-CF_3$, o 1 hasta 3 substituyentes halo;

159) R^6 es $R^{24}R^{25}N$- y R^{24} es piridil-alquilo (C_0-C_1)-NH-C(O)NH-alquilo (C_2-C_4) opcionalmente substituido en la porción piridilo con metilo, $-CF_3$, o 1 hasta 3 substituyentes halo;

160) R^6 es $R^{24}R^{25}N$- y R^{24} es Ar^3-alquilo (C_1-C_2);

161) R^6 es $R^{24}R^{25}N$- y R^{24} es Ar^3-metilo;

Se entenderá que las clases arriba pueden combinarse para formar clases preferidas adicionales. Las combinaciones ejemplares incluyen, pero no se limitan a:

162) Cualquiera de las modalidades preferidas 19) hasta 161) (las secciones preferidas para R^6), combinadas con cualquiera de las modalidades preferidas 1) hasta 9) (las secciones preferidas para R^7);

163) Cualquiera de las modalidades preferidas 19) hasta 161) (las secciones preferidas para R^6), en donde R^7 es halógeno;

164) Cualquiera de las modalidades preferidas 19) hasta 161) (las secciones preferidas para R^6), en donde R^7 es cloro;

165) Una combinación preferida de conformidad a 162), 163), ó 164), en donde R^{1-5}, y R^8 son cada uno hidrógeno;

166) Una combinación preferida de conformidad a 162), 163), ó 164), en donde R^{1-5}, R^8 y R^9, son cada uno hidrógeno.

167) Cualquiera de las modalidades preferidas 37), 38), ó 39), en donde R^7 es diferente a hidrógeno;

168) Cualquiera de las modalidades preferidas 37), 38), ó 39), en donde R^9 es hidrógeno;

169) Cualquiera de las modalidades preferidas 37), 38), ó 39), en donde R^7 es diferente a hidrógeno y R^9 es hidrógeno;

170) Cualquiera de las modalidades preferidas 37), 38), ó 39), en donde R^7 es cloro y R^9 es hidrógeno;

171) Los compuestos de la fórmula (I) en donde R^6 es $-C\equiv C-R^{10}$ y en donde R^{10} se selecciona de valores definidos en cualquiera de las modalidades 19) hasta 28);

172) Los compuestos de la Fórmula (I) en donde R^6 es $-O-R^{12}$ y en donde R^{12} se selecciona de valores definicos en cualquiera de las modalidades 30) hasta 53);

173) Los compuestos de la Fórmula (I) en donde R^6 es $-S-R^{14}$ y en donde R^{14} se selecciona de los valores definidos en cualquier de las modalidades 55) hasta 63) ó 64) en donde L se selecciona de los valores de 65) hasta 71) y R^{15} se

selecciona de los valores definidos en cualquiera de las modalidades 72) hasta 141);

174) Los compuestos de la fórmula (I) en donde R^6 es $R^{24}R^{25}N-$ y en donde R^{24} se selecciona de los valore definidos en cualquiera de las modalidades 142) hasta 161);

175) Los compuestos de conformidad a la modalidad 172) en donde R^{12} se selecciona de los valores definidos en cualquiera de las modalidades 37), 38) ó 39);

176) Los compuestos de la fórmula (I) en donde R^7 es diferente a hidrógeno;

177) Los compuestos de conformidad con cualquiera de las modalidades 171) ó 174) en donde R^7 es diferente a hidrógeno;

178) Los compuestos de conformidad a cualquiera de las modalidades 171) ó 174) en donde R^7 es cloro;

179) Los compuestos de conformidad con cualquiera de las modalidades 171) ó 174) en donde R^9 es hidrógeno;

180) Los compuestos de conformidad con cualquiera de las modalidades 171) ó 174) en donde R^9 es alcoxi (C_1-C_3);

181) Los compuestos de conformidad con cualquiera de las modalidades 171) ó 174) en donde R^9 es metoxi;

182) Los compuestos de conformidad con cualquiera de las modalidades 171) ó 174) en donde R^7 es cloro y R^9 es hidrógeno;

183) Los compuestos de conformidad con cualquiera de las modalidades 171) ó 174) en donde R^7 es cloro y R^9 es alcoxi (C_1-C_3);

184) Los compuestos de conformidad con cualquiera de las modalidades 171) ó 174) en donde R^7 es cloro y R^9 es metoxi;

185) Los compuestos de conformidad con cualquiera de las modalidades 171) ó 185) en donde R^9 es hidrógeno;

186) Los compuestos de conformidad con cualquiera de las modalidades 171) ó 185) en donde R^9 es alcoxi (C_1-C_3);

187) Los compuestos de conformidad con cualquiera de las modalidades 171) ó 185) en donde R^9 es metoxi;

188) Los compuestos de conformidad con cualquiera de las modalidades 171) ó 187) en donde R^{1-5} son cada uno hidrógeno;

Generalmente, cuando R^6 es -S-R^{14}, entonces R^{15}-L- es más preferido R^{14}. Cuando R^{14} ó R^{15} es Ar^2 substituido, la para-substitución es preferida. Cuando L está presente, particularmente se prefieren metileno, y metil-metileno. Particularmente preferido R^{15}-L- es cuando R^{15} es Ph^2 y L es metileno. También particularmente preferido es cuando R^{15} es Ph^2 y L es metil-metileno. También particularmente preferido es cuando R^{15} es Ar^2 y L es metileno. También particularmente preferido es cuando R^{15} es Ar^2 y L es metil-metileno.

También generalmente, cuando R^6 es -$NR^{24}R^{25}$, entonces Ph^2-alquilo (C_1-C_3)-n- es particularmente preferido sobre fenil alquilo (C_1-C_3)-n-.

Los compuestos preferidos de la Fórmula (I) son aquellos en donde

R^6 es $-C\equiv C-R^{10}$ y en donde R^{10} se selecciona de los valores definidos en cualquiera de las modalidades 19) hasta 28); o

R^6 es $-O-R^{12}$ y en donde R^{12} se selecciona de los valores definidos en cualquiera de las modalidades 30) hasta 53); o

R^6 es $-S-R^{14}$ y en donde R^{14} se selecciona de los valores definidos en cualquiera de las modalidades 55) hasta 63) o modalidad 64) en donde L se selecciona de los valores definidos en cualquiera de las modalidades 65) hasta 71) y R^{15} se selecciona de los valores definidos en cualquiera de las modalidades 72) hasta 111) y 121 hasta 141), o $R^{15}-L-$ se selecciona de los valores definidos en cualquiera de las modalidades 112) hasta 120); o

R^6 es $R^{24}R^{25}N-$ y en donde R^{24} se selecciona de los valores definidos en cualquiera de las modalidades 143) hasta 161).

Particularmente los compuestos preferidos de la Fórmula (I) son aquellos en donde R^6 es $-O-R^{12}$ y en donde R^{12} se selecciona de los valores definidos en cualquiera de las modalidades 37), 38) ó 39).

Además los compuestos preferidos de la fórmula (I) son aquellos en donde R^7 es diferente a hidrógeno. En particular, R^7 es preferiblemente seleccionado de los valores definidos en cualquiera de las modalidades 1) hasta 8). Más preferiblemente, R^7 se selecciona de halo (especialmente

cloro), alquilo (C_1-C_3) opcionalmente substituido con 1 hasta 6 substituyentes de fluoro (especialmente metilo, etilo, n-propilo o CF_3), y ciano.

Particularmente los compuestos preferidos de la fórmula (I) son aquellos en donde R^7 es halógeno, y en particular en donde R^7 es cloro.

Los compuestos preferidos de la fórmula (I) son aquellos en donde R^9 es alcoxi (C_1-C_3), preferiblemente metoxi, o halo, preferiblemente cloro.

También son preferidos aquellos compuestos de la fórmula (I) en donde R^9 es hidrógeno.

Particularmente los compuestos preferidos de la fórmula (I) son aquellos en donde R^7 es diferente a hidrógeno y R^9 es hidrógeno, y más especialmente en donde R^7 es cloro y R^9 es hidrógeno.

Además los compuestos preferidos de la fórmula (I) son aquellos en donde R^1 es hidrógeno.

También son preferidos aquellos compuestos de la fórmula (I) en donde R^2 es hidrógeno.

También son preferidos aquellos compuestos de la fórmula (I) en donde R^3 es hidrógeno o metilo, y especialmente en donde R^3 es hidrógeno.

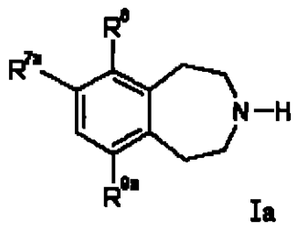
Otras clases preferidas de compuestos de la fórmula (I) es que en donde R^4 es hidrógeno, metilo o etilo,

particularmente en donde R^4 es hidrógeno o metilo, y especialmente en donde R^4 es hidrógeno.

Además son preferidos aquellos compuestos de la fórmula en donde R^5 es hidrógeno.

También son preferidos aquellos compuestos de la fórmula (I) en donde R^8 es hidrógeno.

Un grupo favorito de los compuestos de la presente invención es aquel que se representa por la fórmula (Ia), y sales farmacéuticamente aceptables de los mismos:



Ia

en donde

R^{7a} es halógeno, y especialmente cloro;

R^{9a} es hidrógeno, halógeno o alcoxi (C_1-C_3), particularmente hidrógeno, cloro o metoxi, y especialmente hidrógeno; y

R^6 como se define en relación a la fórmula (I).

Los compuestos preferidos específicos de la presente invención son aquellos descritos en los Ejemplos en la presente, incluyendo las bases libres y las sales farmacéuticamente aceptables de los mismos.

Se apreciará que las definiciones preferidas de los diversos substituyentes mencionados en la presente pueden

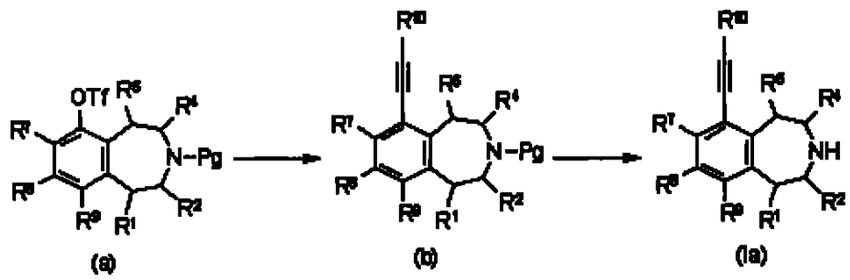
tomarse solos o en combinación y, a menos que se establezca de otra manera, aplicar a la fórmula genérica (I) para compuestos de la presente invención, así como a las clases preferidas de los compuestos representados por la fórmula (Ia).

Los compuestos de la invención pueden prepararse de conformidad a los siguientes esquemas sintéticos por métodos bien conocidos y apreciados en la técnica. Las condiciones de reacción adecuadas para las etapas de estos esquemas son bien conocidos en la técnica y substituciones apropiadas de solventes y co-reactivos están dentro de la experiencia en la técnica. Similarmente, se apreciará por los técnicos en la técnica que los esquemas intermediarios sintéticos pueden aislarse y/o purificarse por varias técnicas bien conocidas como necesarias o deseadas, y que frecuentemente, será posible para uso de varios intermediarios directamente en etapas sintéticas subsecuentes con poca o sin purificación. Adicionalmente, el técnico experimentado apreciará que en algunas circunstancias, el orden en que las porciones se introduce no es crítica. El orden particular de las etapas requeridas para producir los compuestos de la fórmula I depende del compuesto particular que es sintetizado, el compuesto de partida, y la confiabilidad relativa de las porciones substituidas como es bien apreciado por aquellos de experiencia ordinaria en la técnica. Todos los substituyentes, a menos que se indique de otra manera, como

son previamente definidos, y todos los reactivos son bien conocidos y apreciados en la técnica.

Los compuestos de la fórmula I donde R^6 es un substituyente ligado a acetileno puede prepararse como se ilustra en el esquema de reacción I donde Pg es un grupo protector adecuado para una amina secundaria tal como, pero no se limita a, 2,2,2-trifluoroacetilo o tert-butoxicarbonilo, y variables R^1, R^2, R^4, R^5, R^7, R^8, R^9 y R^{10} como se definen previamente.

Esquema de reacción I



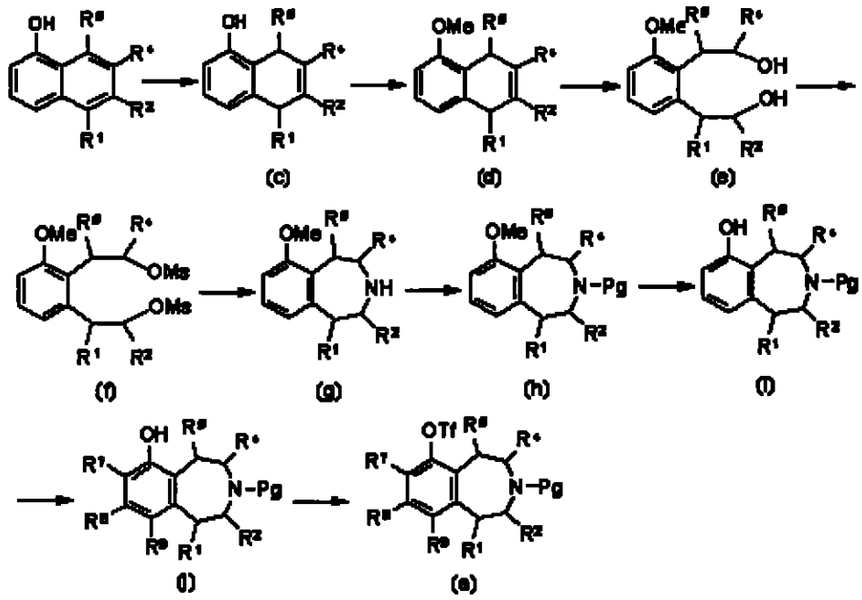
La mezcla de 6-triflato de las 2,3,4,5-tetrahidro-1H-benzo[d]azepinas (a) con un acetileno apropiadamente substituido, un catalizador de paladio/cobre adecuado mezclado en un solvente, típicamente DMF, usan trietilamina como una base, y se calienta para proporciona el compuesto deseado (b). La reacción de desprotección y las técnicas cromatográficas y extractivas estándar proporcionan el compuesto deseado (Ia).

El 6-triflato apropiado de 2,3,4,5-tetrahidro-1H-benzo[d]azepinas (a) puede prepararse como se describe en el Esquema de reacción II. El compuesto (a) puede prepararse de 1-naftol. 1-Naftol puede convertirse a 5-hidroxi-1,4-dihidronaftaleno (c) por reducción Birch usando amoniaco y metal de litio a temperatura inferior. La metilación del grupo 6-hidroxi proporciona el compuesto (d). Ozonolísis de (d) y reducción posterior con borohidruro de sodio propociona el diol (e). Después de que se convierten los 2 grupos hidroxilo en 2 grupos de partida buenos, por ejemplo metansulfonatos, se cicliza el compuesto (f) a las 6-metoxi-2,3,4,5-tetrahidro-1H-benzo[d]azepinas (g) con amoniaco acuoso bajo presión. Se protege el nitrógeno en el anillo con una variedad de haluros de alquilo, cluroros ácidos o anhídridos tales como anhídrido trifluoroacético para dar el compuesto (h). Subsecuentemente se convierte el metil éter (h) al fenol (i) con BBr_3 en diclorometano u otros métodos bien conocidos en la literatura [ver por ejemplo, Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley and sons, Capítulo III, New York (1999)].

La funcionalización del anillo aromático para introducir los substituyentes R^7, R^8 y R^9 es bien conocida en la técnica y muy dependientes en la substitución deseada. La trifluorometansulfonilación posterior del 6-hidroxi (j)

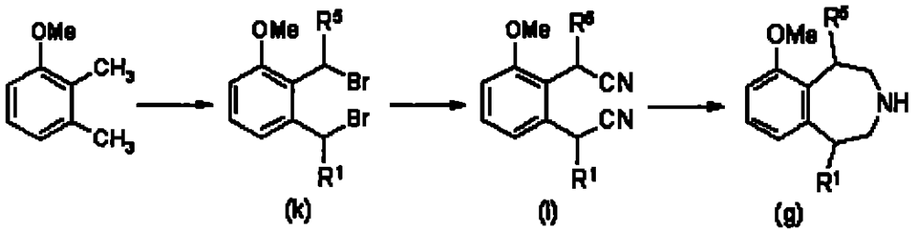
proporciona las 2,3,4,5-tetrahidro-1H-benzo[d]azepinas deseadas (a).

Esquema de Reacción II



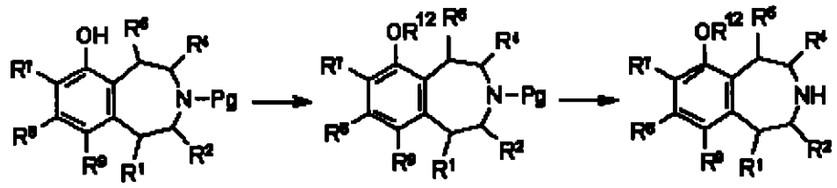
Alternativamente, el compuesto (g) puede prepararse de 1,2-bis(cianometil)-3-metoxibenceno (l), previamente descrito en la literatura (J. Med. Chem. 1984, 27, 918-921), como se muestra en el Esquema de Reacción III a continuación.

Esquema de reacción III



Los compuestos de la fórmula I donde R^6 es un substituyente ligado a oxígeno puede prepararse como se ilustra en el Esquema de Reacción IV donde Pg es un grupo protector adecuado para amina secundaria, tales como 2,2,2-trifluoroacetilo o tert-butoxicarbonilo, y variables R^7, R^9 y R^{12} son como se definen previamente.

Esquema de Reacción IV



(l) (m) (Ib)

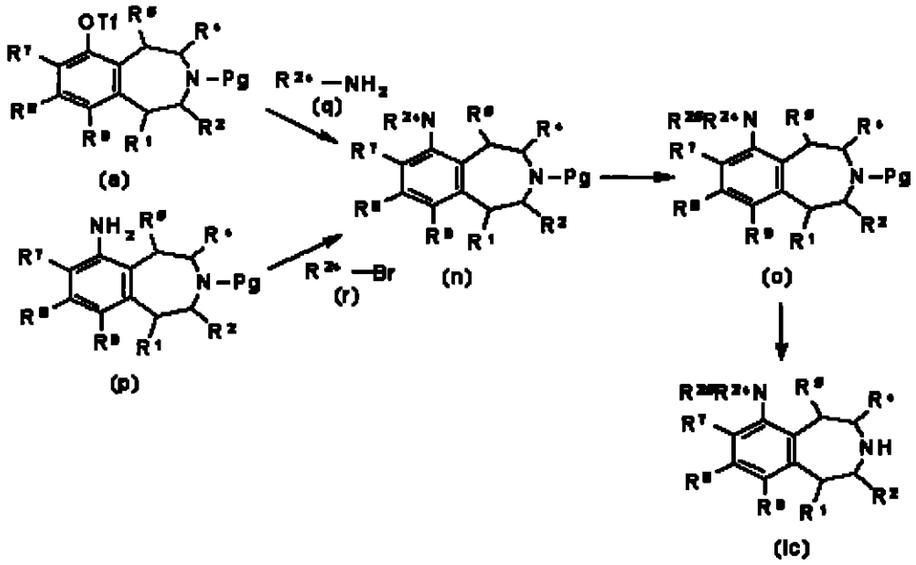
El compuesto (m) puede prepararse al tratar 6-hidroxi-2,3,4,5-tetrahidro-1H-benzo[d]azepinas (j) con un reactivo de alquilación apropiado, tal como un haluro o sulfonato de alquilo, y una base en un solvente adecuado, típicamente acetona, etanol o acetonitrilo, seguido por las técnicas cromatográficas y extractivas estándar. La desprotección del anillo de nitrógeno da el compuesto (Ib). Alternativamente, el compuesto (m) puede obtener por reacción Mitsunobu con un alcohol apropiado, un reactivo de fosfina tal como trifenilfosfina, y dietil azodicarboxilato (DEAD) o 1,1'-(azodicarbonil)-dipiperidina en un solvente anhidro, por ejemplo THF.

Los compuestos de la fórmula Ic donde R^6 es un substituyente ligado a nitrógeno puede prepararse como se ilustra en el Esquema de Reacción V. Las 2,3,4,5-tetrahidro-1H-benzo[d]azepinas protegidas por 6-triflato (a) pueden convertirse a los compuestos (n), bajo condiciones Buchwald, por tratamiento con una amina apropiada (q) en presencia de un catalizador de paladio efectivo, y una base en un solvente adecuado, típicamente tolueno o 1,4-dioxano bajo una atmósfera inerte. La introducción de un segundo substituyente R^{25}, si es necesario, puede llevarse a cabo. Las técnicas cromatográficas y de trabajo estándar seguido por desprotección, da el compuesto (Ic).

Alternativamente las 6-amino-2,3,4,5-tetrahidro-1H-benzo[d]azepinas (p) pueden transformarse para el compuesto deseado (n) por reacción con un bromuro apropiado (r), y una base apropiada en un solvente adecuado.

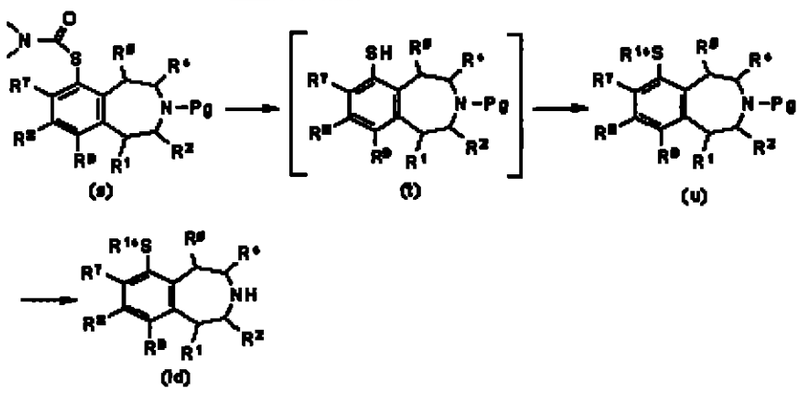
Los bromuros (r) son ya sea comercialmente disponibles o pueden prepararse por métodos bien conocidos por alguien de experiencia en la técnica. Las aminas (q) son y sea comercialmente disponibles o pueden prepararse por métodos bien conocidos por el técnico experimentado.

Esquema de Reacción V



Los compuestos de la fórmula I donde el R^6 es un substituyente ligado a azufre puede prepararse como se ilustra en el Esquema de Reacción VI.

Esquema de Reacción VI



Se calienta la o las 3-(tert-butoxicarbonil-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepinas

apropiadamente substituidas con una base apropiada en un solvente adecuado, tal como metanol, para obtener el intermediario tiol (t). Se aísla el intermediario tiol (t), si se requiere, y se trata con un electrofilo apropiado (haluro o sulfonato de alquilo). Se aisla el compuesto (u) por técnicas cromatográficas y extractivas estándar y se desprotege para proporcionar el compuesto deseado (Id).

Los haluros y alquil sulfonatos requeridos son ya sea comercialmente disponibles o pueden prepararse por métodos bien conocidos por el técnico experimentado.

El técnico experimentado también apreciará que no todos los substituyentes en los compuestos de la Fórmula I tolerarán ciertas condiciones de reacción empleadas para sintetizar los compuestos. Estas porciones pueden introducirse a un punto conveniente en la síntesis, o pueden protegerse y luego desprotegerse como sea necesario o deseado, como es bien conocido en la técnica. El técnico experimentado apreciará que los grupos protectores pueden eliminarse en cualquier punto conveniente en la síntesis de los compuestos de la presente invención. Los métodos para introducir y eliminar los grupos protectores usados en esta invención son bien conocidos en la técnica; ver, por ejemplo, Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley and sons, New York (1999).

Las siguientes preparaciones y ejemplos son ilustrativos de métodos útiles para la síntesis de los compuestos de la presente invención. Los compuestos ejemplificados también son particularmente preferidos los compuestos de la presente invención.

Procedimiento general 1-1

Se disuelve la 3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina apropiadamente substituida en solución de amoniaco/metanol (1.0-7.0 M). Se agita durante 1-16 h a temperatura ambiente a menos que se especifique de otra manera. Se eliminan los volátiles in vacuo. Se purifica por cromatografía en gel de sílice eluido con 1-20% amoniaco 2M/metanol en DCM, o por cromatografía SCX eluido con amoniaco 1.0-7.0 M en metanol.

Procedimiento general 1-2

Se disuelve la 3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina apropiadamente substituida (1.0 equiv.) en metanol. Se agrega una solución acuosa 0.5 M de carbonato de potasio (4.0 equiv.) y se agita a temperatura ambiente durante 6 h. Se concentra in vacuo y se divide el residuo entre agua y DCM. Se extrae la fase acuosa 2 veces con DCM. Se secan los extractos orgánicos combinados sobre Na_2SO_4, se filtran y se concentran in vacuo. Si es necesario,

se purifican por cromatografía en gel de sílice eluido con 1-20% amoniaco 2M/metanol en DCM, o por cromatografía SCX eluido con 1.0-7.0 M amoniaco en metanol.

Procedimiento general 1-3

Se disuelve la 3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina apropiadamente substituida (1.0 equiv.) en metanol o etanol (solución 0.1 hasta 2M) y se agrega desde 10-50% por volumen de una solución acuosa 1.0-5.0 N de hidróxido de sodio o hidróxido de litio. Se agita la mezcla de reacción a temperatura ambiente durante 0.25-16 h y se concentra in vacuo. Se divide el residuo entre EtOAc o DCM y agua. Se separa y se seca la fracción orgánica sobre Na_2SO_4, se filtra, y se concentra in vacuo. Se purifica por cromatografía SCX, seguido por cromatografía en gel de sílice eluido con 1-20% amoniaco/metanol 2M en DCM o fase inversa CLAR.

Procedimiento general 1-4

Se disuelve la 3-tert-butoxicarbonil-2,3,4,5-tetrahidro-1H-benzo[d]azepina apropiadamente substituida en cloruro de hidrógeno 4M en dioxano o cloruro de hidrógeno 1M en éter etílico y se agita la mezcla durante 2-16 h a temperatura ambiente a menos que se especifique de otra manera. Se elimina el solvente in vacuo. Si un sólido se obtiene, se lava el sólido con éter y se filtra bajo vacío para

proporcionar la sal de clorohidrato deseada. Si un aceite se obtiene, se disuelve el aceite en un volumen mínimo de DCM, metanol o EtOAc y se agrega éter para precipitar el sólido. Se elimina el solvente in vacuo, se lava el sólido con éter y se filtra. Se seca el sólido in vacuo o bajo una corriente de nitrógeno.

Procedimiento general 1-5

Se disuelve la 3-tert-butoxicarbonil-2,3,4,5-tetrahidro-1H-benzo[d]azepina apropiadamente substituida en una mezcla de ácido trifluoroacético/DCM (desde 1:0 hasta 1:10 relación) y se agita la reacción durante 1-16 h a temperatura ambiente. Se concentra in vacuo y ya sea se somete el residuo a cromatografía SCX o se divide el residuo entre $NaHCO_3$ acuoso saturado y DCM o EtOAc. Se seca la capa orgánica sobre Na_2SO_4 y se concentra in vacuo. Se purifica ya sea por cromatografía en gel de sílice (eluido con 1-20% amoniaco/metanol 2M en DCM) o fase inversa CLAR.

Procedimiento general 1-6

Se agrega cloruro de acetilo (40 equiv.) para metanol frío (0 °C) y se agita durante 5 min. Luego se agrega una solución de 7-cloro-3-(tert-butoxicarbonil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina apropiadamente substituida (1 equiv.) en metanol. Se agita la reacción a temperatura

ambiente durante 12 h. Se elimina el solvente in vacuo, se basifica con $NaHCO_3$ acuoso saturado y se extre 3 veces con DCM. Se secan los extractos orgánicos combinados sobre Na_2SO_4, se filtran y se concentran in vacuo. Se purifica por cromatografía en gel de sílice, eluido con 1-20% amoniaco/metanol 2M en DCM.

Procedimiento general 2-1

Se disuelve la base libre purificada (1 equiv.) en acetona, éter o metanol y se agrega una solución de ácido succínico (1 equiv.) en un volumen mínimo de acetona o metanol. Se agita durante 1 h a temperatura ambiente. Se concentra a un aceite, se agrega un volumen mínimo de DCM y éter etílico para precipitar la sal. Alternativamente, para precipitar la sal, se permite la mezcla de reacción al reposar 1-16 h a temperatura ambiente, 4°C o -10°C y se agrega éter o hexano. Se filtra y se lava el sólido con éter o hexano para obtener la sal de succinato. Alternativamente, se evapora el solvente in vacuo, se lava el sólido con éter y se filtra o decanta el solvente para obtener el succinato como un sólido. Se seca el sólido in vacuo o bajo una corriente de nitrógeno.

Procedimiento general 2-2

Se disuelve la base libre purificada (1 equiv.) en un volumen mínimo de acetona, dioxano, metanol o DCM y se agrega un exceso de cloruro de hidrógeno 4M en dioxano o una solución 1M de cloruro de hidrógeno en éter etílico. Se agita durante 1 h y se evapora el solvente para obtener la sal como un sólido. Alternativamente, se permite la mezcla de reacción al reposar 1 hasta 16 h a temperatura ambiente y se agrega éter o hexano para precipitar la sal. Se filtra y se lava el sólido con éter o hexano para obtener la sal como un sólido. Alternativamente, se evapora el solvente in vacuo, se lava el sólido con éter, se filtra o decanta el solvente para obtener la sal de clorohidrato como un sólido. Se seca el sólido in vacuo o bajo una corriente de nitrógeno.

Procedimiento general 2-3

Se disuelve la base libre purificada en metanol, se agrega una solución de cloruro de amonio (1 equiv.) en metanol y se agita durante 1 h. Lentamente se eliminan los volátiles in vacuo. Se disuelve el residuo en metanol y se elimina más del solvente in vacuo. Se agrega éter etílico anhidro o EtOAc para precipitar la sal de clorohidrato. Se recolecta el sólido, se lava el sólido con éter y luego se seca el sólido in vacuo o bajo una corriente de nitrógeno.

Procedimiento general 2-4

Se disuelve la base libre purificada (1.0 equiv.) en metanol. Se agrega una solución 0.5 M de ácido metansulfónico en metanol (2.0 equiv). Se mezcla bien, se agita durante 1 h, luego se elimina el solvente in vacuo. Se disuelve el residuo en un volumen mínimo de DCM. Se agrega éter etílico para precipitar el sólido. Se elimina el solvente in vacuo para formar una espuma. Se seca in vacuo o bajo una corriente de nitrógeno para obtener la sal del ácido metansulfónico.

Procedimiento general 2-5

Se disuelve la base libre purificada (1 equiv.) en un volumen mínimo de acetona y se agrega una solución de ácido oxálico (1 equiv.) en un volumen mínimo de acetona. se permite la mezcla reposar 10 min hasta 16 h a temperatura ambiente hasta -10°C, y/o se agrega éter o hexano para precipitar el sólido. Se filtra y se lava el sólido con éter o hexano para obtener la sal de ácido oxálico como un sólido. Se seca el sólido in vacuo o bajo una corriente de nitrógeno.

Procedimiento general 2-6

Se disuelve la base libre purificada (1 equiv.) en un volumen mínimo de ciclohexano, isohexano, cloroformo, diclorometano, metanol o una mezcla de los mismos y se agrega una solución de ácido (L)-tartárico en isopropanol o metanol.

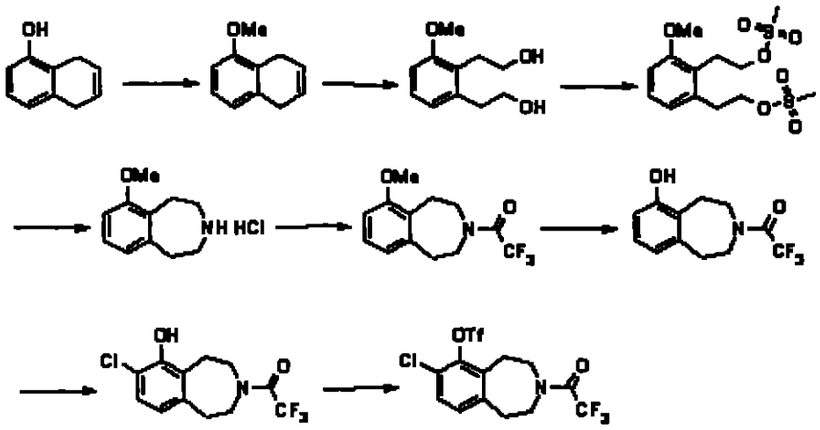
Si un sólido precipitado, se filtra y se lava el sólido con éter, ciclohexano, isohexano o EtOAc. Si la formación del no sólido se observa, se eliminó todos los volátiles in vacuo para formar una espuma. Se seca in vacuo o bajo una corriente de nitrógeno para obtener la sal de ácido tartárico.

Procedimiento general 3

Se disuelve el 3-tert-butoxicarbonil-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina apropiadamente substituido o 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (1 equiv.), $PdCl_2(PPh_3)_2$ (0.1 equiv.), yoduro de tetrabutil amonio (3 equiv.), y yoduro de cobre (I) (0.3 equiv.) en trietilamina/DMF (1:5). Se agita la mezcla durante 5 min a temperatura ambiente, se agrega el acetileno apropiadamente substituido (2 equiv.) y se calienta a 70°C durante 2-16 h en un tubo sellado. Se enfría la mezcla de reacción a temperatura ambiente, se diluye con EtOAc/hexano (1:1) y se lava con agua. Se seca la fracción orgánica sobre Na_2SO_4, se filtran y se concentran in vacuo. Se purifica por cromatografía en gel de sílice eluido con mezclas de hexano/EtOAc.

Preparación 1

7-Cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina



5-Metoxi-1,4-dihidronaftaleno: Se agrega carbonato de potasio en polvo (193.1 g, 1.397 mol) a una solución de 5-hidroxi-1,4-dihidronaftaleno [68.08 g, 90% de potencia con base en ^{1}H-RMN, 0.4657 mol, de Societa Italiana Medicinala Scandicci, s.r.l., Reggello (Florencia), Italia] en etanol (700 mL). Se enfría la solución a 0°C con hielo/agua y se agrega dimetil sulfato (88.1 g, 66.1 mL, 0.699 mol) gota a gota, manteniendo la temperatura entre 5°C y 10°C. Luego se calienta la mezcla de reacción hasta 40°C hasta que el CCD (10:1 hexano/EtOAc) muestra la ausencia de material de partida (alrededor de 2 h). Se filtran completamente los sólidos por filtración al vacío y se elimina el solvente in vacuo. Se diluye el aceite café residual con dietil éter (500 mL), se lava con 10% de

NH_4OH acuoso (500 mL), agua (500 mL), salmuera (500 mL), se seca la capa orgánica sobre Na_2SO_4, se filtran y se concentran in vacuo para dar el producto crudo como un aceite café (73 g). Se purifica el producto crudo por una destilación de trayectoria corta bajo vacío (pe 120-130°C/ 5 Torr) para dar el intermediario deseado como un aceite claro (69.0 g, 92.5% de potencia correcta) (contiene algunos 1,2,3,4-tetrahidro-5-metoxinaftaleno como una impureza). ^1H RMN (300 MHz, $CDCl_3$), δ 7.15 (t, 1H, J = 7.9), 6.72 (dd, 2H, J = 15.7, 7.9), 5.93-5.88 (m, 2H), 3.83 (s, 3H), 3.42-3.39 (m, 2H), 3.30-3.28 (m, 2 H); R_f = 0.58 eluido con 10:1 hexano/EtOAc.

2,3-Bis-(2-hidroxietil)-1-metoxibenceno: Se cambia un matraz de 4 cuellos de 5 L equipado con un agitador mecánico de domo, condensador de reflujo, termoacoplador, y aparatos de dispersión de gas con 5-metoxi-1,4-dihidronaftaleno (264.54 g, 89.5% de potencia con base en ^1H-RMN, 1.478 mol) en DCM (1.3 L) y 2B-3 etanol (1 L). Se agrega sudan III (10 mg) para dar un color rojo tenue. Se enfría la solución a -65°C o inferior, luego se pasa O_3 a través de la solución hasta que la solución se vuelve color amarillo ligero y el CCD (10:1 hexano/EtOAc, $KMnO_4$ teñido) muestra la ausencia del material de partida (alrededor de 30 h). Se transfiere la solución por medio de una cánula en una mezcla espesa de $NaBH_4$ (97.8 g, 2.59 mol) en 2B-3 etanol (500 mL) se enfria en hielo/agua. Es

importante que la temperatura se mantenga a o arriba de 0°C, como por ejemplo entre 0°C y 10°C, a lo largo de la transferencia para asegurar que el ozónido es completamente reducido al diol. Después de que la transferencia se completa, se calienta la solución a temperatura ambiente y se agita durante alrededor de 30 min. Se enfría la solución espesa hasta 0°C con hielo/agua luego lentamente se agrega acetona (540 mL, 7.4 mol) para remover el exceso de $NaBH_4$. Después todos los sólidos se disuelven, se elimina el solvente in vacuo. Se disuelve el sólido amarillo en DCM (1 L) y agua (1 L), se separan las capas y se extrae la capa acuosa con DCM (750 mL). Se lavan las capas orgánicas combinadas con salmuera (1.5 L), se agrega tolueno (750 mL) y se elimina el solvente in vacuo. Se disuelve el sólido en DCM (500 mL) con calentamiento, luego se agrega tolueno (750 mL) y se concentra la solución in vacuo para dar el intermediario deseado como un sólido amarillo ligero (283.7 g, 89% de potencia correcta, pf 82-83°C) (contiene 1,2,3,4-tetrahidro-5-metoxinaftaleno como una impureza (8.6%)). Se purifica además el producto por vacío secado durante la noche a 75°C, 5 Torr, para retirar todo excepto una cantidad en trazas de la impureza 1,2,3,4-tetrahidro-5-metoxinaftaleno. ^1H RMN (300 MHz, $CDCl_3$), δ 7.16 (dd, 1H, J = 8.2, 7.6), 6.83 (s, 1H, J = 7.0), 6.76 (s, 1H, J = 8.2), 3.85-3.77 (m, 7H), 3.01-2.91 (m,

4H), 2.35 (s, 2H); ^{13}C RMN (300 MHz, DMSO-d_6), δ 157.5, 138.9, 126.5, 125.2, 122.0, 108.4, 62.1, 60.5, 55.3, 36.1, 29.6; IR (KBr): 3006, 2960, 2886, 2829, 1583, 1461, 1440, 1264, 1091, 1041 cm^{-1}; EM (ES+) m/z 178 $(M+H)^+$; Análisis calculado para $C_{11}H_{16}O_3$: C, 67.32; H, 8.22; N, 0. Encontrado: C, 67.26, H, 8.10, N, 0.21; R_f = 0.23 eluido con 95:5 DCM/metanol.

2,3-Bis-(2-metansulfoniloxietil)-1-metoxibenceno: A una mezcla espesa de 2,3-bis-(2-hidroxietil)-1-metoxibenceno (50.6 g, 0.258 mol, 1 equiv.) y trietilamina (78.3 g, 0.774 mol, 3 equiv.) en DCM (500 mL) a 0°C, se agrega gota a gota una solución de cloruro de metansulfonilo (65.0 g, 0.567 mol, 2.2 equiv.) en DCM (100 mL) durante 45 min. La adición es exotérmica y el cloruro de metansulfonilo se agrega a una relación para mantener la temperatura debajo de 10°C. Después de que la adición se completa, se calienta la reacción a temperatura ambiente. Se lava la solución con agua (2 x 500 mL), y luego salmuera (750 mL). Se seca la capa orgánica sobre Na_2SO_4, se filtran y se concentran in vacuo para obtener el intermediario deseado como un aceite amarillo oscuro (87.4 g, 96.2%), que se usa en la siguiente reacción sin purificación adicional. Una muestra analítica se obtiene por cromatografía en columna instantánea eluido con 100% dietil éter. ^1H RMN (300 MHz, $CDCl_3$), δ 7.20 (t, 1H, J = 7.9), 6.82

(s, 1H, J = 7.2), 6.80 (s, 1H, J = 8.2), 4.41-4.34 (m, 4H), 3.83 (s, 3H), 3.16-3.09 (m, 4H), 2.91 (s, 3H), 2.87 (s, 3H); ^{13}C RMN (300 MHz, $CDCl_3$), δ 158.07, 136.55, 128.26, 123.34, 122.39, 109.24, 69.88, 69.08, 55.55, 37.35, 37.14, 32.57, 26.47; ^{13}C RMN (300 MHz, DMSO-d_6), δ 157.58, 136.79, 127.81, 122.91, 122.00, 109.33, 70.19, 68.88, 55.55, 36.49, 36.47, 31.56, 25.72; IR (KBr): 1586.8, 1469.4, 1358.51, 1267.3, 1173.9, 1105.4, 972.4, 954.6, 914.3 cm^{-1}; EM (ES+) m/z 257 $(M+H)^+$; Análisis calculado para $C_{13}H_{20}O_7S_2$: C, 44.31; H, 5.72; N, 0. Encontrado: C, 44.22, H, 5.68, N, 0.13; R_f = 0.72 eluido con 95:5 DCM/metanol.

6-Metoxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Se disuelve 2,3-bis-(2-metansulfoniloxietil)-1-metoxibenceno (474.4 g, 1.346 mol) en acetonitrilo (7 L) y se dividió la mezcla en 2 lotes iguales. En 2 corridas separadas, se agrega NH_4OH acuoso concentrado (3.5 L) y se cambia la solución a un recipiente a presión (aparato PARR). Se calienta la solución en un reactor cerrado hasta 100°C durante 20 min (se alcanza la presión interna alrededor de 100 psi (7.03 kg/cm^2)), y se mantiene a 100°C hasta que la reacción se completa (alrededor 1 h, CLAR se monitorea). Se enfría la mezcla de reacción a temperatura ambiente. Se combinan los 2 lotes y se elimina el solvente in vacuo. Se disuelve el residuo en MTBE (3.5 L) y

agua (3.5 L). Se ajusta el pH hasta 6.5 usando NaOH acuoso 2M o HCl acuoso 1M como sea apropiado (típicamente el pH es alrededor de pH = 5.1 y el ajuste requiere alrededor de 50 mL NaOH acuoso 2M). Se descarta la capa orgánica, se ajusta la capa acuosa hasta pH=13 usando 50% de NaOH (alrededor 150 mL). Se extrae con MTBE (2 x 3.5 L), se lavan las capas orgánicas combinadas con salmuera (3.5 L), se secan sobre Na_2SO_4, se filtran y se concentran in vacuo para dar el compuesto del título como un aceite amarillo crudo que se solidifica durante el reposo (179.3 g). Se usa el material para la siguiente etapa sin purificación adicional. Se prepara una muestra analítica por purificación por 2 destilaciones Kugelrohr para dar un aceite claro que solidifica al reposar, pf 44.3-45.0°C. ^{13}C RMN (300 MHz, DMSO-d_6) δ 156.1, 144.4, 130.3, 126.2, 121.5, 108.9, 55.5, 48.2, 47.9, 39.9, 29.1; EM (ES+) m/z 163 $(M+H)^+$; Análisis calculado para $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Encontrado: C, 74.28, H, 8.62, N, 7.86.

Clorohidrato de 6-Metoxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Se disuelve 6-metoxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina crudo (35.1 g, 0.198 mol) en 2B-3 etanol (250 mL), se calienta la solución hasta reflujo y se agrega HCl 2M en etanol (108.9 mL, 0.218 mol, 1.1 equiv.). Lentamente se agrega heptano (700 mL) durante 10 min, luego se elimina la

capa de calentamiento y se enfría la solución a temperatura ambiente, y finalmente se continua el enfriamiento con una mezcla hielo/agua. Se recolecta el sólido resultante por filtración al vacío y se lava con etanol:heptano frío (1:2) (3 x 100 mL), se seca con aire durante 15 min bajo vacío, luego además se seca el producto en un horno al vacío a 60°C durante 1 h para dar el intermediario deseado como un sólido granular blanco (35.53 g, 63%): pf 246.6-246.9°C; ^{1}H RMN (300 MHz, DMSO-d_6), δ 9.82 (amplio s, 1H), 7.12 (dd, 1H, J = 7.6, 7.9), 6.88 (d, 1H J = 8.2), 6.78 (d, 1H, J = 7.3), 3.75 (s, 3H), 3.20-3.00 (m, 8H); ^{13}C RMN (300 MHz, DMSO-d_6), δ 156.2, 141.3, 127.4, 127.2, 121.6, 109.7, 55.7, 44.9, 44.7, 31.6, 21.7; EM (ES+) m/z 178 $(M+H)^+$; Análisis calculado para $C_{11}H_{15}ClNO$: C, 62.12; H, 7.11; N, 6.59. Encontrado: C, 61.95, H, 7.64, N, 6.58.

6-Metoxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina: A una mezcla espesa de clorohidrato de 6-metoxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (35.3 g, 0.165 mol, 1 equiv.) y trietilamina (69.1 mL, 0.496 mol, 3 equiv.) en DCM (300 mL) se enfría a 0°C con hielo/agua, se agrega gota a gota una solución de anhidrido trifluoroacético (25.7 mL, 0.182 mol, 1.1 equiv.) en DCM (40 mL) durante 30 min, pero a una relación que mantiene la temperatura debajo de

10°C. Después de que la adición se completa, se calienta la mezcla de reacción a temperatura ambiente y se agita hasta que la reacción se completa (verificar por CCD usando 9:1 CH_2Cl_2:metanol, alrededor de 2 h.). Se lava la solución con agua (2 x 350 mL), y luego salmuera (350 mL), se seca la capa orgánica sobre Na_2SO_4, se filtran y se concentran in vacuo para dar el intermediario deseado como un aceite amarillo que se solidifica durante el reposo (44.9 g, 96%). Se usa el material sin purificación adicional en la siguiente etapa. Se prepara una muestra analítica por cromatografía en gel de sílice eluido con 40% dietil éter en hexano, pf 74-76°C. ^{1}H RMN (300 MHz, $CDCl_3$), δ 7.16-7.11 (m, 1H), 6.81-6.74 (m, 2H), 3.81 (s, 3H), 3.79-3.64 (m, 4H), 3.11-3.07 (m, 2H), 2.99-2.95 (m, 2H); ^{1}H RMN (300 MHz, DMSO-d_6), δ 7.13 (dd, 1H, J = 1.5, 7.0), 7.08 (d, 1H, J = 1.5), 6.88-6.74 (m, 1H), 3.75 (s, 3H), 3.67-3.61 (m, 4H), 3.04-2.92 (m, 4H); ^{13}C RMN (300 MHz, DMSO-d_6), δ 156.43. 156.38, 155.06, 155.00, 154.60, 154.54, 154.14, 154.08, 141.31, 141.04, 127.44, 127.18, 127.05, 127.01, 122.27, 121.94, 121.90, 118.46, 114.64, 110.80, 109.52, 109.41, 55.63, 55.61, 47.11, 47.07, 46.67, 46.63, 45.61, 45.16, 35.90, 34.65, 26.18, 24.91; Análisis calculado para $C_{13}H_{14}F_3NO_2$: C, 57.14; H, 5.16; N, 5.13. Encontrado: C, 57.17, H, 5.27, N, 5.08.

6-Hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina: A una solución 1M de BBr_3 (1.1 L, 1.6 equiv.), se enfría a 0°C con un baño de hielo-agua, se agrega 6-metoxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (187 g, 0.684 mol) en DCM (200 mL) durante 1 h., mientras se mantiene la temperatura entre 0°C y 10°C. Se calienta la mezcla de reacción a temperatura ambiente y se agita hasta que el CLAR indica la completación de la reacción (alrededor de 2 h.). Se enfría la solución a 0°C y se transfiere por medio de una cánula en una solución de hielo/agua (1.2 L), por ello se precipita el producto como un sólido blanco. Se agrega EtOAc (2 L) para disolver más del precipitado, se separan las capas y se concentra la capa orgánica in vacuo. Se extrajo la capa acuosa 3 veces con EtOAc (2 x 2 L, 1 x 1 L). Se lavan las capas orgánicas combinadas con agua (2 L), y luego salmuera (2 L), se seca sobre Na_2SO_4, se filtran y se concentran in vacuo para dar el intermediario deseado como un sólido amarillo ligero (166.3 g, 94%). Se usa el producto para la siguiente etapa sin purificación adicional. Se prepara una muestra analítica por cromatografía en gel de sílice eluido con 40% dietil éter en hexano: p.f. 183.0-185.2°C. ^1H RMN (300 MHz, DMSO-d_6), δ 9.39 (s, 1H), 6.94-6.88 (m, 1H), 6.72-6.68 (m, 1H), 6.61-6.57 (m, 1H), 3.67-3.32 (m, 4H), 2.99-2.86 (m, 4H); ^{13}C RMN (300 MHz,

DMSO-d_6), δ 154.50, 141.47, 141.18, 126.77, 126.64, 125.77, 125.33, 120.38, 120.32, 118.49, 114.67, 113.64, 113.47, 47.31, 47.27, 47.00, 46.96, 45.83, 45.49, 36.17, 34.93, 26.46, 25.18, 20.66, 14.00; EM (ES+) m/z 260 $(M+H)^+$; Análisis calculado para $C_{12}H_{12}F_3NO_2$: C, 55.60; H, 4.67; N, 5.40. Encontrado: C, 55.51, H, 4.71, N, 5.29.

7-Cloro-6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Se calienta una mezcla de 6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (120 g, 0.4629 mol) y tolueno (14.4 L) hasta 70°C durante 45 min hasta que más del material de partida se disuelve. Se agrega diisobutilamina (1.197 g, 1.62 mL, 9.26 mmol) seguido por la adición de cloruro de sulfurilo (62.48 g, 37.19 mL, 0.463 mol) en tolueno (360 mL) durante 20 min. Se agita la mezcla de reacción durante 50 min y luego se agrega cloruro de sulfurilo adicional (4.536 g, 2.70 mL, 0.0336 mol) puro y se agita la mezcla de reacción durante 15 min a 70°C. Se enfría la mezcla de reacción hasta 24°C durante 30 min y luego se agrega ácido clorhídrico 1N (2.00 L). Se separa, se lava la capa orgánica con $NaHCO_3$ acuoso saturado (2.00 L), salmuera (2.00 L) y luego se seca sobre Na2SO4. Se filtra y se elimina el solvente con un evaporador rotatorio a 70°C hasta que alrededor de 672.5 g restante usando el vacío mínimo efectivo en orden para mantener una fase de vapor

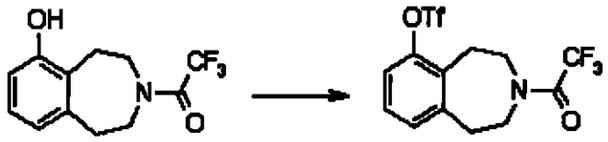
suficiente para prevenir el secado arriba de la línea del solvente y auto secado, de esta manera se previene la cristalización bajo estas condiciones. Al usar tolueno caliente a 70°C, se transfiere la solución amarillo ligero a un matraz de 3 cuellos precalentado (70°C) equipado con un agitador mecánico. Se reduce la temperatura hasta 58°C durante 1 h. Si está disponible, se siembra la solución con cristales de 7-cloro-6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina de una síntesis previa para aumentar la cristalización. Después de 30 min, se reduce la temperatura adicional hasta 55°C y se observa la iniciación del proceso de cristalización. Se mantiene la temperatura a 55°C durante 2 h. después por 4 h. a 45°C, luego se apaga el calor para permitir que la mezcla lentamente alcance los 24°C (temperatura ambiente). Después de agitación durante 8 h. con el calor apagado, se enfría la mezcla a 0°C durante 2 h. después por 2 h. a -10°C. Se colectaron los cristales resultantes densos, blancos y granulares por filtración al vacío a -10°C. Se enjuagan los cristales 2 veces con tolueno frío (-10°C) y se seca al vacío a 50°C, 5 Torr, durante 12 h., para obtener el intermediario deseado como un sólido blanco (120.7 g, 99.5% de pureza, 88.8%): pf 133-134°C. EM (ES+) m/z 294 $(M+H)^+$. Análisis calculado para $C_{12}H_{11}ClF_3NO_2$: C, 49.08; H, 3.78; N, 4.77; Cl, 12.07. Encontrado: C, 49.01; H, 3.63; N, 4.72; Cl, 12.32.

7-Cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Se enfría una solución de 7-cloro-6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (60 g, 0.204 mol), trietilamina (62.6 mL, 0.448 mol, 2.2 equiv.), y DCM (590 mL) en un baño de hielo y se agrega gota a gota anhídrido trifluorometansulfónico (43.5 mL, 0.258 mol, 1.26 equiv.) durante 70 min. Se elimina el baño de hielo y se agita la mezcla de reacción durante 2 h. Se lava la mezcla de reacción secuencialmente con agua (500 mL), HCl acuoso 1N (500 mL), agua (500 mL), y salmuera (500 mL). Se seca la capa orgánica sobre Na_2SO_4 y se concentra in vacuo para dar el producto crudo como un sólido café (90 g). Se disuelve el sólido en tolueno caliente (200 mL). Se purifica además por cromatografía de filtración de tapón sobre gel de sílice (500 g) eluido secuencialmente con hexano (1 L), hexano/EtOAc (9:1, 1L), hexano/EtOAc (4:1, 1L), y hexano/EtOAc (7:3, 9L). Se agrupan los eluyentes y se evapora el solvente para obtener el producto como un sólido amarrillo marrón (86.3 g). Se disuelve el sólido en EtOAc caliente (86 mL) y luego se agrega hexano (700 mL). Si está disponible, se siembra la solución con cristales de 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometanolsulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina de una síntesis previa para

aumentar la cristalización. Se le permite a la mezcla reposar a temperatura ambiente durante 30 min. Se enfría la mezcla a alrededor de -10°C durante 2 h., se filtra, se enjuagan los cristales con hexano/EtOAc frío (-10°C), y se seca con aire en el filtro bajo vacío para obtener el compuesto del título como una primera cosecha de cristales (73.54 g). Se concentra el licor madre para obtener un sólido (12.7 g). se recristaliza el sólido en una mezcla de EtOAc/hexano (15 mL:121 mL) para obtener el compuesto del título adicional (7.65 g, rendimiento total: 81.19 g, 93%).

Preparación 2

3-(2,2,2-Trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina

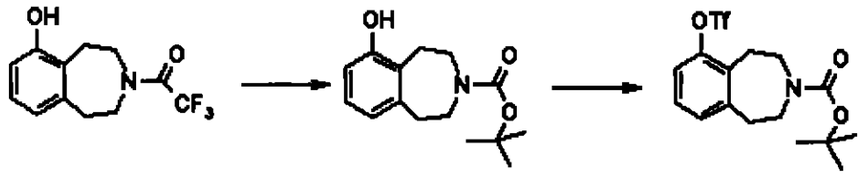


Se enfría una solución de 6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (2 g, 7.72 mmol), trietilamina (1.4 mL, 10.1 mmol) y DCM (50 mL) en un baño criogénico se fija a -30 °C y se agrega gota a gota anhidrido trifluorometansulfónico (1.7 mL, 10.1 mmol) durante 20 min. Se agita a -30°C durante 2 h y luego se calienta a temperatura ambiente durante la noche. Se lava la mezcla de reacción secuencialmente con agua (100 mL), HCl acuoso 1N

(100 mL), agua (200 mL), y salmuera (200 mL). Se seca la capa orgánica sobre Na_2SO_4 y se concentra in vacuo para dar el compuesto del título como un aceite incoloro hasta amarillo ligero (2.7 g, 89%) que se usan sin purificación. Se obtiene una muestra analítica por cromatografía en gel de sílice eluido con hexano/EtOAc (9:1) para dar el compuesto del título como un sólido ceroso completamente blanco. CG-EM m/z: 391 (M^+).

Preparación 3

3-tert-Butoxicarbonil-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina

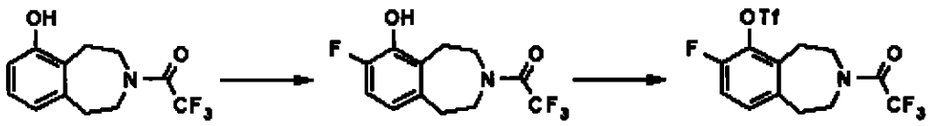


Se disuelve 6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (5 g, 19.3 mmol) en amoniaco 7N en metanol (50 mL) y se agita a temperatura ambiente durante 16 h. Se concentra la mezcla de reacción hasta un aceite y se usa sin purificación adicional. Se disuelve el residuo en una mezcla de solvente que consiste de metanol (20 mL), DCM (10 mL) y agua (100 mL), y se agrega carbonato de potasio (5 g) y di-tert-butil-dicarbonato (5.05 g, 23.2 mmol). Se agita la mezcla de reacción a temperatura ambiente durante 16 h y se concentra in vacuo. Se extrae la fase acuosa con DCM, se seca

sobre Na_2SO_4, se filtran y se concentran. Se usa el residuo sin purificación adicional. Se disuelve el material en una mezcla de DCM (300 mL) y piridina (30 mL) y se enfría en un baño de hielo. Se agrega gota a gota a la solución agitada de anhídrido trifluorometansulfónico (5.84 mL, 34.7 mmol) y se agita la mezcla de reacción durante 2 h a temperatura ambiente. Se diluye la mezcla de reacción con DCM (400 mL) y se lava con HCl acuoso 2.5N. Se seca la fracción orgánica sobre Na_2SO_4, se filtran y se concentran para dar el compuesto del título como un sólido amarillo (6.1 g, 80%). EM (ES+) m/z: 396 $(M+H)^+$.

Preparación 4

7-Fluoro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina

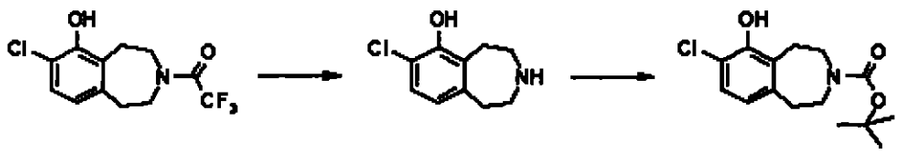


Se agrega 2-sulfonato de N-fluoro-4,6-bis(trifluorometil)-piridinio (3.02 g, 9.6 mmol) a una mezcla agitada de 6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (2.5 g, 9.6 mmol) y hexafluoro-2-propanol (10 mL) en DCM (150 mL). Se agita a temperatura ambiente durante 16 h. Se concentra la mezcla de reacción y

se divide el residuo entre EtOAc y HCl acuoso 1N. Se lava la fracción orgánica con $NaHCO_3$ acuoso saturado, salmuera, se secan sobre Na_2SO_4, se filtran y se concentran. Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (20:1, 10:1, 6:1, 5:1 y 3:1) para dar 7-fluoro-6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un sólido blanco (1.8 g, 68%). Se disuelve 7-fluoro-6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (1.5 g, 5.41 mmol) en una mezcla de DCM (20 mL) y piridina (2 mL) y se enfría en un baño de hielo. Se agrega gota a gota a la solución agitada una mezcla de anhídrido trifluorometansulfónico (1.64 mL, 9.74 mmol) en DCM y se agita la reacción durante 1.5 h a temperatura ambiente. Se diluye la reacción con DCM (300 mL) y se lava con HCl acuoso 2.5N. Se seca la fracción orgánica sobre Na_2SO_4, se filtra y se concentra para dar el producto del título como un sólido blanco (2.2 g, 99%). EM (ES+) m/z: 410 $(M+H)^+$.

Preparación 5

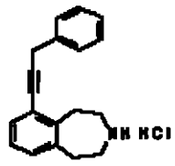
3-tert-Butoxicarbonil-7-cloro-6-hidroxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se disuelve 7-cloro-6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (3 g, 10.2 mmol) en amoniaco 7 N en metanol (50 mL) y se agita a temperatura ambiente durante 16 h. Se concentra la mezcla de reacción hasta un aceite y se usa sin purificación adicional. Se disuelve el residuo en una mezcla de solvente que consiste de DCM (25 mL) y solución de carbonato de potasio acuoso saturado (25 mL) y se agrega di-tert-butil-dicarbonato (2.2 g, 10.2 mmol). Se agita la mezcla de reacción a temperatura ambiente durante 4 h, se concentra in vacuo y se extrae el residuo acuoso con DCM. Se seca la fracción orgánica sobre Na_2SO_4, se filtran y se concentran in vacuo. Se purifica por cromatografía en gel de sílice eluido con EtOAc/hexano (1:5) para dar el compuesto del título como un sólido blanco (2.3 g, 76%). EM (ES-) m/z: 296 $(M-H)^-$.

Ejemplo 1

Clorohidrato de 6-(3-Fenil-prop-1-inil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

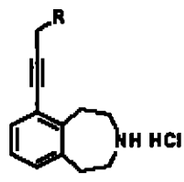


Se usa un método similar al Procedimiento general 3 para acoplar 3-tert-butoxicarbonil-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (0.6 g, 1.5 mmol) con

3-fenil-1-propina (0.38 mL, 3 mmol). Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (1:0, 40:1 y 20:1) para dar 3-tert-butoxicarbonil-6-(3-fenil-prop-1-inil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite aanaranjadodo (400 mg, 74%).

Se usa un método similar al Procedimiento general 1-5 para desproteger 3-tert-butoxicarbonil-6-(3-fenil-prop-1-inil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (68 mg, 0.19 mmol). Se purifica por cromatografía en gel de sílice eluido con DCM/amoniaco 2M en metanol (1:0, 20:1 y 10:1) para obtener la base libre del compuesto del título. Se usa un método similar al Procedimiento general 2-2 para dar el compuesto del título como un sólido marrón (48 mg, 85%). EM (ES+) m/z: 262 $(M+H)^+$.

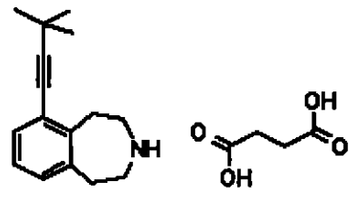
Ejemplos 2-4 pueden prepararse esencialmente como se describe en el Ejemplo 1 al usar 3-tert-butoxicarbonil-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina y la alquina apropiada. Los datos de rendimiento general y EM (ES+) se muestran en la Tabla a continuación.



Ej.	R	Compuesto	Rendimiento (%)	EM (ES+) m/z
2	Bencilo	Clorohidrato de 6-(4-Fenil-but-1-inil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	60	276 $(M+H)^+$
3	Ciclopentilo	Clorohidrato de 6-(3-Ciclopentil-prop-1-inil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	73	254 $(M+H)^+$
4	Ciclohexilo	Clorohidrato de 6-(3-Ciclohexil-prop-1-inil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	79	268 $(M+H)^+$

Ejemplo 5

Succinato de 6-(3,3-Dimetil-but-1-inil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

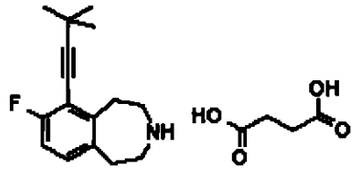


Se usa un método similar al Procedimiento general 3 para acoplar 3-tert-butoxicarbonil-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (0.5 g, 1.3 mmol) con 3,3-dimetil-1-butino (0.311 mL, 2.5 mmol). Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (10:1) para dar 3-tert-butoxicarbonil-6-(3,3-dimetil-but-1-inil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite amarillo (304 mg, 74%).

Se usa un método similar al Procedimiento general 1-5 para desproteger 3-tert-butoxicarbonil-6-(3,3-dimetil-but-1-inil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina. Se purifica por cromatografía en gel de sílice eluido con DCM/amoniaco 2M en metanol (1:0, 50:1, 20:1, 15:1 y 10:1) para obtener la base libre del compuesto del título. Se usa un método similar al Procedimiento general 2-1 para dar el compuesto del título como un sólido marrón (171 mg, 53%). EM (ES+) m/z: 228 $(M+H)^+$.

Ejemplo 6

Succinato de 6-(3,3-dimetil-but-1-inil)-7-fluoro-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al Procedimiento general 3 para acoplar 7-fluoro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (1 g, 2.4 mmol) con 3,3-dimetil-1-butino (0.599 mL, 4.9 mmol). Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (10:1) para dar 6-(3,3-dimetil-but-1-inil)-7-fluoro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite amarillo (700 mg, 84%).

Se usa un método similar al Procedimiento general 1-3 para desproteger 6-(3,3-dimetil-but-1-inil)-7-fluoro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina. Se purifica por cromatografía SCX seguido por cromatografía en gel de sílice eluido con DCM/amoniaco 2M en metanol (1:0, 50:1, 20:1, 15:1 y 10:1) para obtener la base libre del compuesto del título. Se usa un método similar al Procedimiento general 2-1 para dar el compuesto del título como un sólido blanco (589 mg, 83%). EM (ES+) m/z: 246 $(M+H)^+$.

Procedimiento general 4-1

Se agrega 7-cloro-6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (1 equiv.), el agente alquilante apropiado (1.2 equiv.), K_2CO_3 molido (3 equiv.) y KI (0.1 equiv.) para un solvente adecuado

(acetona, etanol o acetonitrilo) y se calienta hasta reflujo durante 6 hasta 16 h a menos que se especifique de otra manera. Se enfría la mezcla de reacción a temperatura ambiente, se apaga con HCl acuoso 1N y se extrae la capa acuosa 3 veces con EtOAc. Se combinan las fracciones orgánicas, se lava con $NaHCO_3$ acuoso sturado, salmuera, se seca sobre Na_2SO_4, se filtran y se concentran in vacuo. Se purifica por cromatografía en gel de sílice eluido con mezclas de hexano/EtOAc.

Procedimiento general 4-2

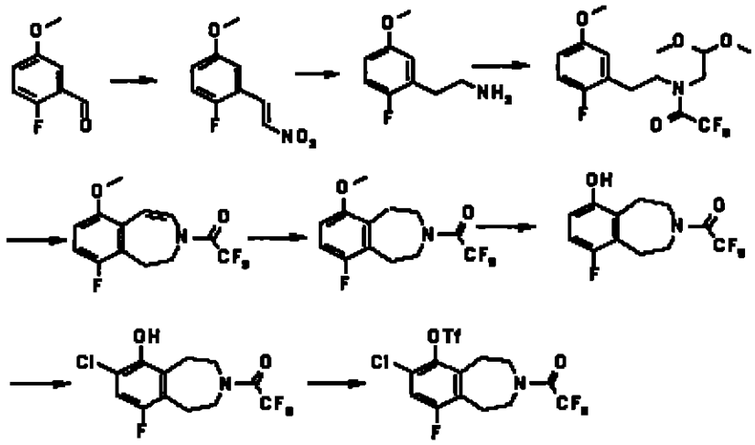
Se agrega 7-cloro-6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (1 equiv.), el alcohol apropiado (1.1 equiv.), trifenilfosfina (1.2 equiv.) y dietil azodicarboxilato (1.1 equiv.) secuencialmente para THF anhidro. Se agita la mezcla a temperatura ambiente bajo nitrógeno. Se vuelve a agregar trifenilfosfina (1.2 equiv.) y dietil azodicarboxilato (1.1 equiv.) si la reacción no se ha completado (monitoreado por CCD). Se diluye la mezcla con EtOAc, se lava con $NaHCO_3$ acuoso saturado, salmuera, se seca sobre Na_2SO_4 y se concentra in vacuo. Se purifica por cromatografía en gel de sílice eluido con mezclas de hexano/EtOAc.

Procedimiento general 4-3

Se agrega 7-cloro-6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (1 equiv.), el alcohol apropiado (1.2-1.5 equiv.) y trifenilfosfina (1.5 equiv.) secuencialmente para THF anhidro. Se agita la mezcla a 0°C bajo nitrógeno durante 10 min. Se agrega 1,1'-(azodicarbonil)dipiperidina (1.5 equiv.) y se deja la mezcla entibiar a temperatura ambiente durante 16 h. Se diluye con éter, se filtra y se concentra in vacuo. Se purifica por cromatografía en gel de sílice eluido con mezclas de hexano/EtOAc.

Preparación 6

7-Cloro-9-fluoro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina



1-Fluoro-4-metoxi-2-(2-nitro-vinil)-bencen : Se calienta 2-fluoro-5-metoxibenzaldehído (15 g, 97.4 mmol) con nitrometano (32 mL, 584 mmol) y acetato de amonio (30 g, 390 mmol) en ácido acético (136 mL) bajo reflujo durante 30 min. Se evapora el solvente y se disuelve el residuo en éter. Se lava la fracción orgánica con agua, $NaHCO_3$ acuoso saturado y se evapora para dar el intermediario deseado (18.7 g, 97%). CG-EM m/z: 197 $(M)^+$.

2-(2-Fluoro-5-metoxifenil)-etilamina: Cuidadosamente se agrega ácido sulfúrico (14.7 mL, 265 mmol) gota a gota a 0°C para hidruro de aluminio de litio (solución 1M en THF, 565 mL) con agitación eficiente. Se calienta la mezcla a temperatura ambiente durante 20 min y luego se enfría de regreso hasta 0°C. Se agrega una solución de 1-fluoro-4-metoxi-2-(2-nitro-vinil)-benceno (18.7 g, 95 mmol) en THF (150 mL) por una cánula y se agita 2.5 h a temperatura ambiente. Se enfría la mezcla a 0°C, cuidadosamente se agrega agua (4.6 mL) seguido por NaOH acuoso 2N (4.6 mL) y agua (6.5 mL). Se elimina el precipitado por filtración y se evapora el filtrado para dar el intermediario deseado (16 g, 100 %). EM (ES+) m/z: 170 $(M+H)^+$.

N-(2,2-Dimetoxi-etil)-2,2,2-trifluoro-N-[2-(2-fluoro-5-metoxi-fenil)-etil]-acetamida: Se disuelve 2-(2-fluoro-5-metoxifenil)-etilamina (16 g, 95 mmol) y dimetoxi acetaldehído (60% acuoso, 21.5 mL, 142 mmol) en metanol (500 mL). Después de 1.5 h, cuidadosamente se agrega borohidruro de sodio (5.39 g, 142 mmol) a 0°C y luego se agita a temperatura ambiente durante 3 h. Se agrega acetona y se evapora la mezcla. Se disuelve el residuo en DCM (250 mL), se enfría a 0° C y se agrega trietilamina (26.5 mL, 190 mmol) y anhídrido trifluoroacético (20.1 mL, 142 mmol). Después de 30 min, se lava la mezcla con HCl acuoso 1N (4 x 100 mL), salmuera y $NaHCO_3$ acuoso saturado. Se seca la capa orgánica sobre Na_2SO_4 y se concentra in vacuo. Se purifica por cromatografía en gel de sílice para dar el intermediario deseado (19.7 g, 59%). EM (ES+) m/z: 322 $(M-OMe)^+$.

9-Fluoro-6-metoxi-3-(2,2,2-trifluoroacetil)-2,3-dihidro-1H-benzo[d]azepina: Se disuelve N-(2,2-dimetoxi-etil)-2,2,2-trifluoro-N-[2-(2-fluoro-5-metoxi-fenil)-etil]-acetamida (5 g, 14.2 mmol) en clorobenceno (100 mL). Se agrega ácido polifosfórico (5 g) y P_2O_5 (2.5 g) y se calienta a 80°C durante 2 h. Se agrega agua a la mezcla caliente, se enfría hasta temperatura ambiente y se extrae con DCM. Se secan los

extractos orgánicos sobre Na_2SO_4 y se concentra in vacuo para obtener el intermediario deseado (3.0 g, 73%). EM (ES+) m/z: 290 $(M+H)^+$.

9-Fluoro-6-metoxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Se disuelve 9-fluoro-6-metoxi-3-(2,2,2-trifluoroacetil)-2,3-dihidro-1H-benzo[d]azepina (9.4 g, 32.4 mmol) con 10% de Pd/C (la base seca, tipo Degussa, 1.4 g, 0.65 mmol) en EtOAc/etanol (1:1, 200 mL) y se agita a temperatura ambiente bajo un globo de hidrógeno durante 4.5 h. Se filtra la mezcla a través de una almohadilla de gel de sílice y se evapora el filtrado para obtener el intermediario deseado (8.6 g, 91%). EM (ES+) m/z: 292 $(M+H)^+$.

9-Fluoro-6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Se disuelve 9-fluoro-6-metoxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (8.1 g, 27.7 mmol) en DCM (250 mL), se enfría a 0°C y se agrega tribromuro de boro (5.24 mL, 55.5 mmol). Se agita a temperatura ambiente durante 1.5 h, se lava la mezcla con salmuera, se seca la capa orgánica sobre Na_2SO_4 y se concentra in vacuo para obtener el intermediario deseado (7.6 g, 99%). EM (ES+) m/z: 278 $(M+H)^+$.

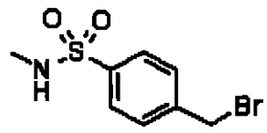
7-Cloro-9-fluoro-6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Se disuelve 9-fluoro-6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (1.0 g, 3.6 mmol) en tolueno (36 mL) con diisopropilamina (41 µL, 0.29 mmol). Se calienta a 60°C y se agrega gota a gota una solución de cloruro de sulfurilo (0.32 mL, 3.97 mmol) en tolueno (10 mL). Después de 2 h, se lava la mezcla con salmuera, se seca la capa orgánica sobre Na_2SO_4 y se evapora en gel de sílice. Se purifica por cromatografía en gel de sílice eluido con EtOAc/hexano (0:1 to 1:0) para obtener el intermediario deseado (1.0 g, 92%). EM (ES+) m/z: 312 $(M+H)^+$.

7-Cloro-9-fluoro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Se enfría una solución de 7-cloro-9-fluoro-6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (2.5 g, 8.0 mmol), piridina (3.25 mL, 40.2 mmol) y DCM (80 mL) a 0°C y se agrega gota a gota anhídrido trifluorometansulfónico (2.43 mL, 14.5 mmol) durante 20 min. Se agita a temperatura ambiente durante 1 h. Se lava la mezcla de reacción secuencialmente con HCl acuoso 1N, solución de $NaHCO_3$ saturada y salmuera. Se seca la fracción

orgánica sobre Na_2SO_4 y se concentra in vacuo. Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (gradiente desde 19:1 hasta 1:1) para obtener el compuesto del título (3.1 g, 87%).

Preparación 7

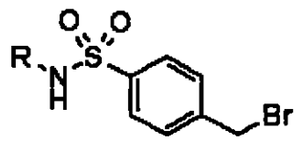
4-Bromometil-N-metil-bencensulfonamida



Se mezcla cloruro de 4-(bromometil)bencensulfonilo (2.7 g, 10 mmol), carbonato de potasio anhidro (1.4 g, 10 mmol) y THF anhidro (60 mL) bajo nitrógeno. Se enfría la mezcla en un baño de hielo, se agrega gota a gota una solución 2M de metilamina en THF, y se agita a esta temperatura durante 30 min. Se elimina el baño de hielo y se agita a temperatura ambiente durante 16 h. Se diluye con EtOAc luego se lava con HCl acuoso 1N. Se separa la capa orgánica, se seca sobre Na_2SO_4 y se concentra in vacuo. Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (1:0, 4:1, 7:3 y 13:7) para obtener el compuesto del título (1.5 g, 71%). EM (ES+) m/z: 266 $(M+H)^+$.

Los compuestos de las preparaciones 8-9 pueden prepararse esencialmente como se describen en la Preparación 7 al usar cloruro de 4-(bromometil)bencensulfonilo y la amina

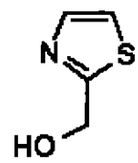
apropiada. Los datos de rendimiento y EM (ES+) se muestran en la Tabla a continuación.



Prep.	NH-R	Compuesto	Rendimiento (%)	EM (ES+) m/z
8	NH-CH_2CH_3	4-Bromometil-N-etil-bencensulfonamida	43	278 $(M+H)^+$
9	NH-CH_2CH_2F	4-Bromometil-N-(2-fluoroetil)-bencensulfonamida	39	296 $(M+H)^+$

Preparación 10

Tiazol-2-il-metanol

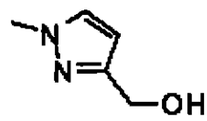


Se mezcla bajo nitrógeno 2-tiazolcarboxaldehído (1.1 g, 10 mmol) y etanol (30 mL). Se agrega borohidruro de sodio (416 mg, 11 mmol) a 0°C. Se agita y se calienta la mezcla lentamente a temperatura ambiente durante 12 h. Se apaga con cloruro de amonio acuoso saturado y se concentra in vacuo. Se

diluye el residuo con EtOAc y se lava con salmuera. Se seca la fracción orgánica sobre Na_2SO_4 y se concentra in vacuo para obtener el compuesto del título como un aceite (1.0 g, 87%). EM (ES+) m/z: 116 $(M+H)^+$.

Preparación 11

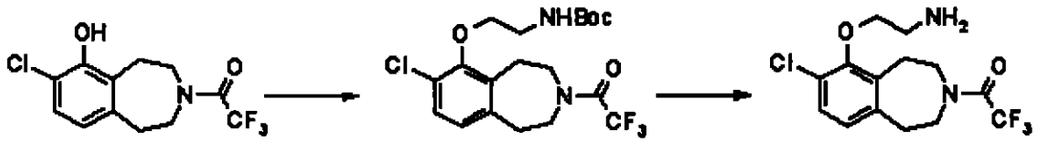
(1-Metil-1H-pirazol-3-il)-metanol



Se disuelve 3-dimetoximetil-1-metilpirazol (1.562 g, 10 mmol) en acetona (100 mL), se agrega ácido p-toluensulfónico (190 mg, 1.0 mmol) y se agita a temperatura ambiente durante 12 h. Se eliminan los volátiles in vacuo, se disuelve el residuo en EtOAc, se lava con $NaHCO_3$ acuoso saturado, se seca sobre Na_2SO_4, se filtran y se concentran in vacuo para proporcionar un aceite. Se disuelve el aceite en metanol (15 mL), se agrega borohidruro de sodio (567 mg, 15 mmol) y se agita la mezcla de reacción a temperatura ambiente durante 12 h. Se eliminan los volátiles in vacuo, se disuelve el residuo en EtOAc, se lava con $NaHCO_3$ acuoso saturado, se seca sobre Na_2SO_4, se filtran y se concentran in vacuo. Se purifica por cromatografía en gel de sílice eluido con EtOAc/hexano (6:1) para dar el compuesto del título como un aceite (530 mg, 47%).

Preparación 12

6-(2-Amino-etoxi)-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

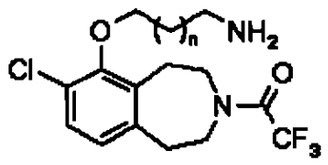


6-(2-tert-Butoxicarbonilamino-etoxi)-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Se usa un método similar al Procedimiento general 4-3, al usar 7-cloro-6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (277 mg, 0.94 mmol) y N-(tert-butoxicarbonil)etanolamina (244 mg, 1.51 mmol) para dar, después de la cromatografía en gel de sílice eluido con hexano/EtOAc (1:0 and 3:1), el intermediario deseado (392 mg, 95%). EM (ES+) m/z: 337 $(M+H-Boc)^+$.

6-(2-Amino-etoxi)-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Se disuelve 6-(2-tert-butoxicarbonilamino-etoxi)-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (997 mg, 2.28 mmol) en cloruro de hidrógeno 4M en dioxano (15 mL) y se agita a temperatura ambiente durante 30 min. Se concentra para obtener la sal de clorohidrato. Se disuelve la sal en DCM y se lava con $NaHCO_3$ acuoso saturado. Se extrae la capa acuosa básica con DCM. Se secan los extractos orgánicos combinados

sobre $MgSO_4$, y se concentra in vacuo para proporcionar el compuesto del título (731 mg, 95%). EM (ES+) m/z: 337 $(M+H)^+$.

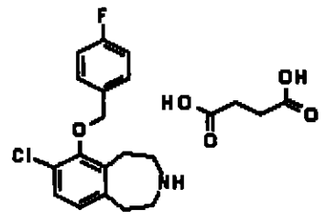
Los compuestos de las preparaciones 13-14 pueden prepararse esencialmente como se describen en la Preparación 12 al usar 7-cloro-6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina y el alcohol apropiado. Los datos de rendimiento general y EM (ES+) se muestran en la Tabla a continuación.



Prep.	n	Compuesto	Rendimiento (%)	MS (ES+) m/z
13	1	6-(3-Amino-propoxi)-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	94	351 $(M+H)^+$
14	2	6-(4-Amino-butoxi)-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	89	365 $(M+H)^+$

Ejemplo 7

Succinato de 7-Cloro-6-(4-fluorobenciloxi)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

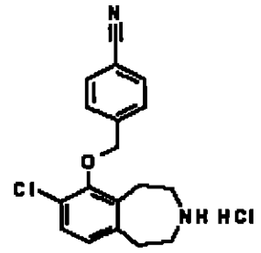


Se prepara una mezcla espesa de hidruro de sodio (60% en aceite mineral; 99 mg, 2.5 mmol) en DMF (4 mL) y se calienta a 65° C. Se agrega una solución de 3-tert-butoxicarbonil-7-cloro-6-hidroxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (250 mg, 0.84 mmol) en DMF (5 mL) gota a gota y se agita durante 1 h. Se agrega una solución de bromuro de 4-fluorobencilo (191 mg, 1.0 mmol) en DMF (1 mL), se agita a 65°C durante 1.5 h y se enfría a temperatura ambiente. Se agrega agua (1 mL) y se concentra la mezcla hasta un residuo aceitoso. Se divide el residuo entre EtOAc/hexano (1:1) y agua. Se seca la capa orgánica sobre Na_2SO_4, se filtran y se concentran in vacuo. Se disuelve el residuo en DCM, se lava con NaOH acuoso 2N, se seca la capa orgánica sobre Na_2SO_4, se filtra, y se concentra in vacuo. Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (20:1, 10:1 y 7:1) para dar 3-tert-butoxicarbonil-7-cloro-6-(4-fluorobenciloxi)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite.

Se usa un método similar al Procedimiento general 1-5 para desproteger 3-tert-butoxicarbonil-7-cloro-6-(4-fluorobenciloxi)-2,3,4,5-tetrahidro-1H-benzo[d]azepina. Se purifica por cromatografía SCX seguido por cromatografía en gel de sílice eluido con DCM/amoniaco 2M en metanol (1:0, 50:1, 20:1, 15:1 y 10:1) para dar la base libre del compuesto del título. Se usa un método similar al Procedimiento general 2-1 para dar el compuesto del título como un sólido blanco (178 mg, 50%). EM (ES+) m/z: 306 $(M+H)^+$.

Ejemplo 8

Clorohidrato de 7-Cloro-6-(4-cianobenciloxi)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



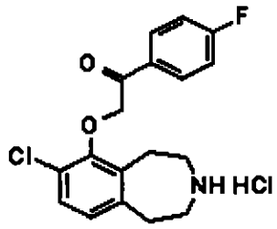
Se combinan 3-tert-butoxicarbonil-7-cloro-6-hidroxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (200 mg, 0.67 mmol), carbonato de potasio (111 mg, 0.8 mmol), y bromuro de 4-cianobencilo (263 mg, 1.34 mmol) en DMSO (5 mL) y se calienta la mezcla agitada a 100° C durante 24 h. Se enfría a temperatura ambiente y se divide la mezcla entre agua y EtOAc/hexano (1:1). Se lava la capa orgánica con salmuera y

se seca sobre Na_2SO_4, se filtran y se concentran in vacuo. Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (5:1) para dar 3-tert-butoxicarbonil-7-cloro-6-(4-cianobenciloxi)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite.

Se usa un método similar al Procedimiento general 1-5 para desproteger 3-tert-butoxicarbonil-7-cloro-6-(4-cianobenciloxi)-2,3,4,5-tetrahidro-1H-benzo[d]azepina. Se purifica por cromatografía SCX para dar la base libre del compuesto del título. Se usa un método similar al Procedimiento general 2-2 para dar el compuesto del título como un solido completamente blanco (66 mg, 27%). EM (ES+) m/z: 313 $(M+H)^+$.

Ejemplo 9

Clorohidrato de 7-Cloro-6-[2-(4-fluorofenil)-2-oxo-etoxi)]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



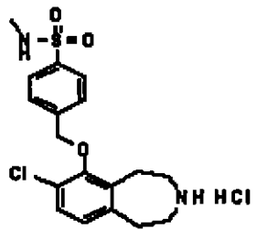
Se usa un método similar al Procedimiento general 4-1, al usar 7-cloro-6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (294 mg, 1.0 mmol) y 2-bromo-4'-fluoroacetofenona (260 mg, 1.2 mmol) para dar, después de

la purificación por cromatografía en gel de sílice eluido con hexano/EtOAc (7:1), 7-cloro-6-[2-(4-fluorofenil)-2-oxo-etoxi)]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un sólido (402 mg, 93%). EM (ES+) m/z: 430 $(M+H)^+$.

Se usa un método similar al Procedimiento general 1-1 para desproteger 7-cloro-6-[2-(4-fluorofenil)-2-oxo-etoxi)]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (402 mg, 0.93 mmol). Se purifica por cromatografía en gel de sílice eluido con DCM/amoniaco 2M en metanol (96:4) para dar la base libre del compuesto del título (278 mg, 89%). EM (ES+) m/z: 334 $(M+H)^+$. Se usa un método similar al Procedimiento general 2-3 para dar el compuesto del título.

Ejemplo 10

Clorohidrato de 7-Cloro-6-(4-metilsulfamoil-benciloxi)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

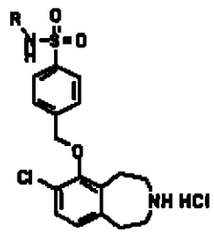


Se disuelve bajo nitrógeno 7-cloro-6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (200 mg, 0.68 mmol) en acetona (30 mL). Se agrega carbonato de

potasio anhidro en polvo (276 mg, 2.0 mmol) y yoduro de potasio en polvo (11.3 mg, 0.068 mmol) seguido por 4-bromometil-N-metil-bencenosulfonamida (528 mg, 2.0 mmol). Se agita la mezcla de reacción a temperatura ambiente durante 12 h. Se concentra in vacuo, se diluye con EtOAc y se lava 2 veces con HCl acuoso 1N. Se separa la capa orgánica, se seca sobre Na_2SO_4 y se concentra in vacuo. Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (1:0 y 4:1) para obtener 7-cloro-6-(4-metilsulfamoil-benciloxi)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (201 mg, 60%).

Se usa un método similar al Procedimiento general 1-1 para desproteger 7-cloro-6-(4-metilsulfamoil-benciloxi)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (196 mg, 0.41 mmol). Se purifica por columna SCX para dar la base libre del compuesto del título (110 mg, 70%). EM (ES+) m/z: 381 $(M+H)^+$. Se usa un método similar al Procedimiento general 2-2 para obtener el compuesto del título.

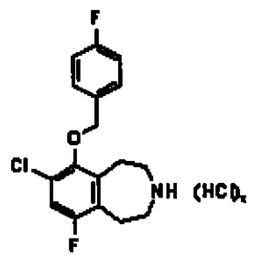
Ejemplos 11-12 pueden prepararse esencialmente como se describe en el Ejemplo 10 al usar 7-cloro-6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina y el bromuro apropiado. Los datos EM (ES+) se muestran en la Tabla a continuación.



Ej.	NH-R	Compuesto	EM (ES+) m/z
11	$NH-CH_2-CH_3$	Clorohidrato de 7-Cloro-6-(4-etilsulfamoil-benciloxi)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	395 $(M+H)^+$
12	$NH-CH_2-CH_2F$	Clorohidrato de 7-Cloro-6-[4-(2-fluoroetilsulfamoil)-benciloxi]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	413 $(M+H)^+$

Ejemplo 13 Allen 1

Clorohidrato de 7-Cloro-9-fluoro-6-(4-fluorobenciloxi)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

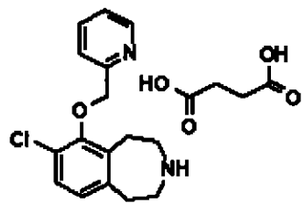


Se disuelve 7-cloro-9-fluoro-6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (0.25 g, 0.8 mmol) en DMF (8 mL), se agrega carbonato de potasio (0.56 g, 4.0 mmol) y bromuro de 4-fluorobencilo (0.46 mL, 2.4 mmol). Después de 14 h a 90°C, se diluye con éter y se lava con salmuera. Se seca la capa orgánica sobre Na_2SO_4 y se evapora en gel de sílice. Se purifica por cromatografía en gel de sílice eluido con EtOAc/hexano (0:1 hasta 1:0) para obtener 7-cloro-9-fluoro-6-(4-fluorobenciloxi)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina.

Se usa un método similar al Procedimiento general 1-1, al usar 7-cloro-9-fluoro-6-(4-fluorobenciloxi)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina, para dar la base libre del compuesto del título. Se usa un método similar al Procedimiento general 2-2 para obtener el compuesto del título (275 mg, 95%). EMAR calculado para $C_{17}H_{17}NOF_2Cl$ 324.0902, encontrado 324.0957.

Ejemplo 14

Succinato de 7-Cloro-6-(piridin-2-ilmetoxi)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

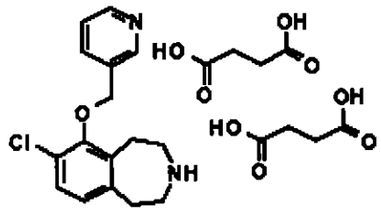


Se prepara una mezcla espesa de hidruro de sodio (60% en aceite mineral, 168 mg, 4.2 mmol) en DMF (4 mL) y se calienta a 65° C. Se agrega gota a gota una solución de 3-tert-butoxicarbonil-7-cloro-6-hidroxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (250 mg, 0.84 mmol) en DMF (5 mL) y se agita durante 1 h. Se agrega una solución de hidrobromuro de 2-(bromometil)-piridina (256 mg, 1 mmol) en DMF (1 mL), se agita a 65° C durante 0.5 h y se enfría a temperatura ambiente. Se agrega agua (1 mL) y se concentra la mezcla de reacción hasta un residuo aceitoso. Se divide el residuo entre EtOAc/hexano (1:1) y agua. Se seca la capa orgánica sobre Na_2SO_4, se filtran y se concentran. Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (10:1, 5:1 y 3:1) para dar 3-tert-butoxicarbonil-7-cloro-6-(piridin-2-ilmetoxi)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite.

Se usa un método similar al Procedimiento general 1-5 para desproteger 3-tert-butoxicarbonil-7-cloro-6-(piridin-2-ilmetoxi)-2,3,4,5-tetrahidro-1H-benzo[d]azepina. Se purifica por cromatografía SCX para dar la base libre del compuesto del título. Se usa un método similar al Procedimiento general 2-1 para dar el compuesto del título como un sólido blanco (228 mg, 67%). EM (ES+) m/z: 289 $(M+H)^+$.

Ejemplo 15

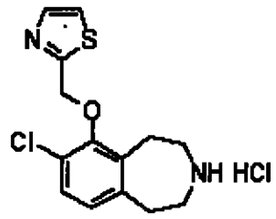
Disuccinato de 7-Cloro-6-(piridin-3-ilmetoxi)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al Ejemplo 14, al usar 3-tert-butoxicarbonil-7-cloro-6-hidroxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (250 mg, 0.84 mmol) y hidrobromuro de 3-(bromometil)-piridina (256 mg, 1 mmol) para dar la base libre del compuesto del título. Se usa un método similar al Procedimiento general 2-1 con 2 equivalentes de ácido succínico para dar el compuesto del título como un sólido blanco (354 mg, 80%). EM (ES+) m/z: 289 $(M+H)^+$.

Ejemplo 16

Clorohidrato de 7-Cloro-6-(tiazol-2-ilmetoxi)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



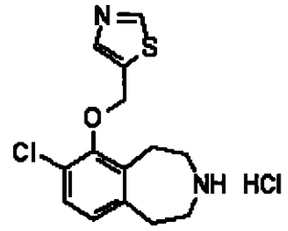
Se usa un método similar al Procedimiento general 4-2, al usar 7-cloro-6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-

tetrahidro-1H-benzo[d]azepina y tiazol-2-il-metanol (86.2 mg, 0.75 mmol) para dar, después de la cromatografía en gel de sílice eluido con hexano/EtOAc (9:1 y 7:3), 7-cloro-6-(tiazol-2-ilmetoxi)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (163 mg, 61%). EM (ES+) m/z 391 $(M+H)^+$.

Se usa un método similar al Procedimiento general 1-1 para desproteger 7-cloro-6-(tiazol-2-ilmetoxi)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina. Se purifica por cromatografía en gel de sílice eluido con DCM/amoniaco 2M en metanol (94:6) para obtener la base libre del compuesto del título (99 mg, 81%). EM (ES+) m/z: 295 $(M+H)^+$. Se usa un método similar al Procedimiento general 2-2 para dar el compuesto del título.

Ejemplo 17

Clorohidrato de 7-Cloro-6-(tiazol-5-ilmetoxi)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

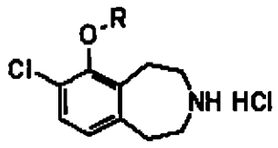


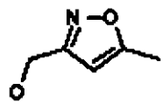
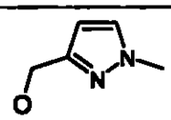
Se usa un método similar al Procedimiento general 4-2, al usar 7-cloro-6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (294 mg, 1.0 mmol) y 5-

hidroximetiltiazol (127 mg, 1.1 mmol) para dar, después de la cromatografía en gel de sílice eluido con EtOAc/hexano (1:3), 7-cloro-6-(tiazol-5-ilmetoxi)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite (350 mg, 89%). EM (ES+) m/z: 391 $(M+H)^+$.

Se usa un método similar al Procedimiento general 1-1 para desproteger 7-cloro-6-(tiazol-5-ilmetoxi)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (350 mg, 0.90 mmol). Se purifica por cromatografía en gel de sílice eluido con DCM/amoniaco 2M en metanol (95:5) para dar la base libre del compuesto del título (203 mg, 76%). EM (ES+) m/z: 295 $(M+H)^+$. Se usa un método similar al Procedimiento general 2-2 para dar el compuesto del título.

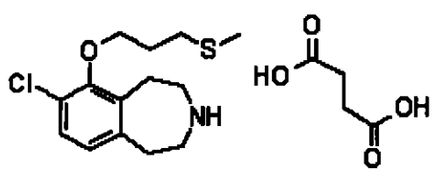
Los ejemplos 18-19 pueden prepararse esencialmente como se describe en el Ejemplo 17 al usar 7-cloro-6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina y el alcohol apropiado. Los datos de rendimiento general y EM (ES+) data se muestran en la Tabla a continuación.



Ej.	-R	Compuesto	Rendimiento (%)	EM (ES+) m/z
18		Clorohidrato de 7-Cloro-6-(5-metil-isoxazol-3-ilmetoxi)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	47	293 $(M+H)^+$
19		Clorohidrato de 7-Cloro-6-(1-metil-1H-pirazol-3-ilmetoxi)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	39	292 $(M+H)^+$

Ejemplo 20

Succinato de 7-Cloro-6-(3-metiltio-propoxi)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



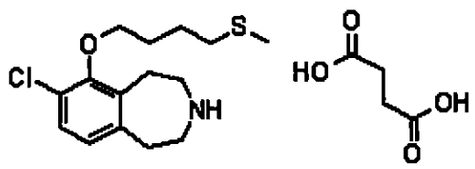
Se usa un método similar al Procedimiento general 4-2, al usar 7-cloro-6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 3-(metiltio)-1-propanol (191

mg, 1.8 mmol) para dar, después de la cromatografía en gel de sílice eluido con EtOAc/hexano (1:8), 7-cloro-6-(3-metiltio-propoxi)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite (65 mg, 14%).

Se usa un método similar al Procedimiento general 1-1 para desproteger 7-cloro-6-(3-metiltio-propoxi)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (65 mg, 0.17 mmol). Se purifica por cromatografía en gel de sílice eluido con DCM/amoniaco 2M en metanol (94:6) para dar la base libre del compuesto del título (25 mg, 51%). EM (ES+) m/z: 286 $(M+1)^+$. Se usa un método similar al Procedimiento general 2-1 para dar el compuesto del título.

Ejemplo 21

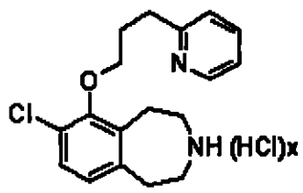
Succinato de 7-Cloro-6-(4-metiltio-butoxi)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al Ejemplo 20, al usar 7-cloro-6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 4-(metiltio)-1-butanol para dar el compuesto del título. EM (ES+) m/z: 300 $(M+1)^+$.

Ejemplo 22

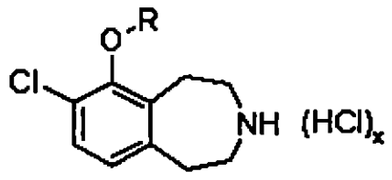
Clorohidrato de 7-Cloro-6-(3-piridin-2-il-propoxi)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

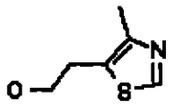
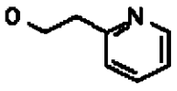


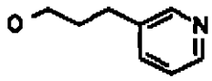
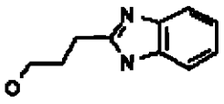
Se usa un método similar al Procedimiento general 4-3, al usar 7-cloro-6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (50 mg, 0.17 mmol) y 3-(2-piridil)-1-propanol (35 mg, 0.255 mmol) para dar, después de la fase inversa CLAR (10-95% del solvente B en 12.8 min, 25 mL/min; solvente A: agua, 0.1% ácido trifluoroacético; solvente B: acetonitrilo, 0.1% ácido trifluoroacético; columna: YMC SH-341-5, S-5□m, 12 nm, 100 x 20 mm), 7-cloro-6-(3-piridin-2-il-propoxi)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina.

Se usa un método similar al Procedimiento general 1-1, al usar 7-cloro-6-(3-piridin-2-il-propoxi)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina para dar la base libre del compuesto del título. Se usa un método similar al Procedimiento general 2-2 para dar el compuesto del título como un sólido (26 mg, 39%). EM (ES+) m/z: 317 $(M+H)^+$.

Los Ejemplos 23-26 pueden prepararse esencialmente como se describe en el Ejemplo 22 al usar 7-cloro-6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina y el alcohol apropiado. Los datos de rendimiento general y EM (ES+) se muestran en la Tabla a continuación.

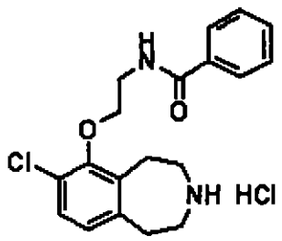


Ej.	O-R	Compuesto	Rendimiento (%)	EM (ES+) m/z
23		Clorohidrato de 7-Cloro-6-[2-(4-metil-tiazol-5-il)-etoxi]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	83	323 $(M+H)^+$
24		Clorohidrato de 7-Cloro-6-(2-piridin-2-il-etoxi)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	83	303 $(M+H)^+$

Ej.	-R	Compuesto	Rendimiento (%)	EM (ES+) m/z
25		Clorohidrato de 7-Cloro-6-(3-piridin-3-il-propoxi)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	83	317 $(M+H)^+$
26		Clorohidrato de 6-[3-(1H-Benzimidazol-2-il)-propoxi]-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina	8	356 $(M+H)^+$

Ejemplo 27

Clorohidrato de 6-(2-Benzoilamino-etoxi)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina



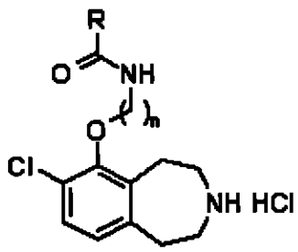
Se combina cloruro de benzoilo (19.3 mg, 0.137 mmol), PS-morfolina (109 mg, 0.272 mmol), 6-(2-amino-etoxi)-7-cloro-

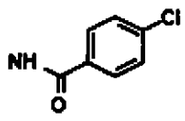
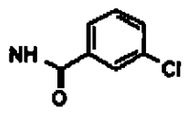
3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (46 mg, 0.137 mmol) en DCM (1.5 mL) y se agita a temperatura ambiente durante 16 h. Se filtra la resina, se lava con DCM y se concentra in vacuo. Se purifica por fase inversa CLAR (10-95% del solvente B en 12.8 min, 25 mL/min; solvente A: agua, 0.1% ácido trifluoroacético; solvente B: acetonitrilo, 0.1% ácido trifluoroacético; columna: YMC SH-341-5, S-5 μm, 12 nm, 100 x 20 mm) para dar 6-(2-benzoilamino-etoxi)-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina.

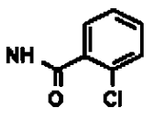
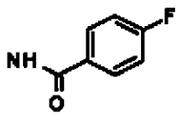
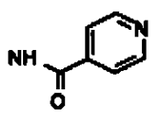
Se usa un método similar al Procedimiento general 1-1, al usar 6-(2-benzoilamino-etoxi)-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina para dar la base libre del compuesto del título. Se usa un método similar al Procedimiento general 2-2 para dar el compuesto del título como un sólido (51 mg, 98%). EM (ES+) m/z: 345 $(M+H)^+$.

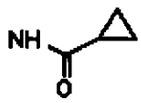
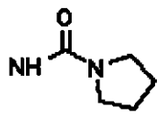
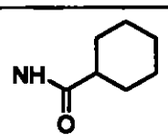
Los Ejemplos 28-40 pueden prepararse esencialmente como se describe en el Ejemplo 27, al usar 6-(2-amino-etoxi)-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina o 6-(3-amino-propoxi)-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina o 6-(4-amino-butoxi)-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina y el cloruro de acilo

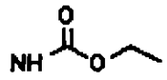
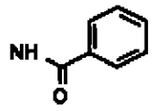
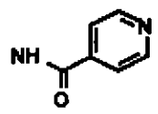
apropiado. Los datos de rendimiento general y EM (ES+) se muestran en la Tabla a continuación.

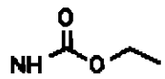
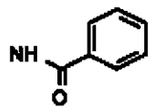


Ej.	NH-CO-R	n	Compuesto	Rendimiento (%)	MS (ES+) m/z
28		2	Clorohidrato de 7-Cloro-6-[2-(4-clorobenzoilamino)-etoxi]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	46	380 $(M+H)^+$
29		2	Clorohidrato de 7-Cloro-6-[2-(3-clorobenzoilamino)-etoxi]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	63	380 $(M+H)^+$

Ej.	NH-CO-R	n	Compuesto	Rendimiento (%)	EM (ES+) m/z
30		2	Clorohidrato de 7-Cloro-6-[2-(2-clorobenzoil amino)-etoxi]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	18	380 $(M+H)^+$
31		2	Clorohidrato de 7-Cloro-6-[2-(4-fluoro benzoilamino)-etoxi]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	18	363 $(M+H)^+$
32		2	Clorohidrato de 7-Cloro-6-{2-[(piridina-4-carbonil)-amino]-etoxi}-2,3,4,5-tetrahidro-1H-benzo[d]azepina	4	346 $(M+H)^+$

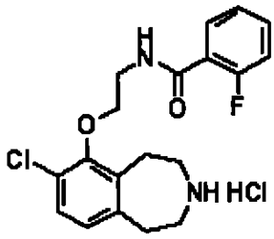
Ej.	NH-C -R	n	Compuesto	Rendimiento (%)	EM (ES+) m/z
33		2	Clorohidrato de 7-Cloro-6-[2-(ciclopropan carbonil-amino) -etoxi]-2,3,4,5 -tetrahidro-1H-benzo[d]azepina	47	309 $(M+H)^+$
34		2	Clorohidrato de 7-Cloro-6-{2-[(pirrolidina-1-carbonil)-amino]-etoxi}-2,3,4,5-tetrahidro-1H-benzo[d]azepina	6	338 $(M+H)^+$
35		2	Clorohidrato de 7-Cloro-6-[2-(ciclohexan carbonil-amino) -etoxi]-2,3,4,5 -tetrahidro-1H-benzo[d]azepina	40	351 $(M+H)^+$

Ej.	NH-CO-R	n	Compuesto	Rendimiento (%)	ES (ES+) m/z
36		3	Clorohidrato de 7-Cloro-6-(3-etoxicarbonil amino-propoxi)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	63	327 $(M+H)^+$
37		3	Clorohidrato de 6-(3-Benzoil amino-propoxi)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina	72	359 $(M+H)^+$
38		3	Clorohidrato de 7-Cloro-6-{3-[(piridina-4-carbonil)-amino]-propoxi}-2,3,4,5-tetrahidro-1H-benzo[d]azepina	12	360 $(M+H)^+$

Ej.	NH-CO-R	n	Compuesto	Rendimiento (%)	ES (ES+) m/z
39		4	Clorohidrato de 7-Cloro-6-(4-etoxicarbonilamino-butoxi)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	49	341 $(M+H)^+$
40		4	Clorohidrato de 6-(4-Benzoil amino-butoxi)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina	56	373 $(M+H)^+$

Ejemplo 41

Clorohidrato de 7-Cloro-6-[2-(2-fluorobenzoilamino)-etoxi]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



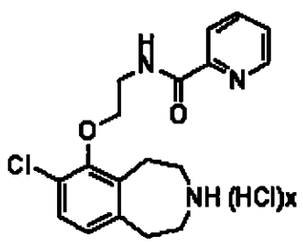
Se disuelve 6-(2-amino-etoxi)-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (100

mg, 0.297 mmol) en DCM (5 mL). Se agrega cloruro de 2-fluorobenzoilo (39 µL, 0.326 mmol), trietilamina (62 µL, 0.445 mmol) y se agita a temperatura ambiente durante 72 h bajo atmósfera de nitrógeno. Se diluye con DCM, se agrega HCl acuoso 1M y se extrae la fase acuosa con DCM. Se secan los extractos orgánicos combinados sobre $MgSO_4$ y se concentra in vacuo. Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (7:3 y 2:1) para dar 7-cloro-6-[2-(2-fluorobenzoilamino)-etoxi]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (111 mg, 82%).

Se usa un método similar al Procedimiento general 1-1, al usar 7-cloro-6-[2-(2-fluorobenzoilamino)-etoxi]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina para dar la base libre del compuesto del título. Se usa un método similar al Procedimiento general 2-2 para dar el compuesto del título como un sólido (112 mg, 95%). EM (ES+) m/z: 363 $(M+H)^+$.

Ejemplo 42

Clorohidrato de 7-Cloro-6-{2-[(piridina-2-carbonil)-amino]-etoxi}-2,3,4,5-tetrahidro-1H-benzo[d]azepina

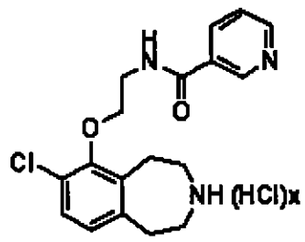


Se combina el ácido picolínico (40 mg, 0.327 mmol), EDC (57 mg, 0.297 mmol) y HOBT (40 mg, 0.297 mmol) en DCM (3 mL). Se agita durante 10 min a temperatura ambiente. Se agrega 6-(2-amino-etoxi)-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (100 mg, 0.297 mmol). Se agita durante 16 h a temperatura ambiente. Se diluye con DCM, se agrega agua y se extrae la capa acuosa con DCM. Se lava los extractos orgánicos combinados con NaOH acuoso 1M y salmuera. Se seca la capa orgánica sobre $MgSO_4$ y se concentra in vacuo. Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (3:2) para dar 7-cloro-6-{2-[(piridina-2-carbonil)-amino]-etoxi}-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (94 mg, 74%).

Se usa un método similar al Procedimiento general 1-1, al usar 7-cloro-6-{2-[(piridina-2-carbonil)-amino]-etoxi}-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina para dar la base libre del compuesto del título. Se usa un método similar al Procedimiento general 2-2 para dar el compuesto del título como un sólido (81 mg, 72%). EM (ES+) m/z: 346 $(M+H)^+$.

Ejemplo 43

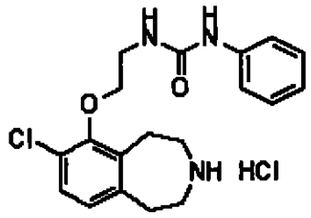
Clorohidrato de 7-Cloro-6-{2-[(piridina-3-carbonil)-amino]-etoxi}-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método al Ejemplo 42, al usar ácido nicotínico (40 mg, 0.327 mmol) y 6-(2-amino-etoxi)-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (100 mg, 0.297 mmol) para dar el compuesto del título como un sólido (105 mg, 93%). EM (ES+) m/z: 346 $(M+H)^+$.

Ejemplo 44

Clorohidrato de 7-Cloro-6-[2-(3-fenil-ureido)-etoxi]-2,3,4,5-tetrahidro-1H-benzo[d]azepina

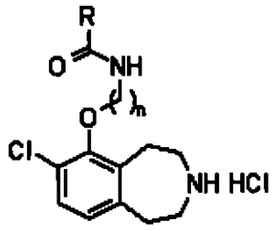


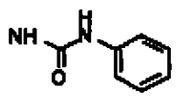
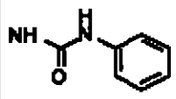
Se combina el fenil isocianato (16.3 mg, 0.137 mmol), 6-(2-amino-etoxi)-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (46 mg, 0.137 mmol) en DCM (1.5 mL) y se agita a temperatura ambiente durante 16 h. Se concentra in vacuo. Se purifica por fase inversa CLAR (10-95% del solvente B en 12.8 min, 25 mL/min; solvente A: agua, 0.1% ácido trifluoroacético; solvente B:

acetonitrilo, 0.1% ácido trifluoroacético; columna: YMC SH-341-5, S-5µm, 12 nm, 100 x 20 mm) para dar 7-cloro-6-[2-(3-fenil-ureido)-etoxi]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina.

Se usa un método similar al Procedimiento general 1-1, al usar 7-cloro-6-[2-(3-fenil-ureido)-etoxi]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina para dar la base libre del compuesto del título. Se usa un método similar al Procedimiento general 2-2 para dar el compuesto del título como un sólido (8 mg, 15%). EM (ES+) m/z: 360 $(M+H)^+$.

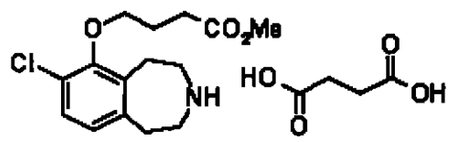
Los Ejemplos 45-46 pueden prepararse esencialmente como se describe en el Ejemplo 44 al usar fenil isocianata y el 6-(3-amino-propoxi)-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina apropiado o 6-(4-amino-butoxi)-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina. Los datos de rendimiento general y EM (ES+) se muestran en la Tabla a continuación.



Ej.	NH-CO-R	n	Compuesto	Rendimiento (%)	EM (ES+) m/z
45		3	Clorohidrato de 7-Cloro-6-[3-(3-fenil-ureido)-propoxi]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	36	374 $(M+H)^+$
46		4	Clorohidrato de 7-Cloro-6-[4-(3-fenil-ureido)-butoxi]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	28	388 $(M+H)^+$

Ejemplo 48

Succinato de 7-Cloro-6-(3-metoxicarbonil-propiloxi)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se agrega 4-bromobutirato de metilo (1.9 mL, 10.4 mmol) a una mezcla de 3-tert-butoxicarbonil-7-cloro-6-hidroxi-2,3,4,5-tetrahidro-benzo[d]azepina (310 mg, 1.0

mmol), DBU (0.23 mL, 1.6 mmol) y DMF (10 mL) a temperatura ambiente bajo nitrógeno. Se agita la mezcla de reacción durante 16 h. Se diluye con hexano/EtOAc (1:1, 60 mL), se lava la mezcla con NaCl acuoso al 10% (4 x 25 mL), se seca la capa orgánica sobre Na_2SO_4 y se concentra in vacuo. Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (19:1 to 2:3) para obtener 3-tert-butoxicarbonil-7-cloro-6-(3-metoxicarbonil-propiloxi)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (303 mg, 73%). EM (ES+) m/z: 398 $(M+H)^+$.

Se usa un método similar al Procedimiento general 1-5 para desproteger 3-tert-butoxicarbonil-7-cloro-6-(3-metoxicarbonil-propiloxi)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (295 mg, 0.74 mmol). Se purifica por cromatografía SCX seguido por cromatografía en gel de sílice eluido con DCM/amoniaco 2M en metanol (99:1 hasta 90:10) para dar la base libre del compuesto del título. Se usa un método similar al Procedimiento general 2-1 para dar el compuesto del título (160 mg, 52%). EM (ES+) m/z: 298 $(M+H)^+$.

Procedimiento general 5-1

Se disuelve el 3-(2,2,2-trifluoroacetil)-6-trifluorometano-sulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina apropiadamente substituido (1 equiv.),

acetato de paladio (II) (0.1-0.4 equiv.), BINAP (0.2-0.8 equiv.; relación de BINAP/catalizador 2:1) y carbonato de cesio (1.4-3.0 equiv.) en tolueno (solución de 0.2-0.05 M). Se agrega la amina (1-3 equiv.), se degasifica la mezcla con vacío/nitrógeno o purga de argón y se calienta a 80-110°C durante 4-16 h. Se enfría la mezcla a temperatura ambiente, se diluye con EtOAc, se filtra a través de una almohadilla de gel de sílice o a través de Celite® se lava con EtOAc o éter, y se evapora el solvente para obtener la mezcla cruda. Alternativamente, se divide la mezcla de reacción entre salmuera o $NaHCO_3$ acuoso saturado y EtOAc, éter o DCM, se seca la capa orgánica sobre Na_2SO_4, y se concentra para obtener la mezcla cruda. Se purifica la mezcla cruda por cromatografía en gel de sílice eluido con mezclas de hexano/EtOAc y además Cromatografía SCX si es necesario.

Procedimiento general 5-2

Se disuelve el 3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina apropiadamente substituido (1 equiv.), tris(dibenzcilidenacetona)dipaladio (0) (0.1-0.5 equiv.), BINAP (0.2-1.0 equiv.; relación BINAP/catalizador 2:1) y carbonato de cesio (1.4 equiv.) en tolueno (solución 0.05-0.5 M). Se degasifica bajo vacío y se rellena 3 veces con

nitrógeno. Se agrega la amina apropiadamente substituido (1.0-5.0 equiv.) y se calienta la mezcla a 80-100°C durante 2-16 h en un matraz sellado bajo una atmósfera de nitrógeno. Se enfría el matraz de reacción a temperatura ambiente, se diluye la mezcla con EtOAc o DCM, se filtra a través de Celite® y se concentra in vacuo. Se purifica por cromatografía en gel de sílice eluido con mezclas de hexano/EtOAc y además cromatografía SCX si es necesario.

Procedimiento general 5-3

Se agrega el 3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina apropiadamente substituido (1 equiv.), la amina apropiada (1.2-3.0 equiv.), acetato de paladio (II) (0.2-0.4 equiv.), tris(dibencilidenacetona)dipaladio (0) (0.1-0.2 equiv.), BINAP (0.6-1.2 equiv.; BINAP/catalizador relación 2:1), carbonato de cesio (2-2.5 equiv.) y tolueno o 1,4-dioxano (solución 0.05-0.2 M) a un matraz, se degasifica y se rellena 3 veces con nitrógeno. Se calienta la mezcla a 80-100°C durante 10-16 h. Se diluye la mezcla con EtOAc, se lava con $NaHCO_3$ acuoso saturado y salmuera, se seca sobre Na_2SO_4, se filtran y se concentran in vacuo para dar la mezcla cruda. Alternativamente se eliminan los volátiles de la mezcla de reacción para dar directamente la mezcla cruda, o

se filtra la mezcla de reacción a través de Celite® y se concentra in vacuo. Se purifica por cromatografía en gel de sílice eluido con meclas hexano/EtOAc y además cromatografía SCX si es necesario.

Procedimiento general 5-4

Se combinan 6-amino-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina, el bromuro apropiado (1.0-2.0 equiv.), carbonato de cesio o potasio (1.0-2.0 equiv.) y tolueno, DMF o acetonitrilo en un tubo sellado y se calienta a 50-150°C durante 3-72 h. Se enfria a temperatura ambiente y se evapora el solvente in vacuo para obtener la mezcla cruda. Alternativamente, se divide la mezcla de reacción entre dietil éter/salmuera (1:1), se seca la capa orgánica sobre Na_2SO_4 anhidro y se concentra para obtener la mezcla cruda. Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (1:0, 9:1, 4:1, 7:3 y 3:2).

Procedimiento general 6-1

Se disuelve ácido 4-(tert-butoxicarbonilamino-metil)-benzoico (1 equiv.), HATU (1 equiv.), DIEA (2 equiv.) y la amina apropiadamente substituido (1 equiv.) en DCM o DCM/DMF y se agita a temperatura ambiente durante 4-16 h. Se concentra in vacuo, se disuelve el residuo en DCM y se

lava sucesivamente con $NaHCO_3$ acuoso saturado, HCl acuoso 1N, agua, salmuera, y se seca sobre Na_2SO_4. Se filtran y se concentran la solución y se usa el material sin purificación adicional. Se deprotege el residuo al usar el Procedimiento general 1-5 y se purifica por cromatografía SCX.

Procedimiento general 6-2

Se disuelve ácido 4-(tert-butoxicarbonilamino-metil)-benzoico o sal de litio del ácido 5-(tert-butoxicarbonilamino-metil)-piridina-2-carboxílico (1 equiv.), HATU (1 equiv.), DIEA (2 equiv.) y la amina apropiadamente substituida (1 equiv.) en DCM o DCM/DMF y se agita a temperatura ambiente durante 4-16 h. Se concentra in vacuo, se disuelve el residuo en DCM y se lava sucesivamente con $NaHCO_3$ acuoso saturado, agua, salmuera, y se seca sobre Na_2SO_4. Se filtran y se concentran la solución y se usa el material sin purificación adicional. Se desprotege el residuo al usar el Procedimiento general 1-5 y se purifica por cromatografía SCX.

Procedimiento general 6-3

Se disuelve la acetofenona apropiadamente substituida (1.0-1.2 equiv.) en THF, se agrega etóxido de titanio (IV) (33-35% TiO_2, 2.0 equiv.) y el correspondiente (R)-2-metil-2-

propansulfinamida o (S)-2-metil-2-propansulfinamida (1.0 equiv.). Se calienta la mezcla a 40-60 °C durante 2-16 h bajo una atmósfera de nitrógeno. Se enfría la reacción a -78°C, luego se agrega la mezcla fría sobre 3-10 min a una mezcla espesa de THF/$NaBH_4$ (2-4 M) a -78 °C. Se permite que la mezcla se calienta hasta a temperatura ambiente durante 2-16 h. Se vacía la mezcla en salmuera, se filtra la mezcla espesa resultante a través de Celite® y se lava completamente con EtOAc. Se concentra in vacuo. Se diluye el aceite con EtOAc, se lava con salmuera y se extrae la fase acuosa con EtOAc. Se secan los extractos orgánicos combinados sobre Na_2SO_4 y se concentra in vacuo. Se purifica la sulfinamida cruda en gel de sílice eluido con mezclas de hexano/EtOAc para obtener el diastereómero mayor. Se disuelve el diastereómero mayor en exceso de cloruro de hidrógeno 4M en dioxano, se agita la mezcla durante 1 h y se concentra in vacuo hasta un sólido. La mezcla espesa del sólido en dietil éter, luego se filtra in vacuo para obtener la sal de clorohidrato de la amina deseada. La base libre de la amina se prepara ya sea por medio de Cromatografía SCX o por extracción básica.

Procedimiento general 6-4

Se agrega el benzonitrilo apropiadamente substituido en porciones a un matraz que contiene una mezcla espesa de

hidruro de aluminio de litio (3.0-6.0 equiv.) en dietil éter (solución 0.1-0.3 M) bajo una atmósfera de nitrógeno. Se agita la mezcla durante 1 h y se apaga lentamente con agua (0.5-2.0 mL), seguido por NaOH acuoso 5N (0.5-2.0 mL). Se filtra la mezcla espesa a través de Celite® y se lava la torta con dietil éter. Se concentra in vacuo para obtener la amina deseada. Si se necesita purificación adicional, se disuelve la amina en éter y se agrega un exceso de cloruro de hidrógeno 2M en éter. se filtra para obtener la amina deseada como la sal de clorohidrato. Se prepara la base libre al usar Cromatografía SCX o al disolver la sal de clorohidrato en una solución acuosa de carbonato de cesio (1.0-5.0 equiv.) o $NaHCO_3$ acuoso saturado (1.0-5.0 equiv.). Se extrae la mezcla con DCM o tolueno, se seca sobre Na_2SO_4 y se concentra in vacuo para obtener la amina.

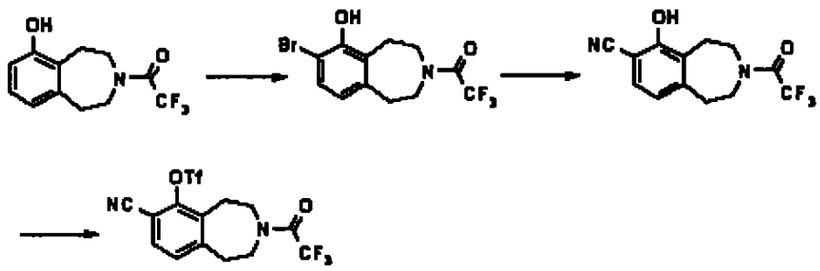
Procedimiento general 6-5

Se agrega complejo BH_3-THF (1-3 equiv., solución 1M en THF) gota a gota a una solución de benzonitrilo apropiadamente substituido en THF anhidro a temperatura ambiente luego se agita durante la noche. Alternativamente la reacción puede calentarse a reflujo durante la noche. Se agrega ya sea metanol o HCl acuoso (3 equiv.) cuidadosamente a temperatura ambiente y se agita vigorosamente hasta que se detiene la evolución gaseosa. Se concentra in vacuo, se

basifica y luego se extrae en EtOAc. Se lava la fase orgánica con salmuera, se seca sobre $MgSO_4$ y se concentra in vacuo. Se purifica por cromatografía SCX eluido con metanol seguido por una solución de amoniaco en metanol (3-7 M) para dar la bencilamina deseada.

Preparación 15

7-Ciano-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina



7-Bromo-6-hidroxi-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Se disuelve 6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (18 g, 69.4 mmol) y DIEA (0.98 mL) en DCM (1.4 L). Se agrega gota a gota una solución de NBS (12.4 g, 69.4 mmol) en DCM (500 mL) durante 75 min. Se agita la mezcla de reacción a temperatura ambiente durante 1 h, se vacía en agua (500 mL) y se extrae la mezcla con DCM. Se lava la fracción orgánica con salmuera, se seca sobre

Na_2SO_4, se filtran y se concentran. Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (4:1) para dar el intermediario deseado como un sólido blanco (20.9 g, 89%). EM (ES-) m/z: 337 $(M-H)^-$.

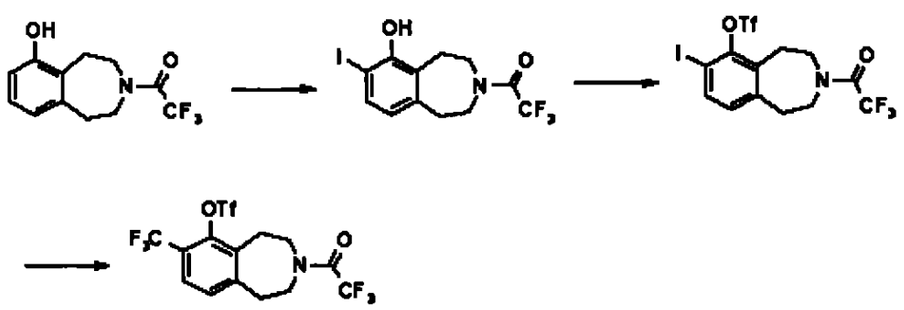
7-Ciano-6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Se agrega nitrilo de cobre (2.6 g, 28 mmol) a una solución de 7-bromo-6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (2.4 g, 7.0 mmol) en NMP anhidro (45 mL), se desgasifica y se purga con nitrógeno y se calienta a 150°C durante 18 h. Se permite la mezcla de reacción hasta enfriar a temperatura ambiente y luego se diluye con EtOAc/heptano (2:1) y se filtra a través de una almohadilla de sílice. Se diluye el filtrado con agua, y se extrae la fase acuosa 2 veces con EtOAc. Se secan los extractos orgánicos combinados sobre $MgSO_4$, se filtran y se concentran in vacuo. Se purifica por cromatografía en gel de sílice eluido con EtOAc/heptano (1:4 hasta 1:1) para obtener el intermediario deseado como un aceite anaranjado (1.7 g, 86%). EM (ES-) m/z: 283 $(M-H)^-$.

7-Ciano-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Se agrega piridina seca (3 mL) a 7-ciano-6-

hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (1.1 g, 3.9 mmol) en DCM anhidro (45 mL) y se enfría a 0°C. Se agrega lentamente anhídrido trifluorometansulfónico (1.3 mL, 7.7 mmol), se permite la mezcla de reacción para calentarse a temperatura ambiente y se agita durante 3 h. Se diluye con DCM y se lava con 2N aqueous HCl. Se seca la capa orgánica sobre $MgSO_4$, se filtra y se concentra in vacuo para obtener el compuesto del título como un aceite anaranjado/café (1.6 g, 100%) que se usan sin purificación. EM (ES-) m/z: 415 $(M-H)^-$.

Preparación 16

3-(2,2,2-Trifluoroacetil)-6-trifluorometansulfoniloxi-7-trifluorometil-2,3,4,5-tetrahidro-1H-benzo[d]azepina



6-Hidroxi-7-yodo-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Se agrega 6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (1.037 g, 4.0 mmol) y diisopropilamina (60.7 mg, 0.6 mmol) a DCM anhidro (350 mL) y se agita a 10-

20°C. Se agrega lentamente una solución de N-yodosuccinimida (1.035 g, 4.6 mmol) en DCM (100 mL) durante un peryodo de 3 h. Se agita la mezcla de reacción durante la noche y gradualmente se calienta a temperatura ambiente. Se apaga la reacción con $NaHCO_3$ acuoso saturado, se separa la capa orgánica, se lava la capa orgánica con 0.1 HCl acuoso 1N, salmuera, se seca sobre Na_2SO_4, se filtran y se concentran in vacuo. Se purifica por cromatografía en gel de sílice eluido con EtOAc/hexano (1:20 to 1:10) para dar el intermediario deseado como un sólido blanco (1.0 g, 65%). EM (ES+) m/z: 386 $(M+H)^+$.

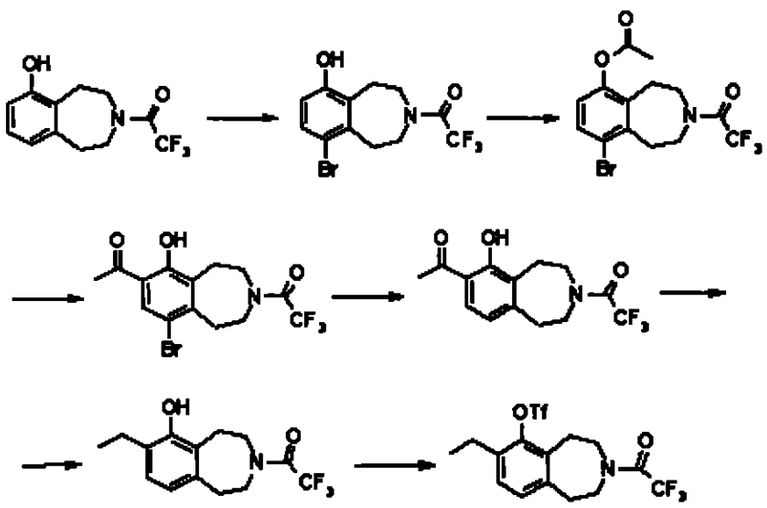
7-yodo-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Se agrega trietilamina (496 mg, 4.90 mmol) a una solución de 6-hidroxi-7-yodo-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (945 mg, 2.45 mmol) en DCM (30 mL) a 0°C. Se agrega gota a gota anhídrido trifluorometansulfónico (1.244 g, 4.41 mmol) y se agita a 0°C durante 1 h. Se calienta a temperatura ambiente durante la noche. Se diluye la mezcla con DCM, se lava con agua, $NaHCO_3$ acuoso saturado y salmuera. Se seca sobre Na_2SO_4, se filtran y se concentran in vacuo. Se purifica por cromatografía en gel de sílice eluido con EtOAc/hexano

(1:6) para dar el intermediario deseado como un sólido blanco (1.246 g, 98%). EM (ES+) m/z: 518 $(M+H)^+$.

3-(2,2,2-Trifluoroacetil)-6-trifluorometansulfoniloxi-7-trifluorometil-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Se agrega CuI (367 mg, 1.93 mmol), 2,2-difluoro-2-(fluorosulfonil)acetato de metilo (1.852 g, 9.64 mmol) y HMPA (1.728 g, 9.64 mmol) a una solución de 7-yodo-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (1.246 g, 2.41 mmol) en DMF (8 mL) y se calienta la mezcla a 70 °C durante 1.5 h. Se agrega la misma cantidad de CuI, 2,2-difluoro-2-(fluorosulfonil)acetato de metilo, y HMPA y se agita además durante 4 h. Se enfría la mezcla a temperatura ambiente, se apaga con cloruro de amonio acuoso saturado, se separa la capa orgánica, y se extrae la capa acuosa con EtOAc tres veces. Se combinan las capas orgánicas, se lava con $NaHCO_3$ acuoso saturado, salmuera, se seca sobre Na_2SO_4, se filtran y se concentran in vacuo. Se purifica por cromatografía en gel de sílice eluido con EtOAc/hexano (1:20 to 1:10) para dar el compuesto del título como un sólido blanco (321 mg, 29%) y para recuperar el material de partida (741 mg, 59%). EM (ES+) m/z: 460 $(M+H)^+$.

Preparación 17

7-etil-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina



9-Bromo-6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Se agrega gota a gota bromo (10.8 mL, 0.21 mol) en acetonitrilo (260 mL) a una mezcla espesa de 6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (51.8 g, 0.2 mol) en acetonitrilo (400 mL) a 0°C se enfria con hielo-agua para mantener la temperatura entre 2-5°C. Se calienta la reacción a temperatura ambiente y se agita durante 30 min. Se vacía la mezcla en agua enfriada con (2 L) para obtener un precipitado blanco. Se recolecta el sólido por filtración al vacío, se lava con agua y se seca bajo vacío a 105°C. Se recristaliza el material crudo en tolueno/heptano y se enfría la mezcla en un baño de hielo. Se recolecta el sólido por filtración al

vacío, se lava con heptano y se seca bajo vacío a 105°C para obtener el intermediario deseado como un sólido blanco (54.63 g, 81%). EM (ES+) m/z: 338 $(M+H)^+$.

6-Acetoxi-9-bromo-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Bajo atmósfera de nitrógeno, se mezcla 9-bromo-6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (6 g, 17.8 mmol), piridina anhidra (0.06 mL, 0.72 mmol), DMAP (222 mg, 1.8 mmol) y anhídrido acético (30 mL). Se calienta la mezcla a reflujo durante 8 h y luego se agita a temperatura ambiente durnte otras 8 h. Se concentra in vacuo, se diluye el residuo en EtOAc, se lava con HCl acuoso 1N, y luego con $NaHCO_3$ acuoso saturado. Se seca la capa orgánica sobre Na_2SO_4, se filtra, y se concentra in vacuo para obtener el intermediario deseado (5.64 g, 84%) que se usa sin purificación adicional. EM (ES+) m/z: 380 $(M+H)^+$.

7-acetil-9-bromo-6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Bajo atmósfera de nitrógeno, se mezcla 6-acetoxi-9-bromo-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (2.8 g, 7.4 mmol) y nitrobenceno (5 mL). Se agrega cloruro de aluminio anhidro (980 mg, 7.4 mmol). Se calienta a 180°C durante 2 h. Se enfría la mezcla a temperatura ambiente. Se agrega HCl

concentrado (10 mL) gota a gota. Se agita la mezcla durante 30 min. Se agrega HCl acuoso 1N luego se extrae con EtOAc. Se seca la capa orgánica sobre Na_2SO_4, se filtra y se concentra in vacuo. Se purifica por cromatografía en gel de sílice eluido con EtOAc/hexano (0:1 hasta 1:4) para proporcionar el intermediario deseado (833 mg, 30%). EM (ES-) m/z: 378 $(M-H)^-$.

7-acetil-6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Se mezcla 7-acetil-9-bromo-6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (833 mg, 2.2 mmol), tetraquis(trifenilfosfina)paladio (0) (150 mg, 0.13 mmol) y formiato de sodio (224 mg, 3.3 mmol) en DMF anhidro (15 mL). Se desgasifica 2 veces luego se moja con argón. Se mantiene el mojado bajo argón y se calienta la reacción a 95°C durante 16 h. Se diluye con EtOAc luego se lava con HCl acuoso 1N. Se separa la capa orgánica, se seca sobre Na_2SO_4, se filtran y se concentran in vacuo. Se purifica por cromatografía en gel de sílice eluido con EtOAc/hexano (0:1, 1:9 y 1:4) para dar el intermediario deseado (448 mg, 68%). EM (ES+) m/z: 302 $(M+H)^+$.

7-etil-6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Bajo nitrógeno se disuelve 7-

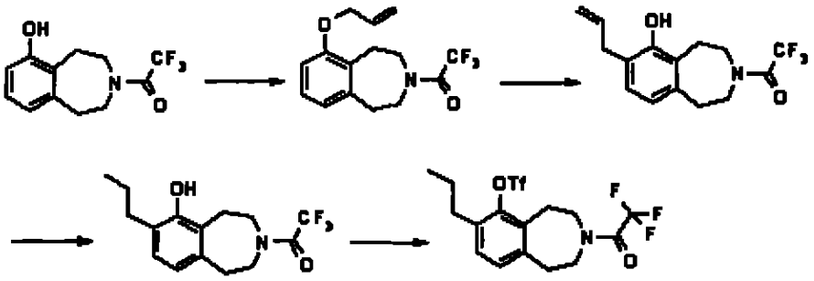
acetil-6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (1.0 g, 3.32 mmol) en THF anhidro (100 mL). Se enfría la solución a 0°C, se agrega dietil eterato de trifluoruro de boro (3.4 mL, 26.6 mmol) y cianoborohidruro de sodio (836 mg, 13.3 mmol). Se remueve el baño de hielo y se agita durante 5 h a temperatura ambiente. Se diluye con EtOAc y se lava con HCl acuoso 0.1N. Se separa la capa orgánica, se seca sobre Na_2SO_4, se filtra y se concentra in vacuo. EM (ES-) m/z: 302 $(M-H)^-$. Se mezcla el residuo con ácido trifluoroacético (40 mL) y DCM anhidro (50 mL) bajo nitrógeno. Se enfría a 0°C en un baño de hielo y se agrega trietil silani (3.5 mL, 21.9 mmol). Después de 15 min, se remueve el baño de hielo y se agita a temperatura ambiente durante 16 h. Se concentra in vacuo y se purifica por cromatografía en gel de sílice eluido con EtOAc/hexano (1:9) para obtener el intermediario deseado (698 mg, 73%). EM (ES-) m/z: 286 $(M-H)^-$.

7-etil-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Bajo nitrógeno se mezcla 7-etil-6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (698 mg, 2.4 mmol), trietilamina (0.67 mL, 4.8 mmol) y DCM anhidro (25 mL). Se enfría la mezcla en un baño de hielo, se agrega gota a gota anhídrido

trifluorometansulfónico (0.81 mL, 4.8 mmol) y se agita a temperatura ambiente durante 3 h. Se apaga con agua y se extrajo 3 veces con DCM. Se lavan los extractos orgánicos con HCl acuoso 0.1N y salmuera. Se seca sobre Na_2SO_4, se filtra y se concentra para obtener el compuesto del título (1.0 g, 100%). EM (ES+) m/z: 420 $(M+H)^+$.

Preparación 18

7-Propil-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina



6-Aliloxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Se disuelve 6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (1 g, 3.9 mmol) en acetona (5 mL) y se agrega carbonato de potasio en polvo (2.8 g, 20 mmol). Se agrega gota a gota una solución de bromuro de alilo (1.04 mL, 12 mmol) en acetona (3 mL) durante 10 min y se agita a temperatura ambiente durante la noche. Se filtran los sólidos, se lava con acetona y se concentra in vacuo para dar el intermediario deseado como un

sólido completamente blanco (1.15 g, 98%). CG-EM m/z: 299 (M^+).

7-Alil-6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Se disuelve 6-aliloxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (1.1 g, 3.7 mmol) en DCM (15 mL) y se enfría a -15°C. Se agrega tricloruro de boro 1M en DCM (15 mL, 15 mmol) y se calienta a temperatura ambiente. Se agita durante 30 min a temperatura ambiente. Se agrega agua (50 mL) y se extrae la capa acuosa 3 veces con DCM. Se lavan los extractos orgánicos combinados con agua (100 mL), salmuera (100 mL), se secan sobre $MgSO_4$, se filtra, y se concentra in vacuo para dar el intermediario deseado (980 mg, 89%) como un aceite amarillo ligero el cual se solidifica hasta un sólido completamente blanco durante el reposo a temperatura ambiente. EM (ES+) m/z: 300 $(M+H)^+$.

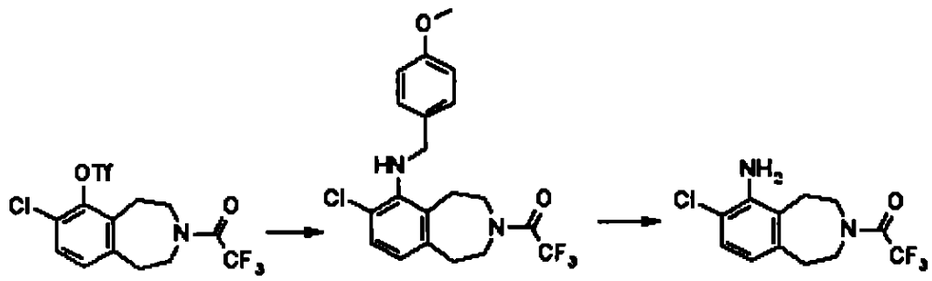
6-Hidroxi-7-Propil-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Se disuelve 7-alil-6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (1.5 g, 5 mmol) en EtOAc (50 mL) que contiene 10% Pd/C (1.3 g). Se agita a temperatura ambiente a 1 atm con H_2 (globo) durante 30 min. Se filtra el catalizador y se lava con agua (100 mL). Se extrae el filtrado resultante 3 veces

con EtOAc, se lavan los extractos orgánicos combinados con salmuera, se secan sobre $MgSO_4$, se filtran y se concentran in vacuo para dar el intermediario deseado como un sólido blanco (1.45 g, 97%). EM (ES+) m/z: 302 $(M+H)^+$.

7-Propil-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Se enfría una solución de 6-hidroxi-7-Propil-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (500 mg, 1.9 mmol), trietilamina (390 µL, 2.3 mmol) y DCM (20 mL) en un baño criogénico se fija a -35°C y se agrega gota a gota durante 20 min anhídrido trifluorometansulfónico (325 µL, 2.3 mmol). Se agita a esta temperature durante la noche. Se lava la mezcla de reacción secuencialmente con agua, HCl acuoso 1N, agua, y salmuera. Se seca la capa orgánica sobre Na_2SO_4 y se concentra in vacuo. Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (9:1) para obtener el compuesto del título como un sólido ceroso completamente blanco (550 mg, 75%). EM (ES+) m/z: 434 $(M+H)^+$.

Preparación 19

6-Amino-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

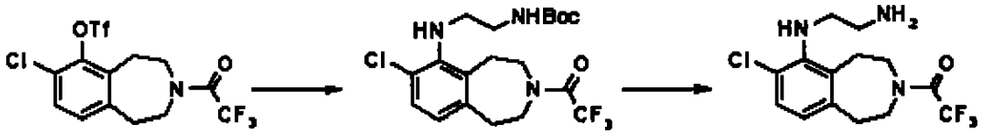


7-Cloro-6-(4-metoxibencilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Se acopla 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (15 g, 35.3 mmol), con 4-metoxibencilamina (13.7 mL, 106 mmol) al usar tris(dibencilidenacetona)-dipaladio (0) (1.62 g, 1.76 mmol), BINAP (4.40 g, 3.5 mmol) y carbonato de cesio (16.1 g, 49.4 mmol) a 80°C durante 17 h. Se filtra la mezcla a través de una almohadilla de Celite® y se evapora el filtrado. Se disuelve el residuo en DCM y se filtra a través de una almohadilla de gel de sílice. Se evapora el filtrado y se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (1:0 to 2:3) para dar el intermediario deseado como un sólido blanco (12.4 g, 86%). EM (ES+) m/z: 412 $(M+H)^+$.

6-Amino-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Se trata 7-cloro-6-(4-metoxibencilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (5.41 g, 13.1 mmol) con 2,3-dicloro-5,6-diciano-1,4-benzoquinona (3.59 g, 15.8 mmol) en tolueno (66 mL) a temperatura ambiente durante 2 h. Se diluye la mezcla con EtOAc y se lava con $NaHCO_3$ acuoso saturado (5 x 100 mL). Se extrajo la capa acuosa con éter, se combinan los extractos orgánicos y se evaporaron para un volumen de 300 mL. Se extrae la fase orgánica con HCl acuoso 1N (5 x 100 mL), y luego se lavan las capas acuosas combinadas con éter (4 x 75 mL). Se enfría la fase acuosa a 0°C, se neutraliza con NaOH acuoso 5N (100 mL), y se extrae con DCM (5 x 200 mL). Se lavan los extractos orgánicos combinados con salmuera, se secan sobre Na_2SO_4 y evaporan para obtener el compuesto del título como un sólido blanco (3.6 g, 94%). EM (ES+) m/z: 293 $(M+H)^+$.

Preparación 20

6-(2-Amino-etilamino)-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

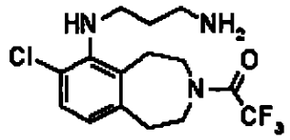


6-(2-tert-Butoxicarbonilamino-etilamino)-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Se usa un método similar al Procedimiento general 5-1, al usar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (150 mg, 0.352 mmol), acetato de paladio (II) (8 mg, 0.0352 mmol), BINAP (22 mg, 0.0352 mmol), carbonato de cesio (163 mg, 0.5 mmol), t-butil N-(2-aminoetil)-carbamato (254 mg, 1.59 mmol) y tolueno (6 mL) para dar, después la cromatografía en gel de sílice eluido con hexano/EtOAc (4:1), el intermediario deseado (136 mg, 89%).

6-(2-Amino-etilamino)-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Se disuelve 6-(2-tert-butoxicarbonilamino-etilamino)-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (136 mg, 0.31 mmol) en cloruro de hidrógeno 4M en dioxano (20 mL) y se agita a temperatura ambiente durante 25 min. Se concentra para proporcionar la sal de clorohidrato. Se disuelve la sal en DCM y se lava con $NaHCO_3$ acuoso saturado. Se extrae la capa acuosa básica con DCM, se seca la capa orgánica sobre $MgSO_4$, se filtra, y se concentra in vacuo para dar el compuesto del título (64 mg, 62%). EM (ES+) m/z: 336 $(M+H)^+$.

Preparación 21

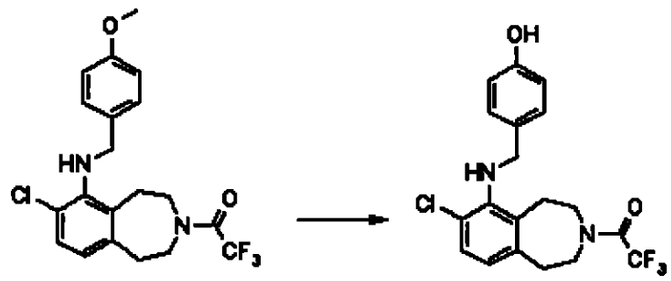
6-(3-Amino-propilamino)-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar a la Preparación 20, al usar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (600 mg, 1.41 mmol) y tert-butilo N-(3-aminopropil)-carbamato (1.11 g, 6.34 mmol) para dar el compuesto del título (34% general).

Preparación 22

7-Cloro-6-(4-hidroxibencilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

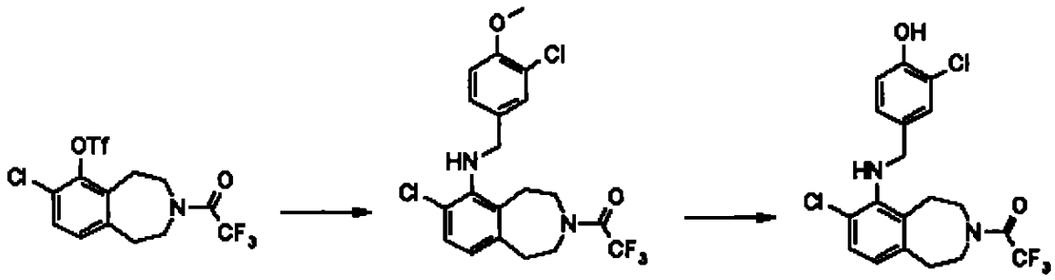


Se disuelve 7-cloro-6-(4-metoxibencilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (1.667 g) en DCM (40 mL). Se agrega una solución 1M de tribromuro de boro en DCM (10 mL) a 0°C. Se agita la reacción durante 12 h y gradualmente se eleva a temperatura ambiente. Se apaga la

reacción con $NaHCO_3$ acuoso saturado y se extrae con DCM 3 veces. Se combinan los extractos orgánicos, se lavan con salmuera, se secan sobre Na_2SO_4, se filtran y se concentran. Se purifica por cromatografía en gel de sílice eluido con EtOAc/hexano (1:3) para dar el compuesto del título como un aceite (888 mg). EM (ES+) m/z: 399 $(M+1)^+$.

Preparación 23

7-Cloro-6-(3-cloro-4-hidroxibencilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

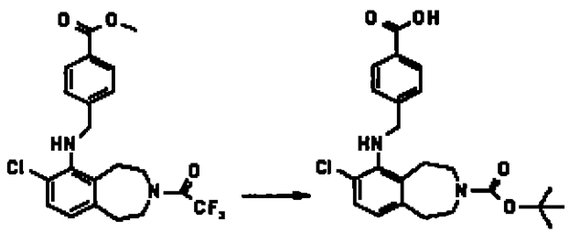


7-Cloro-6-(3-cloro-4-metoxibencilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Se usa un método similar al Procedimiento general 5-3, al usar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (1.277 g, 3.0 mmol) y 3-cloro-4-metoxi-bencilamina (669 mg, 3.9 mmol) para dar el intermediario deseado como un aceite amarillo ligeramente amarillo (1.554 g, 100%).

7-Cloro-6-(3-cloro-4-hidroxibencilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Se usa un método similar a la Preparación 22, al usar 7-cloro-6-(3-cloro-4-metoxibencilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (1.36 g, 3.0 mmol) para dar el compuesto del título como un solido completamente blanco (876 mg, 67% rendimiento). EM (ES+) m/z: 433 $(M+H)^+$. EM (ES-) m/z: 431 $(M-H)^-$.

Preparación 24

3-(tert-Butoxicarbonil)-6-(4-carboxi-bencilamino)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina

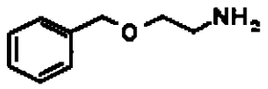


Se combinan 7-cloro-6-(4-metoxicarbonil-bencilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (0.4 g, 0.82 mmol), carbonato de potasio (4 g, 28.9 mmol), metanol (3 mL), agua (3 mL) y se calientan a 50°C durante 2 h. Se enfría la mezcla de reacción a temperatura ambiente, se agrega Na_2CO_3 acuoso saturado y se diluye con DCM (10 mL). Se agrega di-tert-butil-dicarbonato (2.4 g, 10.9 mmol) en porciones. Se separa la capa orgánica y se extrae la capa acuosa con DCM (3 x 10 mL). Se combinan los extractos

orgánicos, se seca sobre Na_2SO_4 anhidro, se evapora el solvente y se purifica por cromatografía en gel de sílice eluido con DCM y DCM/metanol (9:1) para dar el compuesto del título como un sólido blanco (0.3 g, 80%). EM (ES+) m/z: 331 $(M+H-Boc)^+$.

Preparación 25

2-Benciloxietilamina



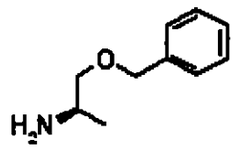
éster de tert-butilo del ácido (2-benciloxietil)-carbámico: Se disuelve tert-butil-N-(2-hidroxietil)-carbamato (10 mL, 64.5 mmol) en THF anhidro (500 mL) a 0°C. Se agrega hidruro de sodio (60% en aceite mineral, 3.1 g, 77.4 mmol) y se agita durante 30 min a 0°C. Se agrega bromuro de bencilo (9.2 mL, 77 mmol) seguido por yoduro de tetrabutilamonio (3.7 g, 10 mmol) y se agita a temperatura ambiente durante la noche. Se apaga con agua (500 mL), se extrae con dietil éter (3 x 100 mL), se lavan los extractos orgánicos combinados con salmuera, se secan sobre $MgSO_4$, se filtran, y evaporan para dar el intermediario deseado (15 g), que se usa sin purificación adicional.

2-Benciloxietilamina: Se disuelve éster de tert-butilo del ácido (2-benciloxietil)-carbámico (15 g) en DCM (50 mL), se

agrega ácido trifluoroacético (20 mL) y se agita a 0°C durante 3 h. Se concentra y se disuelve el residuo en una cantidad mínima de DCM. Se purifica por cromatografía en gel de sílice eluido secuencialmente con hexano/EtOAc (4:1 y 1:1), EtOAc y amoniaco 2M en metanol para dar el compuesto del título (8.3 g, 85%).

Preparación 26

(R)-2-Benciloxi-1-metil-etilamina

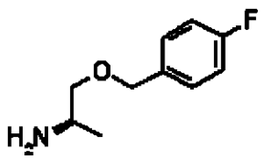


(R)-3-Benciloxi-2-(tert-butoxicarbonilamino)-propano: Se disuelve (R)-(+)-2-(tert-butoxicarbonilamino)-1-propanol (875 mg, 5 mmol) en THF anhidro (50 mL). Se agrega hidruro de sodio (60% en aceite mineral, 210 mg, 5.2 mmol) y se agita a 0°C durante 30 min. Se agrega bromuro de bencilo (620 µL, 5.2 mmol) seguido por yoduro de tetrabutilamonio (20 mg, 0.05 mmol) y se agita durante 3 h a temperatura ambiente. Se vacía la mezcla en agua (200 mL), se extrae con DCM (3 x 50 mL), se lava con salmuera, se seca sobre $MgSO_4$, se filtra y se concentra. Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (19:1) para dar el intermediario deseado como un aceite incoloro (800 mg, 60%).

(R)-2-Benciloxi-1-metil-etilamina: Se disuelve (R)-3-benciloxi-2-(tert-butoxicarbonilamino)-propano (800 mg, 3 mmol) en DCM (10 mL), se agrega ácido trifluoroacético (5 mL), y se agita a 0°C durante 20 min. Se evapora y se purifica por cromatografía SCX para dar el compuesto del título como un aceite incoloro (440 mg, 89%). EM (ES+) m/z: 166 $(M+H)^+$.

Preparación 27

(R)-2-(4-Fluorobenciloxi)-1-metil-etilamina



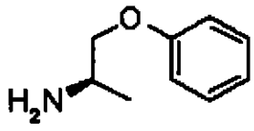
(R)-2-(tert-Butoxicarbonilamino)-3-(4-fluorobenciloxi)-propano: Se disuelve (R)-(+)-2-(tert-butoxicarbonilamino)-1-propanol (1.75 mg, 10.5 mmol) en THF anhidro (50 mL). Se agrega hidruro de sodio (60% en aceite mineral, 480 mg, 12 mmol) y se agita a 0°C durante 30 min. Se agrega 4-fluorobromuro de bencilo (1.5 mL, 12 mmol) seguido por yoduro de tetrabutilamonio (370 mg, 0.1 mmol) y se agita durante 72 h a temperatura ambiente. se vacía la mezcla en agua (500 mL), se extrae con DCM (3 x 150 mL), se lava con salmuera, se seca sobre $MgSO_4$, se filtra y se concentra in vacuo. Se purifica por cromatografía en gel de sílice eluido con

hexano/EtOAc (9:1) para dar el intermediario deseado como un aceite amarillo (2.18 g, 77%).

(R)-2-(4-Fluorobenciloxi)-1-metil-etilamina: Se disuelve (R)-2-(tert-butoxicarbonilamino)-3-(4-fluorobenciloxi)-propano (2.18 g, 7.7 mmol) en DCM (50 mL), se agrega ácido trifluoroacético (25 mL), y se agita a 0°C durante 20 min. Se evapora y se purifica por cromatografía SCX para dar el compuesto del título como un aceite incoloro (1.2 g, 85%). EM (ES+) m/z: 184 $(M+H)^+$.

Preparación 28

(R)-1-Metil-2-fenoxi-etilamina



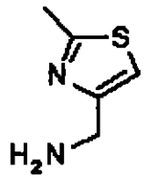
(R)-2-(tert-Butoxicarbonilamino)-3-fenoxi-propano: Se disuelve (R)-(+)-2-(tert-butoxicarbonilamino)-1-propanol (1.75 g, 10 mmol) y fenol (0.95 g, 10 mmol) en THF anhidro (75 mL). Se enfría a 0°C, se agrega trifenilfosfina (4.0 g, 15 mmol) y diisopropilazodicarboxilato gota a gota y se agita a temperatura ambiente durante 18 h. Se vacía la mezcla en agua (300 mL), se basifica a pH 10 con NaOH acuoso 5N, y se extrae con éter etílico (3 x 100 mL). Se lava la fase orgánica con salmuera, se seca sobre $MgSO_4$, se filtran y se

concentran. Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (9:1) para dar el intermediario deseado como un solido completamente blanco (340 mg, 14%).

(R)-1-Metil-2-fenoxi-etilamina: Se disuelve (R)-2-(tert-butoxicarbonilamino)-3-fenoxi-propano (340 mg, 1.35 mmol) en DCM (80 mL), se agrega ácido trifluoroacético (35 mL), y se agita a 0°C durante 2 h. Se evapora y se purifica por cromatografía SCX para dar el compuesto del título como un aceite incoloro (186 mg, 91%). EM (ES+) m/z: 151 $(M+H)^+$.

Preparación 29

4-(Aminometil)-2-metil-tiazol



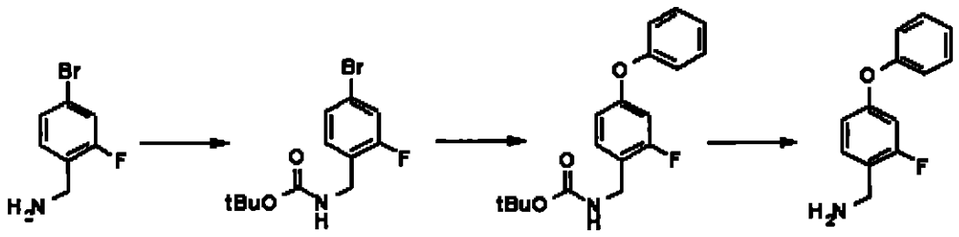
4-(Azidometil)-2-metil-tiazol: Se disuelve 4-(clorometil)-2-metil-tiazol (350 mg, 2.37 mmol) y azidotrimetilsilano (315 µL, 2.37 mmol) en THF anhidro (1 mL) bajo nitrógeno. Se agrega una solución 1M de floruro de tetrabutilamonio (3.6 mL, 3.56 mmol) en THF y se agita a temperatura ambiente durante la noche. Se vacía la mezcla de reacción en agua (10 mL), se extrae con éter etílico (3 x 2 mL), se lavan los extractos orgánicos con salmuera, se secan sobre $MgSO_4$, se filtran, y se evaporan. Se purifica por cromatografía en gel

de sílice eluido con hexano/EtOAc (9:1) para dar el intermediario deseado como un aceite incoloro (165 mg, 45%).

4-(Aminometil)-2-metil-tiazol: Se agrega 4-(azidometil)-2-metil-tiazol (165 mg, 1.07 mmol) a una mezcla espesa de metanol que contiene 10% Pd/C (75 mg) y se agita vigorosamente bajo 1 atm de H_2 durante 1 h. Se filtra, se evapora el solvente, y se purifica por cromatografía SCX para dar el compuesto del título (55 mg, 40%).

Preparación 30

2-Fluoro-4-fenoxi-bencilamina



éster de tert-butilo del ácido (4-Bromo-2-fluorobencil)-carbámico: Se mezcla bajo nitrógeno clorohidrato de 4-bromo-2-fluorobencilamina (7.2 g, 30 mmol), di-tert-butil-dicarbonato (9.8 g, 45 mmol), y carbonato de potasio (12.4 g, 90 mmol) en THF anhidro (200 mL). Se agita a temperatura ambiente durante 16 h. Se filtra y se concentra in vacuo. Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (9:1) para obtener el intermediario deseado (6.4 g, 70%). CG-EM m/z: 247 [$(M-C_4H_9)^+$].

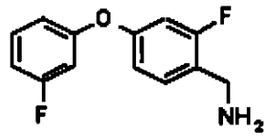
Ester de tet-butil del ácido (2-Fluoro-4-fenoxi-bencil)-carbámico: Se mezcla bajo atmósfera de argon ester de tert-butilo del ácido (4-bromo-2-fluorobencil)-carbámico (2.12 g, 7.0 mmol), fenol (1.32 g, 14 mmol), 2,2,6,6-tetrametilheptano-3,5-diona (129 mg, 0.7 mmol), y carbonato de cesio (4.56 g, 14 mmol) en NMP anhidro (15 mL). Se desgasifica el matraz, se rellena con argón y se agrega cloruro de cobre (I) (346 mg, 3.5 mmol) rápidamente. Se desgasifica el matraz luego se rellena con argón y se calienta a 120°C durante 5 h. Se enfría a temperatura ambiente, se diluye con EtOAc y se filtra. Se lava la mezcla secuencialmente con HCl acuoso 0.5N, NaOH acuoso 0.5N y salmuera. Se separa la capa orgánica, se seca sobre Na_2SO_4 y se concentra in vacuo. Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (1:0, 9:1 y 3:1) para obtener el intermediario deseado (1.28 g, 58%). CG-EM m/z: 260 $[(M-C_4H_9)^+]$.

2-Fluoro-4-fenoxi-bencilamina: Se disuelve éster de tert-butilo del ácido (2-fluoro-4-fenoxi-bencil)-carbámico (2.44 g, 7.72 mmol) en DCM (200 mL). Se agrega ácido trifluoroacético (50 mL) luego se agita a temperatura ambiente durante 16 h. Se evapora el solvente, se disuelve el residuo en DCM y se lava con 1N aqueous NaOH. Se seca sobre Na_2SO_4 y se concentra in vacuo. Se purifica por cromatografía

SCX para obtener el compuesto del título (557 mg, 33%). EM (ES+) m/z: 201 $(M+H-NH_3)^+$.

Preparación 31

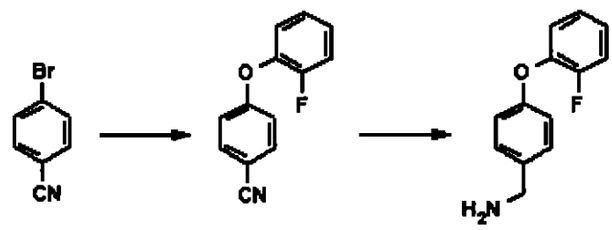
2-Fluoro-4-(3'-fluorofenoxi)-bencilamina



Se usa un método similar a la Preparación 30, al usar éster de tert-butilo del ácido (4-bromo-2-fluorobencil)-carbámico (2.12 g, 7.0 mmol) y m-fluorofenol (1.57 g, 14 mmol) para dar el compuesto del título (468 mg, 47% en general).

Preparación 32

4-(2'-Fluorofenoxi)-bencilamina



4-(2'-Fluorofenoxi)-benzonitrilo: Se mezcla bajo atmósfera de argón 4-bromobenzonitrilo (2.0 g, 11.3 mmol), 2-fluorofenol (2.5 g, 22.6 mmol), 2,2,6,6-tetrametilheptano-3,5-diona (203 mg, 1.1 mmol), y carbonato de cesio (7.4 g, 22.6 mmol) en NMP anhidro (19 mL). Se desgasifica el

matraz, se rellena con argón y se agrega cloruro de cobre (I) (554 mg, 5.6 mmol) rápidamente. Se desgasifica el matraz luego se rellena con argón y se calienta a 120°C durante 3 h. Se enfría a temperatura ambiente, se diluye con EtOAc, se filtra y se lava el filtrado secuencialmente con HCl acuos 2M, HCl acuoso 0.3M, NaOH acuoso 2M y salmuera. Se separa la capa orgánica, se seca sobre Na_2SO_4 y se concentra in vacuo. Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (1:0 y 9:1) para obtener el intermediario deseado (1.6 g, 66%). EM (ES+) m/z: 231 $(M+NH_4)^+$.

4-(2'-Fluorofenoxi)-bencilamina: Se agrega 4-(2'-fluorofenoxi)-benzonitrilo (1.5 g, 7.0 mmol) y etanol, níquel Raney® activado húmedo (0.4 g) a un recipiente de presión Parr. Inmediatamente se agrega una solución 7N de amoniaco en metanol (170 mL) y se sella el recipiente. Se purga el recipiente de reacción con nitrógeno, se presuriza la mezcla de reacción con hidrógeno (3400 KPa), se sella el recipiente, se agita la reacción y se calienta a 60°C. Se continua la reacción durante 18 h, a su vez completamente se calienta y se permite la mezcla de reacción para enfriarse a temperatura ambiente. se ventila el exceso de hidrógeno del recipiente y se purga el recipiente con nitrógeno. Se filtra la mezcla de reacción para eliminar el níquel Raney®. Se concentra in

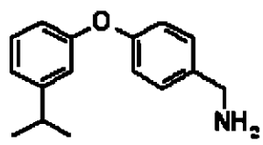
vacuo y se purifica por cromatografía en gel de sílice eluido con DCM/amoniaco 2M en metanol (9:1) para obtener el compuesto del título (1.2 g, 79%). EM (ES+) m/z: 201 $(M+H-NH_3)^+$.

El compuesto de la Preparación 33 puede prepararse esencialmente como se describen en la Preparación 32 al usar 4-bromobenzonitrilo y 3-fluorofenol. Los datos de rendimientos generales y EM (ES+) se muestran en la Tabla a continuación.

Prep.	**Compuesto**	**Rendimiento (%)**	**EM (ES+) m/z**
33	4-(3'-Fluorofenoxi)-bencilamina	53	201 $(M+H-NH_3)^+$

Preparación 34

4-(3'-Isopropilfenoxi)-bencilamina



Se usa un método similar a la Preparación 32 (Etapa 1), al usar 4-bromobenzonitrilo (2.0 g, 11.3 mmol) y 3-isopropilfenol (3.08 g, 22.6 mmol) para dar 4-(3'-isopropilfenoxi)-benzonitrilo (885 mg, 33%). EM (ES+) m/z: 255 $(M+NH_4)^+$.

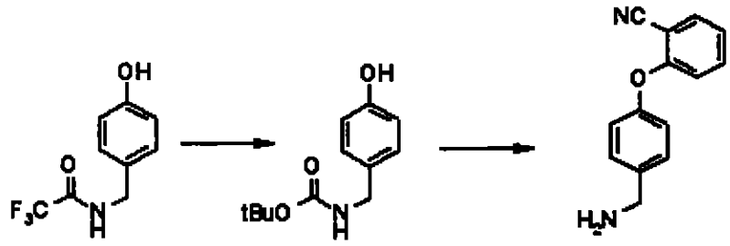
Se usa un método similar al procedimiento de reducción descrito en la preparación 45 (Etapa 2), al usar 4-(3'-isopropilfenoxi)-benzonitrilo (875 mg, 3.7 mmol) para dar el compuesto del título (703 mg, 79%). EM (ES+) m/z: 225 $(M+H-NH_3)^+$.

Los compuestos de las preparaciones 35-39 pueden prepararse esencialmente como se describen en la Preparación 34 al usar 4-bromobenzonitrilo y el fenol apropiado. Los datos de rendimiento general y EM (ES+) se muestran en la Tabla a continuación.

Prep.	**Compuesto**	**Rendimiento (%)**	**EM (ES+) m/z**
35	4-(2'-Isopropilfenoxi)-bencilamina	28	225 $(M+H-NH_3)^+$
36	4-(3'-Metilfenoxi)-bencilamina	60	197 $(M+H-NH_3)^+$
37	4-(2'-Metilfenoxi)-bencilamina	59	197 $(M+H-NH_3)^+$
38	4-(3',5'-Difluorofenoxi)-bencilamina	24	219 $(M+H-NH_3)^+$
39	4-(3'-Clorofenoxi)-bencilamina	44	217 $(M+H-NH_3)^+$

Preparación 40

2-(4-Aminometil-fenoxi)-benzonitrilo



Éster de tert-butilo del ácido (4-Hidroxibencil)-carbámico: Se mezcla 2,2,2-trifluoro-N-(4-hidroxibencil)-acetamida (8.8 g, 40 mmol), y NaOH acuoso 5N (20 mL) en metanol (100 mL). Se agita a temperatura ambiente durante 4 h. Se ajusta el pH hasta alrededor de 8 con HCl acuoso. Se agrega bicarbonato de sodio sólido (4.4 g, 52 mmol), di-tert-butil-dicarbonato (9.3 g, 40 mmol) y DCM. Se agita a temperatura ambiente durante 16 h. Se diluye con DCM, se lava con HCl acuoso 1N y se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (9:1 hasta 5:5) para obtener el intermediario deseado (7.8 g, 87%). EM (ES-) m/z: 222 $(M-H)^-$.

2-(4-Aminometil-fenoxi)-benzonitrilo: Se mezcla bajo argón éster de tert-butilo del ácido (4-hidroxibencil)-carbámico (1.5 g, 6.7 mmol), 2-bromobenzonitrilo (813 mg, 4.5 mmol), 2,2,6,6-tetrametilheptano-3,5-diona (83 mg, 0.45 mmol), y carbonato de cesio (2.2 g, 6.7 mmol) en NMP anhidro (8.5 mL). Se desgasifica el matraz y se rellena con argón. Se agrega

cloruro de cobre (I) (223 mg, 2.25 mmol) rápidamente. Se desgasifica el matraz, se rellena con argón y se calienta a 120°C durante 3 h. Se enfría a temperatura ambiente, se diluye con EtOAc, se filtra y se concentra in vacuo. Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (1:0, 9:1 y 3:1). Se evapora el solvente y se disuelve el residuo en DCM (100 mL). Se agrega ácido trifluoroacético (20 mL) y se agita a temperatura ambiente durante 16 h. Se concentra in vacuo, se disuelve el residuo en EtOAc y se lava con NaOH acuso 1N. Se seca sobre Na_2SO_4 y se concentra in vacuo. Se purifica por cromatografía SCX para obtener el compuesto del título (385 mg, 38%). EM (ES+) m/z: 225 $(M+H)^+$.

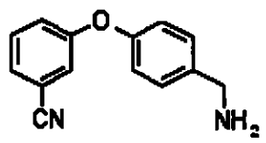
Los compuestos de las preparaciones 41-43 pueden prepararse esencialmente como se describen en la Preparación 40 al usar éster de tert-butilo del ácido (4-hidroxibencil)-carbámico (1.5 g, 6.7 mmol) y el bromuro apropiado. Los datos de rendimiento general y EM (ES+) se muestran en la Tabla a continuación.

Prep.	Compuesto	Rendimiento (%)	EM (ES+) m/z
41	4-(2'-Trifluorometil-fenoxi)-bencilamina	13	251 $(M+H-NH_3)^+$

Prep.	Compuesto	Rendimiento (%)	EM (ES+) m/z
42	4-(3'-Trifluorometil-fenoxi)-bencilamina	27	251 $(M+H-NH_3)^+$
43	4-(Piridin-3-yloxy)-bencilamina	11	201 $(M+H)^+$

Preparación 44

3-(4-Aminometil-fenoxi)-benzonitrilo

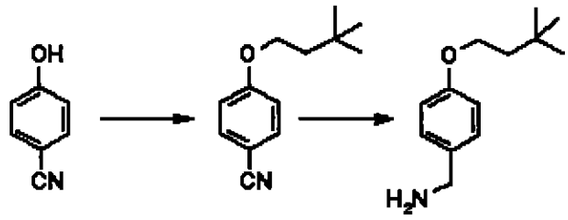


Se usa un método similar a la Preparación 40 (Etapa 2), al usar 2,2,2-trifluoro-N-(4-hidroxibencil)-acetamida (1.0 g, 5.5 mmol) y 3-bromobenzonitrilo (673 mg, 3.7 mmol). Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (1:0 y 3:1). Se concentra in vacuo. Se disuelve el residuo (287 mg, 0.89 mmol) en metanol (25 mL) y se agrega NaOH 5N (7 mL). Se agita a temperatura ambiente durante 4 h. Se diluye con DCM y se agrega cloruro de sodio sólido a la mezcla. Se extrajo la capa acuosa 3 veces con DCM. Se combinan los extractos orgánicos, se seca sobre Na_2SO_4 y se concentra in vacuo. Se purifica por cromatografía en gel de sílice eluido con DCM/amoniaco 2M en metanol (94:6) para

obtener el compuesto del título (124 mg, 62%). EM (ES+) m/z: 500 $(M+H)^+$.

Preparación 45

4-(3,3-Dimetlbutoxi)-bencilamina



4-(3,3-Dimetilbutoxi)-benzonitrilo: Se mezcla 4-cianofenol (1.2 g, 10 mmol), 1-bromo-3,3-dimetilbutano (5.3 g, 32 mmol), carbonato de potasio en polvo (4.14 g, 30 mmol), y yoduro de potasio en polvo (166 mg, 1 mmol) en acetona (60 mL). Se agita bajo atmósfera inerte y se calienta a reflujo durante 48 h. Se enfría la mezcla de reacción a temperatura ambiente. Se diluye con acetona, se filtra y se evapora. Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (1:0 y 9:1) para obtener el intermediario deseado (1.8 g, 89%). EM (ES+) m/z: 221 $(M+NH_4)^+$.

4-(3,3-Dimetilbutoxi)-bencilamina: Se mezcla hidruro de aluminio de litio (1.0 g, 26.6 mmol) y éter etílico anhidro (70 mL) bajo atmósfera de nitrógeno. Se agita y se enfría a 0°C en un baño de hielo. Se agrega gota a gota una solución de 4-(3,3-dimetilbutoxi)-benzonitrilo (1.8 g, 8.87 mmol) en

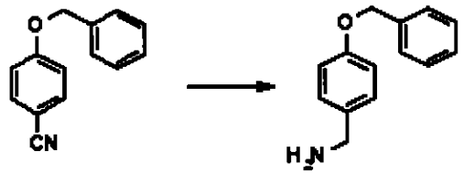
éter etílico anhidro (20 mL). Se agita durante 2 h a 0°C, se remueve el baño de hielo y se agita a temperatura ambiente durante 18 h. Se enfría el matraz de reacción en un baño de hielo y se agrega cuidadosamente gota a gota y secuencialmente agua (1 mL), NaOH acuoso 2N (1 mL), y agua (2 mL). Se agita durante 30 min, se filtra, se separa la capa orgánica, se seca sobre Na_2SO_4 y se concentra in vacuo para obtener el compuesto del título (1.62 g, 88%). EM (ES+) m/z: 191 $(M+H-NH_3)^+$.

Los compuestos de las preparaciones 46-48 pueden prepararse esencialmente como se describen en la Preparación 45 al usar 4-cianofenol y el bromuro apropiado. Los datos de rendimiento general y EM (ES+) se muestran en la Tabla a continuación.

Prep.	**Compuesto**	**Rendimiento (%)**	**EM (ES+) m/z**
46	4-Ciclohexilmetoxi-bencilamina	90	203 $(M+H-NH_3)^+$
47	4-(2-Ciclohexiletoxi)-bencilamina	94	217 $(M+H-NH_3)^+$
48	4-(2,2-Dimetilpropoxi)-bencilamina	4	177 $(M+H-NH_3)^+$

Preparación 49

4-Benciloxi-bencilamina

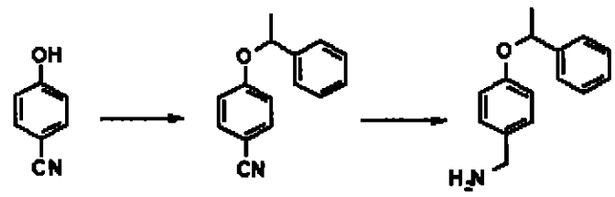


4-Benciloxi-benzonitrilo: Se agrega 4-cianofenol (1.191 g, 10 mmol), bromuro de bencilo (1.881 g, 11 mmol), carbonato de potasio (3.455 g, 25 mmol) y yoduro de potasio (166 mg, 1 mmol) para acetonitrilo (80 mL) y se calienta a reflujo durante 12 h. Se enfría, se divide entre EtOAc y agua, se separa la capa orgánica, y se extrae la capa acuosa con EtOAc. Se combinan los extractos orgánicos, se lava con salmuera, se seca sobre Na_2SO_4, se filtran y se concentran. Se purifica por cromatografía en gel de sílice eluido con EtOAc/hexano (1:6) para dar el intermediario deseado como un sólido blanco (2.098 g, 100%). EM (ES+) m/z: 227 $(M+NH_4)^+$.

4-Benciloxi-bencilamina: Se usa un método similar a la Preparación 58, al usar 4-benciloxi-benzonitrilo (2.098 g, 10 mmol), para dar el compuesto del título como un sólido blanco (2.021 g, 94%). EM (ES+) m/z: 197 $(M+H-NH_3)^+$.

Preparación 50

(±)-4-(1-Feniletoxi)-bencilamina

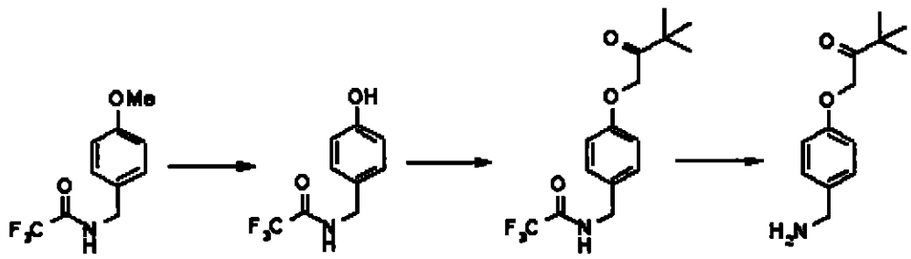


(±)-4-(1-Feniletoxi)-benzonitrilo: Se agrega trifenilfosfina (7.869 g, 30 mmol) a una solución de alcohol sec-feniletilo (1.467 g, 12 mmol), 4-cianofenol (1.191 g, 10 mmol) y dietil azodicarboxilato (4.528 g, 26 mmol) en THF anhidro (50 mL) a 0°C. Se agita la reacción a temperatura ambiente durante 12 h. Se diluye con EtOAc, se lava con salmuera, se seca sobre Na_2SO_4, se filtran y se concentran. Se purifica por cromatografía en gel de sílice eluido con EtOAc/hexano (1:8) para dar (±)-4-(1-feniletoxi)-benzonitrilo con una cantidad pqueña de trifenilfosfina (2.49 g total).

(±)-4-(1-Feniletoxi)-bencilamina: Se usa un método similar a la Preparación 58, al usar (±)-4-(1-feniletoxi)-benzonitrilo curdo, para dar el compuesto del título como un aceite incoloro (1.6 g, 70% two etapas). EM (ES+) m/z: 211 $(M+H-NH_3)^+$, 455.3 $(2M+H)^+$.

Preparación 51

4-(3,3-dimetil-2-oxo-butoxi)-bencilamina



2,2,2-Trifluoro-N-(4-metoxibencil)-acetamida: Se mezcla bajo atmósfera de nitrógeno 4-metoxibencilamina (13.7 g, 100 mmol) y N-metilmorfolina en THF anhidro (300 mL). Se enfría a 0°C en un baño de hielo. Se agrega gota a gota una solución de anhídrido trifluoroacético (15.6 mL, 110 mmol) en THF anhidro (25 mL). Se calienta hasta temperatura ambiente lentamente y se agita durante 16 h. Se concentra in vacuo. Se disuelve en EtOAc y se lava sucesivamente con NaOH acuoso 1N, HCl acuoso 1N, y salmuera. Se separa la capa orgánica, se seca sobre Na_2SO_4 y se concentra in vacuo. Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (9:1 y 4:1) para obtener el intermediario deseado (19 g, 81%). EM (ES-) m/z: 232 $(M-H)^-$.

2,2,2-Trifluoro-N-(4-hidroxi-bencil)-acetamida: Se disuelve bajo atmósfera de nitrógeno 2,2,2-trifluoro-N-(4-metoxibencil)-acetamida (11.6 g, 50 mmol) en DCM (250 mL). Se enfría a 0°C en un baño de hielo. Se agrega gota a gota

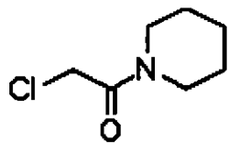
tribromuro de boro 1M en DCM (100 mL, 100 mmol) y se agita durante 20 min después de la adición. Se calienta a temperatura ambiente y se agita durante 16 h. Se enfría la mezcla de reacción en un baño de hielo y se apaga muy cuidadosamente con $NaHCO_3$ acuoso saturado. Se separa la capa orgánica. Se extrajo la capa acuosa 2 veces con cloroformo. Se secan los extractos orgánicos combinados sobre Na_2SO_4 y se concentra in vacuo para obtener el intermediario deseado (8.8 g, 40 mmol). EM (ES-) m/z: 218 $(M-H)^-$.

N-[4-(3,3-dimetil-2-oxo-butoxi)-bencil]-2,2,2-trifluoroacetamida: Se mezcla 2,2,2-trifluoro-N-(4-hidroxi-bencil)-acetamida (438 mg, 2.0 mmol), 1-bromopinacolona (430 mg, 2.4 mmol), carbonato de potasio anhidro (829 mg, 6.0 mmol) y yoduro de potasio (33 mg, 0.1 mmol) con acetona. Se calienta bajo reflujo durante 12 h. Se acidifica con HCl acuoso 1N y se extrae con EtOAc 3 veces. Se combinan los extractos orgánicos, se lavan con salmuera, se secan sobre Na_2SO_4, se filtran y se concentran. Se purifica por cromatografía en gel de sílice eluido con EtOAc/hexano (1:3) para dar el intermediario deseado como un aceite incoloro. EM (ES+) m/z: 335 $(M+NH_4)^+$. EM (ES-) m/z: 316 $(M-H)^-$.

4-(3,3-dimetil-2-oxo-butoxi)-bencilamina: Se agrega NaOH acuoso 5N (15 mL) a una solución de N-[4-(3,3-dimetil-2-oxo-butoxi)-bencil]-2,2,2-trifluoro-acetamida (552 mg, 1.74 mmol) en metanol (10 mL) y se agita durante 2 h a temperatura ambiente. Se extrae la mezcla con DCM 3 veces. Se secan los extractos orgánicos combinados sobre Na_2SO_4, se filtran y se concentran. Se purifica por cromatografía en gel de sílice eluido con DCM/amoniaco 2M en metanol (92:8) para dar el compuesto del título como un aceite incoloro (337 mg, 87%). EM (ES+) m/z: 205 $(M+H-NH_3)^+$.

Preparación 52

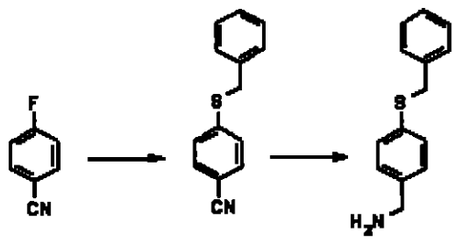
N-(2-Cloro-acetil)-piperidina



Se agrega cloruro de cloroacetilo (1.242 g, 11.0 mmol) a una mezcla de carbonato de potasio (2.073 g, 15 mmol) y piperidina (852 mg, 10 mmol) en THF (50 mL) a 0°C. Se agita la reacción durante 12 h y gradualmente se eleva a temperatura ambiente. Se diluye con agua, se extrae con EtOAc 3 veces. Se combinan los extractos orgánicos y se lavan secuencialmente con $NaHCO_3$ acuoso saturado, HCl acuoso 0.1N y salmuera. Se seca sobre Na_2SO_4, se filtran y se concentran para dar el compuesto del título (1.65 g, 100%).

Preparación 53

4-Benziltio-bencilamina

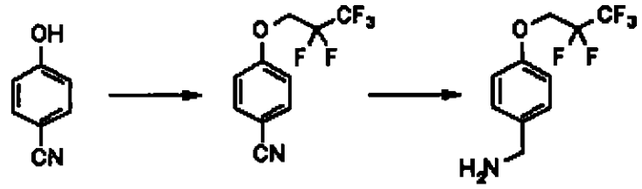


4-Benziltio-benzonitrilo: Se mezcla bajo atmósfera de argón 4-fluorobenzonitrilo (1.21 g, 10 mmol), mercaptano de bencilo (1.86 g, 15 mmol), y carbonato de cesio (6.5 g, 20 mmol) en NMP anhidro (20 mL). Se desgasifica el matraz y se rellena con argón. Se calienta a 120°C durante 3 h. Se enfría a temperatura ambiente, se diluye con EtOAc, se filtra y se lava con HCl acuoso 1N. Se separa la capa orgánica, se seca sobre Na_2SO_4 y se concentra in vacuo. Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (1:0 y 9:1) para obtener el intermediario deseado (689 mg, 31%). CG-EM m/z: 225 (M^+).

4-Benziltio-bencilamina: Se usa el procedimiento de reducción descrito en la preparación 45 (Etapa 2), al usar 4-Benziltio-benzonitrilo (689 mg, 3.1 mmol) para dar, después de la cromatografía SCX, el compuesto del título (464 mg, 64%). EM (ES+) m/z: 213 $(M+H-NH_3)^+$.

Preparación 54

4-(2,2,3,3,3-Pentafluoropropoxi)-bencilamina

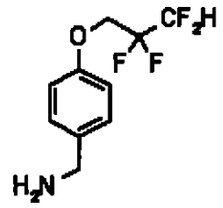


4-(2,2,3,3,3-Pentafluoropropoxi)-benzonitrilo: Se calienta una mezcla de complejo de fluoruro de potasio de 4-hidroxi-benzonitrilo (3.0 g, 16.9 mmol) y 1,1,1,2,2-pentafluoro-3-yodo-propano (10.8 g, 37.2 mmol) en DMSO (80 mL) a 130°C durante 20 h. Se enfría la mezcla a temperatura ambiente, se diluye con hexano/EtOAc (1:1, 200 mL) y se lava con 10% de NaCl acuoso (3 x 50 mL). Se seca la capa orgánica, se concentra in vacuo y se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (10:1, 10:2 y 10:3) para obtener el intermediario deseado (1.1 g, 26%). CG-EM m/z: 251 (M^+).

4-(2,2,3,3,3-Pentafluoropropoxi)-bencilamina: Se usa un método similar al Procedimiento general 6-4, al usar 4-(2,2,3,3,3-pentafluoropropoxi)-benzonitrilo (1.1 g, 4.1 mmol), para obtener el compuesto del título (1.1 g, 99%). CG-EM m/z: 254 (M^+-H).

Preparación 55

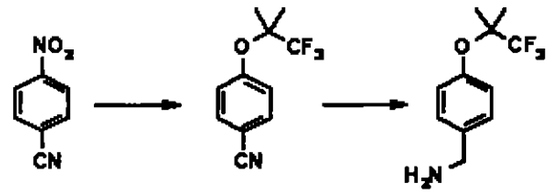
4-(2,2,3,3-Tetrafluoropropoxi)-bencilamina



Se usa un método similar a la Preparación 54, al usar complejo de floruro de potasio de 4-hidroxi-benzonitrilo (4.2 g, 23.7 mmol) y 1,1,2,2-tetrafluoro-3-yodo-propano (10 g, 41.3 mmol), para dar el compuesto del título (38% en general). CG-EM m/z: 236 (M^+-H).

Preparación 56

4-(2,2,2-Trifluoro-1,1-dimetil-etoxi)-bencilamina



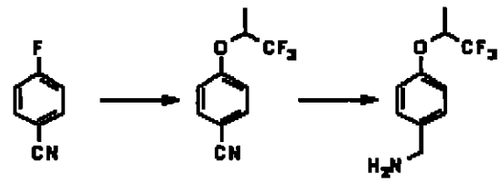
4-(2,2,2-Trifluoro-1,1-dimetil-etoxi)-benzonitrilo: Se agrega 2-trifluorometil-2-propanol (3.4 g, 27 mmol) lentamente a una mezcla espesa de hidruro de sodio (0.6 g, 60% en aceite mineral, se lava con hexano) en HMPA (5 mL) bajo nitrógeno. Se agita la mezcla espesa durante 15 min y se agrega una solución de 4-nitrobenzonitrilo (2.0 g, 13.5 mmol) en HMPA (10 mL). Se agita la mezcla espesa morado resultante a temperatura ambiente durante 16 h, se diluye con dietil éter

(100 mL) y se lava con HCl acuoso al 5% (30 mL). Se separan las capas y se extrae la capa acuosa con dietil éter (2 x 50 mL). Se combinan los extractos orgánicos y se concentra in vacuo. Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (9:1 to 1:1) para obtener el intermediario deseado (780 mg, 25%). CG-EM m/z: 229 (M^+).

4-(2,2,2-Trifluoro-1,1-dimetil-etoxi)-bencilamina: Se usa un método similar al Procedimiento general 6-4 para reducir 4-(2,2,2-trifluoro-1,1-dimetil-etoxi)-benzonitrilo (780 mg, 3.4 mmol). Se purifica por cromatografía en gel de sílice eluido con DCM/amoniaco 2M en metanol (40:1, 20:1 y 10:1) para obtener el compuesto del título (780 mg, 98%). CG-EM m/z: 232 (M^+-H).

Preparación 57

(±)-4-(2,2,2-Trifluoro-1-metil-etoxi)-bencilamina



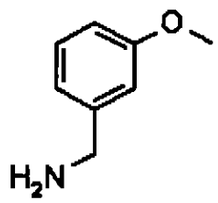
(±)-4-(2,2,2-Trifluoro-1-metil-etoxi)-benzonitrilo: Se agrega 1,1,1-trifluoro-2-propanol (3.8 g, 66 mmol) lentamente a una mezcla espesa de hidruro de sodio (730 mg, 60% en aceite mineral, se lava con hexano) en HMPA (5 mL) bajo nitrógeno. Se agita la mezcla espesa durante 15 min y se agrega 4-

fluorobenzonitrilo (2 g, 16.5 mmol). Se calienta la mezcla espesa en un matraz sellado a 90°C for 16 h. Se enfría la mezcla a temperatura ambiente y se vacía la mezcla en un matraz que contiene HCl acuoso al 5% (20 mL). Se extrae la mezcla con dietil éter (3 x 50 mL), y se lava con HCl acuoso al 5% (25 mL). Se seca la capa orgánica sobre Na_2SO_4 y se concentra in vacuo. Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (9:1) para obtener el intermediario deseado (2.5 g, 70%). CG-EM m/z: 215 (M^+).

(±)-4-(2,2,2-Trifluoro-1-metil-etoxi)-bencilamina: Se usa un método similar al Procedimiento general 6-4, al usar (±)-4-(2,2,2-trifluoro-1-metil-etoxi)-benzonitrilo (1.0 g, 4.6 mmol), para obtener el compuesto del título (1.1 g, 95%). CG-EM m/z: 218 (M^+-H).

Preparación 58

3-Metoxibencilamina

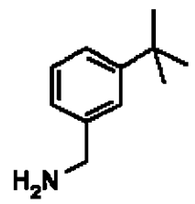


Se agrega hidruro de aluminio de litio (3.795 g, 100 mmol) en porciones a una solución de 3-metoxibenzonitrilo (5.326 g, 40 mmol) en éter etílico anhidro (200 mL) a 0°C. Se agita durante 1 h, se calienta a temperatura ambiente y se

continua agitando durante 12 h. Se apaga la reacción con NaOH acuoso 0.1N, se filtra el sólido, se seca el filtrado sobre Na_2SO_4 y se concentra para dar el compuesto del título como un aceite incoloro (5.107 g, 93%). EM (ES+) m/z: 138 $(M+H)^+$.

Preparación 59

3-(tert-Butil)bencilamina

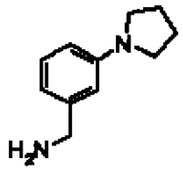


Se disuelve 3-tert-butiltolueno (0.5 mL, 2.9 mmol) en tetracloruro de carbono (20 mL). Se agrega NBS (530 mg, 3 mmol) y se irradia la mezcla de reacción con una lámpara de sol de 250 vatios con calentamiento simultáneo hasta reflujo durante 1 h. Se enfría a temperatura ambiente, se filtra, y se concentra el filtrado para secarse para dar 1-bromometil-3-tert-butilbenceno crudo. Se disuelve 1-bromometil-3-tert-butilbenceno crudo (600 mg) en DMF anhidro. Se agrega en porciones azida de sodio (260 mg, 4 mmol) y se agita a temperatura ambiente durante 2 h. Se vacía la mezcla en agua (250 mL), se extrae con EtOAc (3x50 mL), se lavan los extractos orgánicos combinados con salmuera, se seca sobre $MgSO_4$, se filtra y evapora el solvente para dar 1-azidometil-3-tert-butilbenceno crudo, que se usa sin purificación

adicional. Se disuelve 1-azidometil-3-tert-butilbenceno crudo en metanol que contiene 10% Pd/C (75 mg) a 5°C, y se agita la mezcla espesa resultante bajo 1 atm de H_2 durante 1 h. Se filtra, se concentra in vacuo y se purifica por cromatografía en gel de sílice eluido secuencialmente con hexano/EtOAc (4:1 y 1:1), EtOAc, metanol y amoniaco 2M en metanol para dar el compuesto del título (255 mg, 53% en general). EM (ES+) m/z: 164 $(M+H)^+$.

Preparación 60

(3-Pirrolidin-1-il)bencilamina

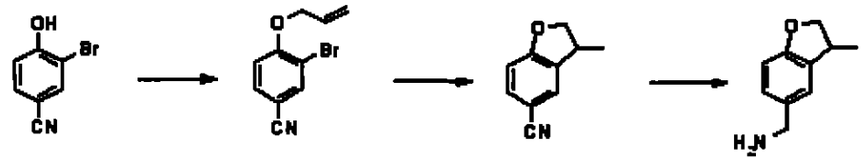


Se hace espesa una mezcla de éster de tert-butilo del ácido (3-bromobencil)-carbámico (600 mg, 2.1 mmol, Publicación de Solicitud de Patente de EUA US 2003134885), pirrolidina (450 mL, 5.2 mmol), tris(dibencilidenacetona)dipaladio (0) (200 mg, 0.21 mmol), BINAP (400 mg, 0.63 mmol) y carbonato de cesio (960 mg, 2.94 mmol) en tolueno anhidro (10 mL). Se desgasifica bajo vacío, se rellena el sistema con nitrógeno y se calienta en un matraz sellado a 90°C durante 18 h. Se enfría hasta temperatura ambiente, se diluye con dietil éter, se filtra, y se concentra in vacuo. Se disuelve el residuo resultante en

DCM (10 mL) y se agrega ácido trifluoroacético (5 mL). Se agita a temperatura ambiente durante 1 h y se concentra in vacuo. Se purifica por cromatografía en gel de sílice eluido secuencialmente con hexano/EtOAc (1:1), EtOAc y amoniaco 2M en metanol. Se purifica nuevamente por cromatografía SCX para dar el compuesto del título como un aceite café (300 mg, 85% en general). EM (ES+) m/z: 178 $(M+H)^+$.

Preparación 61

(±)-C-(3-Metil-2,3-dihidro-benzofuran-5-il)-metilamina

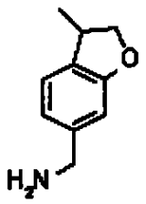
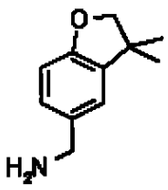
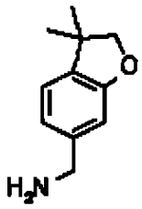


4-Aliloxi-3-bromo-benzonitrilo: Se mezcla 3-bromo-4-hidroxi-benzonitrilo (1.520 g, 8.0 mmol), bromuro de alilo (1.161 g, 9.6 mmol), carbonato de potasio (3.317 g, 24 mmol) y yoduro de potasio (133 mg, 0.1 mmol) en acetona (80 mL). Se calienta la mezcla hasta reflujo durante 12 h. Se enfría a temperatura ambiente, se agrega EtOAc, se lava la capa orgánica con agua, y se extrae la capa acuosa 2 veces con EtOAc. Se secan los extractos orgánicos combinados sobre Na_2SO_4, se filtran y se concentran. Se purifica por cromatografía en gel de sílice eluido con EtOAc/hexano (1:8) para obtener el intermediario deseado.

(±)-3-Metil-2,3-dihidro-benzofuran-5-carbonitrilo: Se agrega hidruro de tri-n-butilestaño (5.821 g, 20 mmol) y AIBN (411 mg, 2.5 mmol) a una solución de 4-aliloxi-3-bromo-benzonitrilo (595 mg, 2.5 mmol). Se calienta la reacción a reflujo durante 20 h. Se diluye con EtOAc y se lava con agua. Se extrajo la capa acuosa con EtOAc 3 veces. Se combinan los extractos orgánicos, se lavan con salmuera, se secan sobre Na_2SO_4, se filtra y se concentra in vacuo. Se purifica por cromatografía en gel de sílice eluido con EtOAc/hexano (1:8) para dar el intermediario deseado como un sólido blanco (474 mg, 100% con una cantidad de trazas del derivado de tributilestaño).

(±)-C-(3-Metil-2,3-dihidro-benzofuran-5-il)-metilamina: Se usa un método similar a la Preparación 58, al usar (±)-3-metil-2,3-dihidro-benzofuran-5-carbonitrilo (474 mg, 2.98 mmol) para dar el compuesto del título como un aceite incoloro (410 mg, 84%).

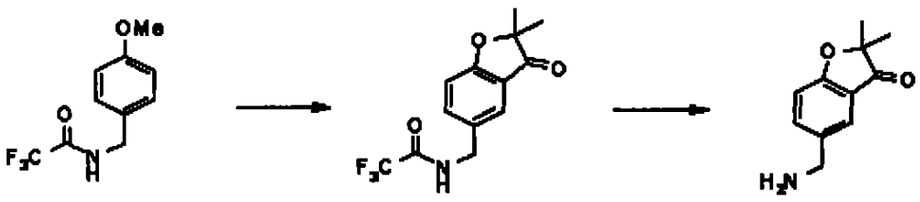
Los compuestos de las preparaciones 62-64 pueden prepararse esencialmente como se describen en la Preparación 61 al usar 3-bromo-4-hidroxi-benzonitrilo o 4-bromo-3-hidroxi-benzonitrilo y el bromuro de alilo apropiadamente substituido. Datos EM (ES+) se muestran en la Tabla a continuación.

Prep.	Estructura	Compuesto	EM (ES+) m/z
62		(±)-C-(3-Metil-2,3-dihidro-benzofuran-6-il)-metilamina	164 $(M+H)^+$
63		C-(3,3-dimetil-2,3-dihidro-benzofuran-5-il)-metilamina	ND
64		C-(3,3-dimetil-2,3-dihidro-benzofuran-6-il)-metilamina	178 $(M+H)^+$

ND= No se determina

Preparación 65

C-(2,2-dimetil-3-oxo-2,3-dihidro-benzofuran-5-il)-metilamina

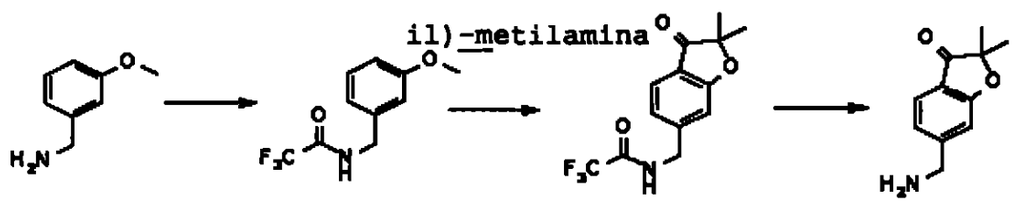


N-(2,2-dimetil-3-oxo-2,3-dihidro-benzofuran-5-ilmetil)-2,2,2-trifluoro-acetamida: Se agrega bromuro de 2-bromoisobutirilo (1.724 g, 7.5 mmol) a una solución de 2,2,2-trifluoro-N-(4-metoxi-bencil)-acetamida (1.166 g, 5.0 mmol) en 1,2-

dicloroetano (8 mL) a 15°C, luego se agrega cloruro de hierro (III) anhidro en polvo (973 mg, 6.0 mmol). Se agita la reacción a 15°C durante 3 h y a temperatura ambiente durante 8 días. Se agrega gota a gota tartrato de potasio y sodio acuoso saturado, luego agua y EtOAc, y se agita durante 1 h. Se filtra completamente el sólido, se separa la capa orgánica, y se extrae la capa acuosa 3 veces con EtOAc. Se combinan los extractos orgánicos, se lavan con salmuera, se seca sobre Na_2SO_4, se filtran y se concentran in vacuo. Se purifica por cromatografía en gel de sílice eluido con EtOAc/hexano (1:3) para dar el intermediario deseado (253 mg, 17%).

C-(2,2-dimetil-3-oxo-2,3-dihidro-benzofuran-5-il)-metilamina: Se disuelve N-(2,2-dimetil-3-oxo-2,3-dihidro-benzofuran-5-ilmetil)-2,2,2-trifluoro-acetamida (253 mg, 0.88 mmol) en amoniaco 7M en metanol y se agita a temperatura ambiente durante 5 días. Se eliminan los volátiles in vacuo, se purifica por cromatografía en gel de sílice eluido con DCM/amoniaco 2M en metanol (92:8) para dar el compuesto del título (44 mg, 26%). EM (ES+) m/z: 175 $(M+H-NH_3)^+$.

Preparación 66 C-(2,2-dimetil-3-oxo-2,3-dihidro-benzofuran-6-il)-metilamina

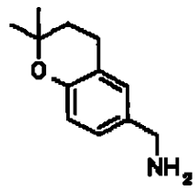


2,2,2-Trifluoro-N-(3-metoxi-bencil)-acetamida: Se agrega anhídrido trifluoroacético (6.3 g, 30 mmol) a una solución de 3-metoxibencilamina (3.43 g, 25 mmol) y N-metil-morfolina (3.793 g, 37.5 mmol) en THF (80 mL) a 0°C y se agita a esta temperatura durante 4 h. Se calienta a temperatura ambiente y se agita durante 12 h. Se diluye con EtOAc, se lava secuencialmente con agua, HCl acuoso 1N, $NaHCO_3$ acuoso saturado y salmuera. Se seca la capa orgánica sobre Na_2SO_4, se filtra y se concentra. Se purifica por cromatografía en gel de sílice eluido con EtOAc/hexano (1:3) para dar el intermediario deseado (5.344 g, 91%).

C-(2,2-dimetil-3-oxo-2,3-dihidro-benzofuran-6-il)-metilamina: Se usa un método similar a la Preparación 65, al usar 2,2,2-trifluoro-N-(3-metoxi-bencil)-acetamida (1.166 g, 5 mmol), para dar el compuesto del título (220 mg, 23% 2 etapas). EM (ES+) m/z: 192 $(M+H)^+$.

Preparación 67

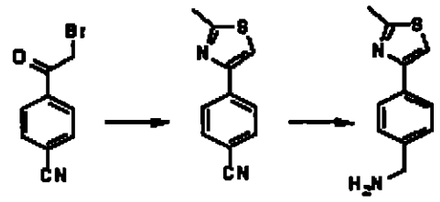
6-Aminometil-2,2-dimetil-2H-cromeno



Se agrega 2,2-dimetil-2H-cromeno-6-carbonitrilo (1.5 g, 8.1 mmol) y etanol níquel activado Raney® húmedo (0.4 g) a un recipiente de presión Parr. Inmediatamente se agrega amoniaco 7N en metanol (170 mL) y se sella el recipiente. Se purga el recipiente de reacción con nitrógeno, se presuriza la mezcla de reacción con hidrógeno (3400 KPa), se sella el recipiente, se agita la reacción y se calienta a 60°C durante 20 h. A su vez completamente se calienta y se permite a la mezcla de reacción enfriar hasta temperatura ambienta. Se ventea el exceso de hidrógeno del recipiente y se purga el recipiente con nitrógeno. Se filtra la mezcla de reacción para remover el níquel Raney®. Se purifica por cromatografía en gel de sílice eluido con DCM/amoniaco 2M en metanol (9:1) para obtener el compuesto del título (1.5 g, 97%). EM (ES+) m/z: 175 $(M+H-NH_3)^+$.

Preparación 68

4-(2-Metiltiazol-4-il)-bencilamina



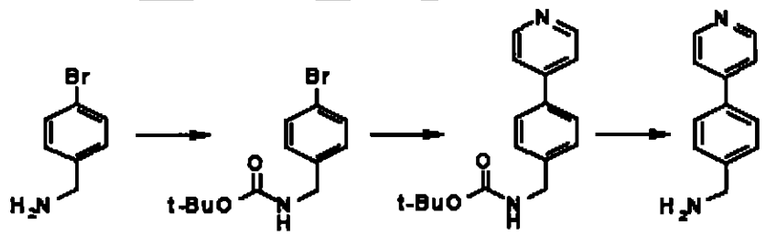
4-(2-Metiltiazol-4-il)-benzonitrilo: Se suspende cloruro de 4-cianofenacilo (515 mg, 2.23 mmol) en etanol (15 mL). Se agrega tioacetamida (171 mg, 2.23 mmol) y bicarbonato de sodio (187 mg, 2.23 mmol) y se calienta la mezcla bajo reflujo durante 2 h. Se concentra in vacuo y se disuelve el residuo en DCM. Se lava la fracción orgánica con agua, se seca sobre Na_2SO_4, se filtra y se concentra para dar un sólido. Se suspendió el sólido en éter/hexano y se filtra bajo vacío se lava con hexano para obtener el intermediario deseado como un sólido blanco (415 mg, 93%). CG-EM m/z: 200 (M^+).

4-(2-Metiltiazol-4-il)-bencilamina: Se disuelve 4-(2-metiltiazol-4-il)-benzonitrilo (305 mg, 1.52 mmol) en THF anhidro (50 mL). Se agrega una solución 1M de hidruro de aluminio de litio en THF (3.05 mL, 3.05 mmol). Se calienta la mezcla durante la noche bajo reflujo. Se enfría la mezcla de reacción con hielo/agua y se trabaja secuencialmente con EtOAc y agua. Se filtra la mezcla sobre Celite®. Se separa la

fase orgánica, y se extrae la fase acuosa con cloroformo. Se secan los extractos orgánicos combinados sobre Na_2SO_4, se filtran y se concentran para obtener el compuesto del título como un aceite (120 mg) que se usa sin purificación adicional. CG-EM m/z: 204 (M^+).

Preparación 69

4-(Piridin-4-il)-bencilamina



N-(tert-Butoxicarbonil)-4-bromo-bencilamina: Se agrega di-tert-butil-dicarbonato (1.173 g, 5.375 mmol) y trietilamina (1.087 g, 1.0 mL, 10.75 mmol) a una solución agitada de 4-bromobencilamina (1.0 g, 5.375 mmol) en DCM anhidro (15 mL). Se agita durante la noche a temperatura ambiente, se diluye con DCM y se lava con agua. Se separa la fase orgánica, se seca sobre Na_2SO_4, se filtran y se concentran in vacuo. Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (1:0, 19:1 y 9:1) para obtener el intermediario deseado como un sólido (1.24 g, 81%).

N-(tert-Butoxicarbonil)-4-(piridin-4-il)-bencilamina: Se disuelve N-(tert-butoxicarbonil)-4-bromo-bencilamina (0.8 g,

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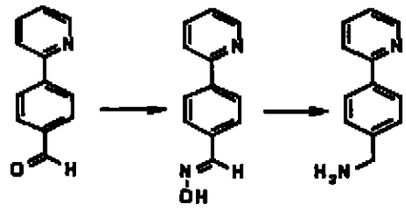
2.807 mmol) en DME anhidro (12 mL) bajo nitrógeno. Se agrega tetraquis(trifenilfosfina)paladio (0) (0.162 g, 0.14 mmol), ácido piridin-4-borónico (0.513 g, 4.211 mmol), y una solución de Na_2CO_3 acuosa 2M (2.8 mL, 5.614 mmol). Se calienta la reacción durante la noche a 70°C. Se enfría la mezcla a temperatura ambiente, se diluye con EtOAc, y se filtra sobre Celite®. Se lava la fracción orgánica con agua, se seca sobre Na_2SO_4, se filtran y se concentran in vacuo. Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (1:0, 4:1 y 1:1) para dar el compuesto del título como un aceite (0.295 g, 37%). CG-EM m/z: 284 (M^+).

4-(Piridin-4-il)-bencilamina: Se disuelve N-(tert-butoxicarbonil)-4-(4-piridil)-bencilamina (363 mg, 1.276 mmol) en DCM anhidro (10 mL). Se agrega cloruro de hidrógeno 4N en dioxano (10 mL) y se agita durante la noche a temperatura ambiente. Se concentra in vacuo para obtener la sal de clorohidrato en forma pura como un sólido. Se disuelve el sólido en $NaHCO_3$ acuoso saturado y se extrae 3 veces con DCM y 3 veces más con EtOAc. Se combinan los extractos orgánicos, se secan sobre Na_2SO_4, se filtran y se concentran para obtener el compuesto del título como un sólido (166 mg, 71 %). CG-EM m/z: 184 (M^+).

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Preparación 70

4-(Piridin-2-il)-bencilamina



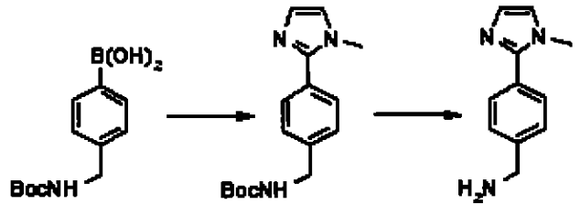
4-(2-Piridil)-benzaldehído oxima: Se agrega clorohidrato de hidroxilamina (0.379 g, 5.458 mmol) y una solución de NaOH (0.327 g, 8.187 mmol) en agua (2 mL) a una solución de 4-(2-piridil)-benzaldehído (0.5 g, 2.729 mmol) en etanol (10 mL). Se calienta la mezcla a 80°C durante 2 h. Se enfría a temperatura ambiente y se elimina el solvente in vacuo. Se divide el residuo entre EtOAc y agua. Se separa y se seca la fase orgánica sobre Na_2SO_4, se filtran y se concentran in vacuo. Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (1:0 y 4:1) para obtener el intermediario deseado (311 mg, 58%). CG-EM m/z: 198 (M^+).

4-(Piridin-2-il)-bencilamina: Se agrega Pd/C (10%, 50 mg) y HCl concentrado (2 mL) a una solución de 4-(2-piridil)-benzaldehído oxima (0.29 g, 1.46 mmol) en etanol absoluto (20 mL). Se hidrogena la mezcla a 50 psi (3.515 kg/cm^2) durante 2 h. Se filtra sobre Celite®, se lava con etanol y se concentra in vacuo para obtener la sal de clorohidrato en forma pura como un sólido. Se disuelve el sólido en $NaHCO_3$ acuoso

saturado, se extrae la solución acuosa 3 veces con DCM y 3 veces más con EtOAc. Se combinan los extractos orgánicos, se secan sobre Na_2SO_4, se filtran y se concentran in vacuo para obtener el compuesto del título como un sólido (130 mg, 48 %). CG-EM m/z: 184 (M^+).

Preparación 71

4-(1-Metil-1H-imidazol-2-il)-bencilamina



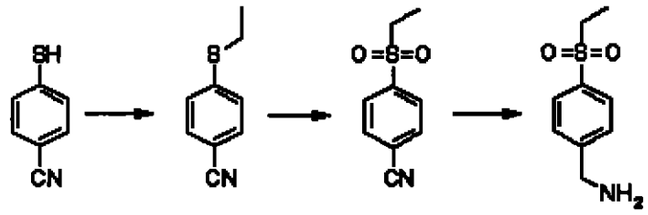
éster de tert-butilo del ácido [4-(1-Metil-1H-imidazol-2-il)-bencil]-carbámico: Se agrega ácido 4-(N-tert-Butoxicarbonil-aminometil)fenilborónico (1.9 g, 7.4 mmol), 2-bromo-1-metil-1H-imidazol (800 mg, 5.0 mmol), tetraquis(trifenilfosfina)-paladio (0) (287 mg, 0.25 mmol) y carbonato de potasio (860 mg, 6.2 mmol) a un matraz que contiene tolueno (10 mL). Se calienta la mezcla en un matraz sellado a 90°C durante 16 h. Se enfría la mezcla, se diluye con EtOAc (50 mL), se filtra a través de Celite®, y se concentra in vacuo. Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc/metanol (49:50:1) para obtener el intermediario deseado (1.2 g, 83%). CG-EM m/z: 287 (M^+).

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4-(1-Metil-1H-imidazol-2-il)-bencilamina: éster de terc-butilo del ácido se disuelve [4-(1-metil-1H-imidazol-2-il)-bencil]-carbámico (500 mg, 1.7 mmol) en DCM (20 mL) y ácido trifluoroacético (5 mL). Se agita la mezcla durante 1 h a temperatura ambiente. Se concentra in vacuo y se purifica por cromatografía SCX para obtener el compuesto del título (240 mg, 74%). EM (ES+) m/z: 188 $(M+H)^+$.

Preparación 72

4-Etansulfonil-bencilamina



4-etiltio-benzonitrilo: Se combina 4-mercapto-benzonitrilo (0.4 g, 2.96 mmol), bromoetano (1.4 mL, 8.88 mmol) y carbonato de potasio (3.3 g, 23.7 mmol) en DMF anhidro (7 mL) y se calienta a 60°C durante 17 h. Se enfría la mezcla de reacción a temperatura ambiente y se divide entre salmuera (20 mL) y EtOAc (20 mL). Se separa la capa orgánica, se seca sobre Na_2SO_4 anhidro y se concentra. Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (1:0, 9:1 y 4:1) para obtener el intermediario deseado como un aceite incoloro (0.4 g, 83%).

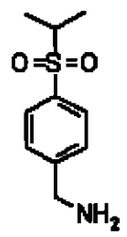
868

4-Etansulfonil-benzonitrilo: Se disuelve 4-etiltio-benzonitrilo (0.4 g, 2.4 mmol) en TFA (10 mL) y se agrega lentamente peróxido de hidrógeno (30 p%, 10 mL) a 5°C. Se agita la mezcla de reacción a temperatura ambiente durante 2 h y se divide entre salmuera (20 mL) y DCM (20 mL). Se separa la capa orgánica, se seca sobre Na_2SO_4 anhidro y se concentra para obtener el intermediario deseado como un sólido blanco (0.5 g, 100%). CG-EM m/z: 195 (M^+).

4-Etansulfonil-bencilamina: Se combina 4-etansulfonil-benzonitrilo (0.7 g, 3.5 mmol), Níquel Raney® 3201 (mezcla espesa en agua, 0.1 g), amoniaco 2N en metanol (20 mL) y se hidrogena a 50 psi (3.515 kg/cm^2) durante 17 h. Se filtra la mezcla de reacción a través de una almohadilla de Celite® y se concentra in vacuo. Se purifica por cromatografía SCX para obtener el compuesto del título como un aceite amarillo (0.3 g, 43%).

Preparación 73

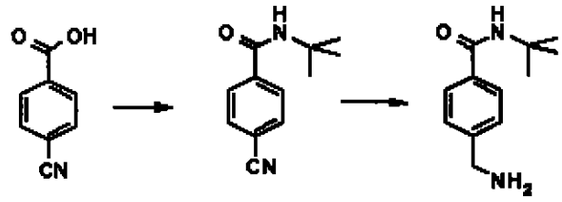
4-(2-Propanosulfonil)-bencilamina



Se usa un método similar a la Preparación 72, al usar 4-mercapto-benzonitrilo (0.5 g, 3.7 mmol) y 2-bromopropano (1.4 g, 11.38 mmol), para obtener el compuesto del título como un aceite amarillo (0.3 g, 39% en general).

Preparación 74

4-Aminometil-N-tert-butil-benzamida



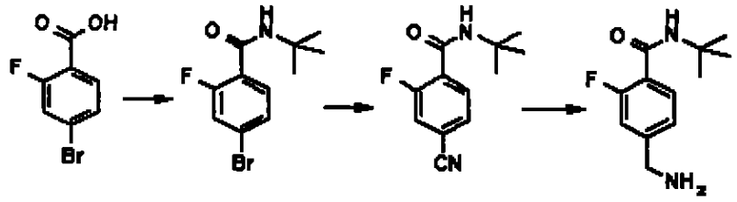
N-tert-butil-4-ciano-benzamida: Se combina ácido 4-cianobenzoico (30 mg, 2.07 mmol), tert-butilamina (0.5 mL, 4.13 mmol), trietilamina (0.4 mL, 2.89 mmol), y HATU (1.1 g, 2.89 mmol) en DMF anhidro (7 mL). Se agita a temperatura ambiente durante 17 h. Se divide la mezcla de reacción entre salmuera (15 mL) y dietil éter (15 mL), se separa la capa orgánica, se seca sobre Na_2SO_4 anhidro y se concentra in vacuo. Se purifica por cromatografía en gel de sílice eluido con DCM para obtener el intermediario deseado como un sólido blanco (0.4 g, 89%). EM (ES+) m/z: 203 $(M+H)^+$.

4-Aminometil-N-tert-butil-benzamida: Se combina N-tert-butil-4-ciano-benzamida (0.4 g, 1.78 mmol), níquel Raney® 3201 (mezcla espesa en agua, 0.03 g), amoniaco 2N en metanol (20

mL) y se hidrogena a 50 psi (3.515 kg/cm^2) durante 1 h. Se filtra la mezcla de reacción a través de una almohadilla de Celite®, se elimina el solvente y se purifica por cromatografía SCX para obtener el compuesto del título como un aceite incoloro (0.4 g, 95%). EM (ES+) m/z: 207 $(M+H)^+$.

Preparación 75

4-Aminometil-2-fluoro-N-tert-butil-benzamida



4-Bromo-N-tert-butil-2-fluoro-benzamida: Se combina ácido 4-bromo-2-fluoro-benzoico (5.0 g, 22.83 mmol), cloruro de tionilo (10 mL, 0.137 mol) en tolueno (10 mL) y se puso a reflujo durante 2 h. Se evapora la mezcla de reacción para obtener cloruro de 4-bromo-2-fluoro-benzoilo (5.0 g, 93%) y se usa para la siguiente etapa sin purificación adicional. Se disuelve tert-butilamina (0.8 mL, 5.12 mmol) y trietilamina (0.8 mL, 6.32 mmol) en DCM anhidro (20 mL), se enfría a 0°C y se agrega una solución de cloruro de 4-bromo-2-fluoro-benzoilo (1.0 g, 4.22 mmol) en DCM anhidro (10 mL). Se agita la mezcla de reacción a 0°C durante 10 min, se calienta a temperatura ambiente y se continua para agitación durante 30 min. Se lava la mezcla de reacción con salmuera (2 x 10 mL),

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se secan los extractos orgánicos sobre Na_2SO_4 anhidro, se evapora el solvente y se purifica por cromatografía en gel de sílice eluido con DCM para obtener el intermediario deseado como un sólido blanco (1.0 g, 87%). EM (ES+) m/z: 275 $(M+H)^+$.

N-tert-Butil-4-ciano-2-fluoro-benzamida: Se combina 4-bromo-N-tert-butil-2-fluoro-benzamida (1.0 g, 3.65 mmol) y cianuro de cobre (I) (0.7 g, 7.29 mmol) en DMF anhidro (10 mL) y se puso a reflujo durante 17 h. Se enfría la mezcla de reacción a temperatura ambiente y se trata con 50% (p/p) etilendiamina acuoso (20 mL). Se extrae la mezcla de reacción con dietil éter (3 x 10 mL), se combinan los extractos orgánicos, se lavan con salmuera (2 x 10 mL) y se seca la capa orgánica sobre Na_2SO_4. Se evapora el solvente y se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (1:0, 9:1, 4:1, 7:3 y 3:2) para obtener el intermediario deseado como un sólido blanco (0.6 g, 77%). EM (ES+) m/z: 221 $(M+H)^+$.

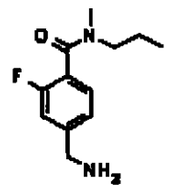
4-Aminometil-2-fluoro-N-tert-butil-benzamida: Se combina N-tert-butil-4-ciano-2-fluoro-benzamida (0.6 g, 1.78 mmol), níquel Raney® 3201 (mezcla espesa en agua, 30 mg), amoniaco 2N en metanol (30 mL) y se hidrogena a 50 psi (3.515 kg/cm^2) durante 1 h. Se filtra la mezcla de reacción a través de una almohadilla de Celite®, se concentra in vacuo y se purifica

812

por cromatografía SCX para obtener el compuesto del título como un aceite incoloro (0.6 g, 96%).

Preparación 76

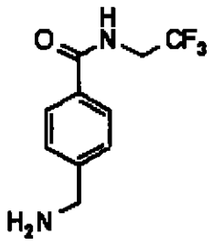
4-Aminometil-2-fluoro-N-metil-N-Propil-benzamida



Se usa un método similar a la Preparación 75, al usar ácido 4-bromo-2-fluoro-benzoico (1.0 g, 4.56 mmol) y N-metil-propilamina (0.5 mL, 5.05 mmol), para dar el compuesto del título como un aceite incoloro (0.5 g, 49%). CG-EM m/z: 224 (M^+).

Preparación 77

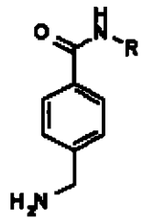
4-Aminometil-N-(2,2,2-trifluoro-etil)-benzamida

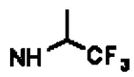


Se usa el Procedimiento general 6-1, al usar 2,2,2-trifluoroetilamina (197 mg, 2 mmol) y ácido 4-(tert-butoxicabonilamino-metil)-benzoico, para dar el compuesto del título como un aceite claro (440 mg, 94%). EM (ES+) m/z: 233 $(M+H)^+$.

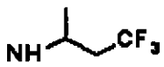
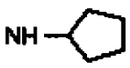
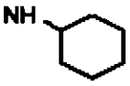
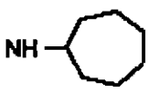
813

Los compuestos de las preparaciones 78-93 pueden prepararse esencialmente como se describen en la Preparación 77 al usar ácido 4-(tert-butoxicabonilamino-metil)-benzoico y la amina apropiada. Datos de rendimiento general y EM (ES) se muestran en la Tabla a continuación.

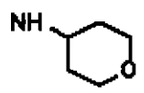
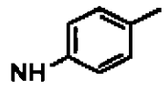
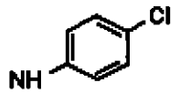
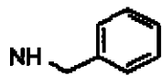
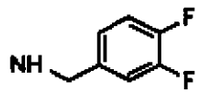


Preparación	NH-R	Compuesto	Rendimiento (%)	EM (ES) m/z
78		4-Aminometil-N-(2,2,3,3,3-pentafluoro-propil)-benzamida	100	283 $(M+H)^+$
79		(±)-4-Aminometil-N-(2,2,2-trifluoro-1-metil-etil)-benzamida	78	247 $(M+H)^+$

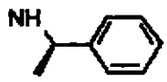
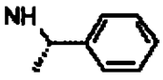
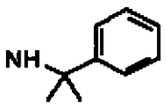
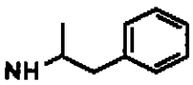
B14

Preparación	NH-R	Compuesto	Rendimiento (%)	EM (ES) m/z
80		4-Aminometil-N-(3,3,3-trifluoro-propil)-benzamida	100	247 $(M+H)^+$
81		(±)-4-Aminometil-N-(3,3,3-trifluoro-1-metil-propil)-benzamida	100	261 $(M+H)^+$
82		4-Aminometil-N-(ciclopentil)-benzamida	100	219 $(M+H)^+$
83		4-Aminometil-N-(ciclohexil)-benzamida	100	233 $(M+H)^+$
84		4-Aminometil-N-(cicloheptil)-benzamida	80	247 $(M+H)^+$

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Preparación	NH-R	Compuesto	Rendimiento (%)	EM (ES) m/z
85		4-Aminometil-N-(tetrahidro-piran-4-il)-benzamida	56	ND
86		4-Aminometil-N-(4-metil-fenil)-benzamida	100	239 $(M-H)^-$
87		4-Aminometil-N-(4-cloro-fenil)-benzamida	84	259 $(M-H)^-$
88		4-Aminometil-N-bencil-benzamida	59	241 $(M+H)^+$
89		4-Aminometil-N-(3,4-difluoro-fenil)-benzamida	100	ND

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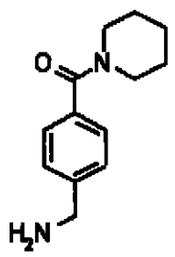
Preparación	NH-R	Compuesto	Rendimiento (%)	EM (ES) m/z
90		(R)-4-Aminometil-N-(1-fenil-etil)-benzamida	94	255 $(M+H)^+$
91		(S)-4-Aminometil-N-(1-fenil-etil)-benzamida	94	255 $(M+H)^+$
92		4-Aminometil-N-(1-metil-1-fenil-etil)-benzamida	22	269 $(M+H)^+$
93		(±)-4-Aminometil-N-(1-metil-2-fenil-etil)-benzamida	85	269 $(M+H)^+$

ND = No se determina

817

Preparación 94

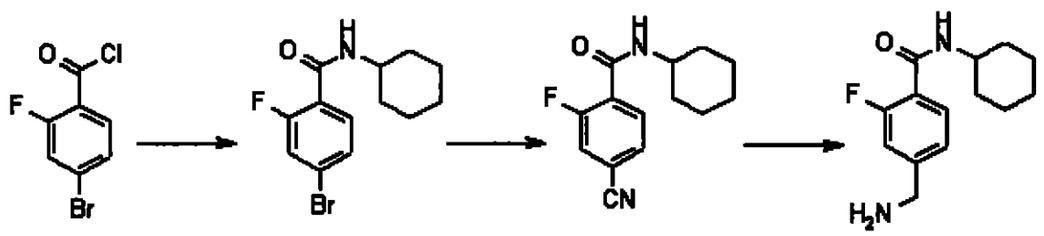
4-(Piperidin-1-ilcarbonil)-bencilamina



Se usa el Procedimiento general 6-1, al usar piperidina (373 mg, 4.4 mmol) y ácido 4-(tert-butoxicabonilamino-metil)-benzoico para dar el compuesto del título como un sólido blanco (1.03 g, 100%). EM (ES+) m/z: 219 $(M+H)^+$.

Preparación 95

4-Aminometil-N-ciclohexil-2-fluoro-benzamida



4-Bromo-N-ciclohexil-2-fluoro-benzamida: Se disuelve cloruro de 4-bromo-2-fluoro-benzoilo (1 g, 4.21 mmol) en DCM y se enfría la solución en un baño de hielo. Se agrega trietilamina (0.87 mL, 6.32 mmol) y ciclohexilamina (502 mg, 5.1 mmol) y se agita la mezcla a temperatura ambiente durante 2 h. Se divide la mezcla de reacción entre salmuera y DCM. Se seca la capa orgánica sobre Na_2SO_4, se filtran y se concentran

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in vacuo para dar el intermediario deseado como un sólido blanco (1.24 g, 98%).

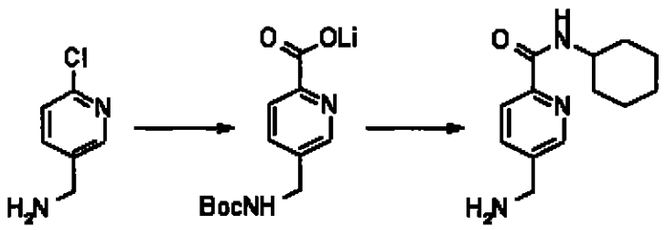
4-Ciano-N-ciclohexil-2-fluoro-benzamida: Se calienta una mezcla de 4-bromo-N-ciclohexil-2-fluoro-benzamida (1.24 g, 4.13 mmol) y cianuro de cobre (740 mg, 8.26 mmol) en DMF (20 mL) se puso a reflujo durante 16 h. Se enfría la mezcla a temperatura ambiente, se agrega etilendiamina y se agita durante 30 min. Se extrae la mezcla con hexano/EtOAc (1:1), se seca la capa orgánica sobre Na_2SO_4, se filtran y se concentran in vacuo. Se purifica el residuo por cromatografía en gel de sílice eluido con hexano/EtOAc (5:1) para dar el intermediario deseado como un sólido blanco (620 mg, 61%). EM (ES-) m/z: 245 $(M-H)^-$.

4-Aminometil-N-ciclohexil-2-fluoro-benzamida: Se disuelve 4-ciano-N-ciclohexil-2-fluoro-benzamida (620 mg, 2.5 mmol) en amoniaco 7N en metanol (150 mL) y se hidrogena a 500 psi (35.15 kg/cm^2) presión en la presencia de níquel Raney® (500 mg) durante 16 h a 60°C. Se filtra la mezcla y se concentra in vacuo. Se purifica por cromatografía SCX para dar el compuesto del título como un sólido blanco (600 mg, 94%). EM (ES-) m/z: 251 $(M-H)^-$.

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Preparación 96

Ciclohexilamida del ácido 5-(Aminometil)-piridina-2-carboxílico



5-(tert-butoxicarbonilamino-metil)-piridina-2-carboxilato de litio: Se disuelve 5-aminometil-2-cloro-piridina (2 g, 14 mmol) y di-tert-butil-dicarbonato (3.37 g, 15.4 mmol) en DCM (30 mL) y se agita a temperatura ambiente durante 2 h. Se concentra la mezcla de reacción y se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (10:1 y 5:1) para dar 5-(tert-butoxicarbonilamino-metil)-2-cloro-piridina como un sólido amarillo (3.6 g, 100%). EM (ES+) m/z: 243 $(M+H)^+$. Se disuelve 5-(tert-butoxicarbonilamino-metil)-2-cloro-piridina (1 g, 4.12 mmol) en una mezcla de etanol (15 mL) y DMF (5 mL), y se agrega carbonato de potasio (427 mg, 3.09 mmol), acetato de paladio (II) (92 mg, 0.4 mmol) y difenilfosfinoferroceno (240 mg, 0.44 mmol). Se presuriza la mezcla a 15 psi (1.0545 kg/cm^2) con gas de monóxido de carbono y se calienta la mezcla de reacción a 90°C durante 16 h. Se filtra la mezcla de reacción, se concentra el filtrado, y se divide el residuo entre agua y hexano/EtOAc

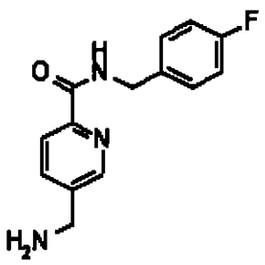
(1:1). Se seca la capa orgánica sobre Na_2SO_4, se filtra, y se concentra in vacuo. Se purifica el residuo por cromatografía en gel de sílice eluido con hexano/EtOAc (3:2) para dar éster de etilo del ácido 5-(tert-butoxicarbonilamino-metil)-piridina-2-carboxílico como un aceite café (920 mg, 80%). EM (ES+) m/z: 281 $(M+H)^+$. Se disuelve éster de etilo del ácido 5-(tert-butoxicarbonilamino-metil)-piridina-2-carboxílico (920 mg, 3.28 mmol) en una mezcla de agua/THF (1:2, 15 mL) y se agrega hidróxido de litio (87 mg, 3.61 mmol). Se agita la mezcla a temperatura ambiente durante 4 h y se concentra hasta un sólido. Se seca el material por destilación azeotropa con tolueno para dar el intermediario deseado como un sólido café (1 g, 100%). EM (ES+) m/z: 253 $(M+H)^+$.

Ciclohexilamida del ácido 5-(Aminometil)-piridina-2-carboxílico: Se usa el Procedimiento general 6-2, al usar ciclohexilamina (1 mL), 5-(tert-butoxicarbonilamino-metil)-piridina-2-carboxilato de litio (1 g, 3.96 mmol) y DIEA (5 mL) como cosolvente, para dar el compuesto del título como un sólido blanco (200 mg, 22%). EM (ES+) m/z: 234 $(M+H)^+$.

Preparación 97

4-fluoro-bencilamida del ácido 5-(Aminometil)-piridina-2-carboxílico

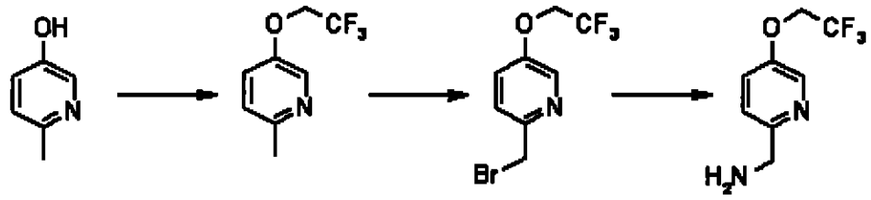
821



Se usa el Procedimiento general 6-2, al usar 4-fluoro-bencilamina (551 mg, 4.4 mmol), 5-(tert-butoxicarbonilamino-metil)-piridina-2-carboxilato de litio (740 mg, 2.93 mmol) y DIEA (2.6 mL) como cosolvente, para dar el compuesto del título como un sólido blanco (200 mg, 26%). EM (ES+) m/z: 260 $(M+H)^+$.

Preparación 98

2-Aminometil-5-(2,2,2-trifluoroetoxi)-piridina



2-Metil-5-(2,2,2-trifluoroetoxi)-piridina: Se agrega 5-hidroxi-2-metil-piridina (3.3 g, 30.6 mmol), carbonato de potasio (17 g, 122.4 mmol) y 2-bromo-1,1,1-trifluoroetano (10 g, 61.2 mmol) a un matraz que contiene DMF (60 mL) y se calienta a 95°C durante 20 h. Se enfría la mezcla, se diluye con 10% de NaCl acuoso (20 mL) y se extrae con hexano/EtOAc 1:1, 100 mL). Se filtra la mezcla bi-fásica a través de

Celite®, se separa y se lava la capa orgánica con NaCl acuoso al 10% (3 x 50 mL) y se concentra in vacuo. Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (9:1 to 1:1) para obtener el intermediario deseado (4.1 g, 70%).

2-Bromometil-5-(2,2,2-trifluoroetoxi)-piridina: Se agrega 2-metil-5-(2,2,2-trifluoroetoxi)-piridina (2.5 g, 13.1 mmol), NBS (2.3 g, 13.1 mmol) y peróxido de benzoílo (50 mg) a un matraz que contiene tetracloruro de carbono (30 mL). Se calienta la mezcla a 80°C en un matraz sellado durante 16 h. Se enfría el matraz, se agrega NBS (1.1 g, 6.5 mmol) y peróxido de benzoílo (100 mg), luego se continua calentando a 80°C durante unas 5 h adicionales. Se enfría la mezcla, se diluye con DCM, luego se lava con bisulfito de sodio saturado (10 mL). Se colecta la capa orgánica y se concentra in vacuo. Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (9:1) para obtener el intermediario deseado (460 mg, 13%).

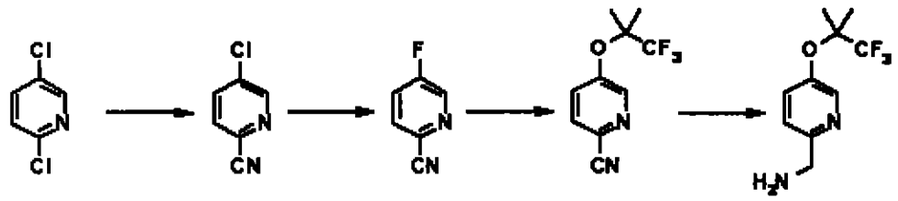
2-Aminometil-5-(2,2,2-trifluoroetoxi)-piridina: Se disuelve azida de sodio (270 mg, 4.0 mmol) en DMF (30 mL). Se enfría la solución a 0°C, luego se agrega 2-bromometil-5-(2,2,2-trifluoroetoxi)-piridina (440 mg, 1.6 mmol) a 0°C. Lentamente se calienta la mezcla desde 0°C hasta 80°C durante 30 min. Se

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enfría la reacción, se diluye con EtOAc (100 mL) y se lava con NaCl acuoso al 10% (3 x 25 mL). Se colecta la capa orgánica y se concentra in vacuo para un volumen de 50 mL. Se transfiere la solución a un recipiente a presión. Se agrega 10% Pd/C (tipo Degussa E101, 50% de agua por peso, 500 mg) y se presuriza el recipiente bajo hidrógeno (10 psi (0.703 kg/cm^2)) durante 1 h con agitación. Se filtra la mezcla a través de Celite® y se lava la torta filtro con metanol caliente seguido por DCM. Se concentra in vacuo, luego se purifica por cromatografía en gel de sílice eluido con DCM/amoniaco 2M en metanol (20:1) para obtener el compuesto del título (180 mg, 54%). EM (ES+) m/z: 207 $(M+H)^+$.

Preparación 99

2-Aminometil-5-(2,2,2-trifluoro-1,1-dimetil-etoxi)-piridina



5-Cloro-piridina-2-carbonitrilo: Se agrega 2,5-dicloropiridina (6.0 g, 40.5 mmol), cianuro de zinc (2.9 g, 24.7 mmol), polvo de zinc (116 mg, 1.8 mmol) y 1,1'-[bis(difenilfosfino)ferroceno]dicloropaladio (II) (20 mg, 0.98 mmol) a un matraz que contiene DMF (40 mL). Se calienta la mezcla a reflujo durante 5 h, luego Se enfría a

temperatura ambiente. Se diluye la mezcla con EtOAc (300 mL) y se lava con NaCl acuoso al 10% (3x75 mL). Se colecta la capa orgánica, se concentra in vacuo y se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (9:1 to 1:1) para obtener el intermediario deseado (2.6 g, 46%).

5-Fluoro-piridina-2-carbonitrilo: Se agrega 5-cloro-piridina-2-carbonitrilo (3.0 g, 21.7 mmol) y fluoruro de potasio (3.9 g, 67.1 mmol) a un matraz que contiene NMP (75 mL). Se calienta la mezcla a reflujo durante 16 h. Se agrega se fluoruro de potasio adicional (1.0 g, 17.2 mmol) y NMP (10 mL), luego se continua calentando a reflujo durante 3 h. Se enfría la mezcla, se diluye con EtOAc, luego se lava con NaCl saturado (3 x 50 mL). Se colecta la capa orgánica, se concentra in vacuo y se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (20:1) para obtener el intermediario deseado (1.5 g, 53%).

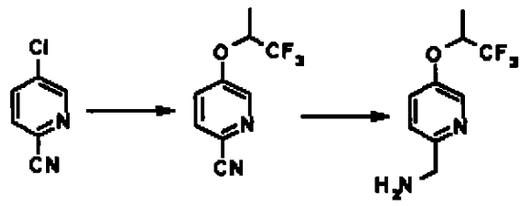
5-(2,2,2-Trifluoro-1,1-dimetil-etoxi)-piridina-2-carbonitrilo: Se agrega 2-trifluorometil-2-propanol (1.1 g, 8.3 mmol) lentamente a una mezcla espesa de hidruro de sodio (202 mg, 60% aceite mineral, se lava con hexano) en HMPA (3 mL) bajo nitrógeno. Se agita la mezcla espesa durante 15 min, luego se agrega 5-fluoro-piridina-2-carbonitrilo (510 mg, 4.2 mmol). Se agita la mezcla espesa durante 16 h a

temperatura ambiente. Se ajusta la mezcla hasta pH 9 con carbonato de sodio luego se extrae con dietil éter (3 x 50 mL). Se colecta la capa orgánica, se seca sobre Na_2SO_4 y se concentra in vacuo. Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (95/5 hasta 80/20) para obtener el intermediario deseado (768 mg, 79%). CG-EM m/z: 230 (M^+).

2-Aminometil-5-(2,2,2-trifluoro-1,1-dimetil-etoxi)-piridina: Se agrega 5-(2,2,2-trifluoro-1,1-dimetil-etoxi)-piridina-2-carbonitrilo (580 mg, 2.5 mmol), 10% Pd/C (tipo Degussa E101, 50% de agua por peso, 400 mg) y ácido trifluoroacético (2 mL) en etanol (20 mL) a un recipiente a presión. Se presuriza el recipiente a 50 psi (3.515 kg/cm^2) con hidrógeno durante 1 h. Se filtra la mezcla a través de Celite® y se lava la torta con etanol caliente seguido por DCM bajo una atmósfera de nitrógeno. Se concentra in vacuo para obtener el producto crudo como la sal del ácido trifluoroacético. Se prepara la base libre con Cromatografía SCX, luego se purifica al usar cromatografía en gel de sílice eluido con DCM/amoniaco 2M en metanol (20:1) para obtener el compuesto del título (261 mg, 45%). EM (ES+) m/z: 235 $(M+H)^+$.

Preparación 100

(±)-2-Aminometil-5-(2,2,2-trifluoro-1-metil-etoxi)-piridina



(±)-5-(2,2,2-Trifluoro-1-metil-etoxi)-piridina-2-carbonitrilo: Se agrega 1,1,1-trifluoro-2-propanol (971 mg, 8.5 mmol) lentamente a una mezcla espesa de hidruro de sodio (205 mg, 60% aceite mineral, se lava con hexano) en HMPA (8 mL) bajo nitrógeno a 0°C. Se permite que la mezcla espesa se entibie a temperatura ambiente y se agita durante 5 min. Se agrega 5-cloro-piridina-2-carbonitrilo (590 mg, 4.2 mmol), luego se calienta la mezcla a 90°C durante 4 h. Se ajusta la mezcla hasta pH 9 con carbonato de sodio luego se extrae con dietil éter (2 x 50 mL). Se secan los extractos orgánicos combinados sobre Na_2SO_4 y se concentra in vacuo. Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (95/5 hasta 80/20) para obtener el intermediario deseado (818 mg, 89%). CG-EM m/z: 216(M^+).

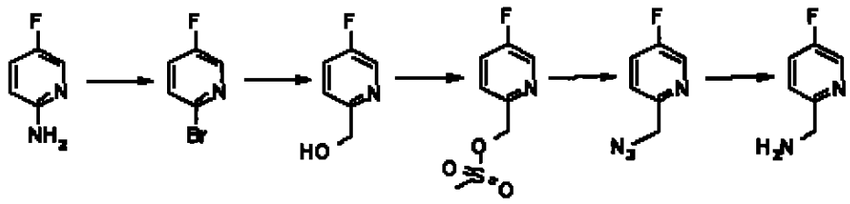
(±)-2-Aminometil-5-(2,2,2-trifluoro-1-metil-etoxi)-piridina: Se agrega (±)-5-(2,2,2-trifluoro-1-metil-etoxi)-piridina-2-carbonitrilo (810 mg, 3.7 mmol), 10% Pd/C (tipo Degussa E101,

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50% de agua por peso, 300 mg), y ácido trifluoroacético (4 mL) en metanol (50 mL) a un recipiente a presión. Se presuriza el recipiente a 40 psi (2.812 kg/cm^2) con hidrógeno durante 0.25 h. Se filtra la mezcla a través de Celite® y se lava la torta con etanol caliente seguido por DCM bajo una atmósfera de nitrógeno. Se concentra in vacuo para obtener el producto crudo como una sal del ácido trifluoroacético. Se prepara la base libre con cromatografía de ión SCX, luego se purifica por cromatografía en gel de sílice eluido con DCM/amoniaco 2M en metanol (20:1) para obtener el compuesto del título (676 mg, 82%). CG-EM m/z: 220 (M^+).

Preparación 101

2-Aminometil-5-fluoro-piridina



2-Bromo-5-fluoro-piridina: Se enfría ácido bromhídrico 48% (44 mL, 4.4 equiv.) en un baño de hielo/acetona a -5°C, luego se agrega 2-amino-5-fluoropiridina (10.0 g, 89.2 mmol, 1.0 equiv.) en porciones durante 10 min y se mantienete la temperatura debajo de 5°C a lo largo de la adición. Se agrega bromo (14 mL, 3 equiv.) a 0°C durante 2 h y se mantiene la

temperatura a 0°C a lo largo de la adición. Se agita la mezcla durante 30 min, luego se agrega una solución de nitrito de sodio (15.4 g) en agua (30 mL) por medio del embudo de adición durante 2 h y se mantiente la temperatura debajo de 0°C a lo largo de la adición. Se agita la mezcla durante 30 min., luego se agrega una solución de NaOH (34 g) en agua (34 mL) durante 1 h y se mantiene la temperatura debajo de 10°C. Se agita la mezcla durante 3 min. se extrae con dietil éter (5 x 250 mL), se secan los extractos orgánicos combinados sobre Na_2SO_4 y se concentra in vacuo para dar el intermediario deseado (12.1 g, 77%).

(5-Fluoro-piridin-2-il)-metanol: A -78°C bajo nitrógeno, se agrega n-butilitio (2.5 M en hexano, 16.4 mL, 40.9 mmol) por medio de una jeringa a una solución de 2-bromo-5-fluoro-piridina (6.0 g, 34.1 mmol) en tolueno (220 mL), mientras se mantiente la temperatura de reacción debajo de -60°C. Se agita la mezcla a -78°C y luego se agrega DMF (3.4 mL, 44.3 mmol) y se agita durante 1 h a esta temperatura. Se calienta a -10°C y se apaga con metanol (10 mL). Se concentra la mezcla para la mitad del volumen in vacuo. Se diluye con metanol (150 mL), Se enfría la mezcla a -78°C y se agrega borohidruro de sodio (3.2 g, 85.2 mmol) en porciones durante 5 min. Se calienta la mezcla a temperatura ambiente y se

agita durante 2 h. Se apaga con agua (10 mL) y se remueve el solvente orgánico in vacuo para obtener una mezcla de aceite/agua. Se extrae con dietil éter (3 x 100 mL), se secan los extractos orgánicos combinados, se lavan con salmuera, se secan y se concentran in vacuo para obtener el intermediario deseado como un aceite (3.9 g, 91%).

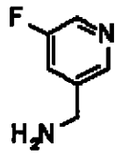
Éster de (5-fluoro-piridin-2-il)metilo del ácido metansulfónico: Se agrega cloruro de metansulfonilo (1.8 mL, 23.5 mmol) a una solución de (5-fluoro-piridin-2-il)-metanol (2.5 g, 19.7 mmol) y trietilamina (8.2 mL, 59.0 mmol) en DCM (150 mL) a 0°C bajo nitrógeno. Se agita la mezcla durante 30 min y se concentra in vacuo. Se diluye con agua (20 mL) y se extrae la mezcla con EtOAc (3 x 50 mL). Se combinan los extractos orgánicos y se concentra in vacuo. Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc para obtener el intermediario deseado (2.2 g, 54%).

2-Aminometil-5-fluoro-piridina: Se disuelve éster de (5-fluoro-piridin-2-il)-metilo del ácido metansulfónico (1.5 g, 7.3 mmol) en DMF (5mL) y se agrega azida de sodio (950 mg, 14.6 mmol). Se agita la mezcla durante 30 min, luego se diluye con hexano/EtOAc (1:1, 50 mL). Se lava la mezcla con NaCl acuoso al 10% (3 x 10 mL). Se secan los extractos orgánicos combinados sobre Na_2SO_4 y remueve la mitad del

solvente in vacuo. Se agrega EtOAc (20 mL) y una suspensión de 10% Pd/C (200 mg) en EtOAc (2 mL). Se agita la mezcla durante 1 h a temperatura ambiente en un recipiente presurizado bajo 50 psi (3.515 kg/cm^2) de hidrógeno. Se filtra la mezcla espesa a través de Celite® y se concentra in vacuo para obtener 2-aminometil-5-fluoro-piridina (613 mg, 60% de rendimiento, 80% de pureza por GC/MS). CG-EM m/z: 126 (M^+).

Preparación 102

3-Aminometil-5-fluoro-piridina

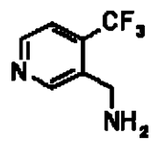


En una botella Parr se agrega 2,6-dicloro-3-ciano-5-fluoropiridina (20 g, 0.105 mol), etanol (336 mL), trietilamina (24 mL), y 5% Pd/C (4 g). Se coloca en un aparato de agitación Parr bajo 60 psi (4.218 kg/cm^2) durante 1 h a temperatura ambiente. Se filtra la mezcla de reacción y se burbujea gas de amoniaco en un filtro durante 10 min. Se agrega níquel Raney® (5.2 g) y se coloca en un aparato de agitación Parr bajo 500 psi (35.15 kg/cm^2) de hidrógeno durante 18 h a 60-70°C. Se filtra la mezcla de reacción y se concentra in vacuo. Se disuelve en metanol y se agrega cloruro de hidrógeno 1N en éter hasta que forma un

precipitado. Se enfría en un baño de hielo, se filtra completamente el precipitado, se lava el sólido varias veces con éter, y se seca para dar el compuesto del título como la sal de clorohidrato (12 g, 70%). EM (ES+) m/z: 127 $(M+H)^+$. Se disuelve la sal de clorohidrato en agua, se agrega NaOH 0.1 N acuoso para ajustar hasta pH 10, se extrae con DCM, se seca la capa orgánica sobre Na_2SO_4, se filtra y se concentra para dar el compuesto del título.

Preparación 103

3-Aminometil-4-trifluorometil-piridina



Se agrega 4-trifluorometil-nicotinonitrilo (1.0 g, 5.8 mmol) y níquel activado Raney® húmedo con etanol (0.2 g) a un recipiente de presión Parr. Inmediatamente se agrega, a temperatura ambiente, 2B-etanol (25 mL) previamente saturado con gas de amoniaco y se sella el recipiente. Se purga el recipiente de reacción con nitrógeno, se presuriza la mezcla de reacción con hidrógeno (400 KPa), se sella el recipiente, se agita la reacción y se calienta a 40°C. Se continua la reacción durante 20 h luego a su vez completamente se calienta y se permite la mezcla de reacción para enfriarse a temperatura ambiente. Se ventea el exceso de hidrógeno del

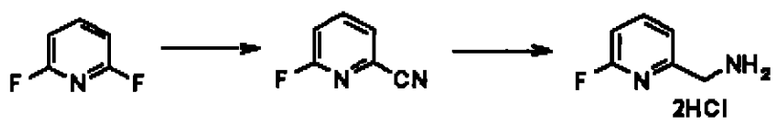
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calienta la mezcla a reflujo durante la noche. Se enfría a temperatura ambiente y se concentra in vacuo. Se disuelve el residuo en EtOAc y se lava con $NaHCO_3$ acuoso saturado. Se seca la capa orgánica sobre Na_2SO_4, se filtra, y se concentra in vacuo. Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (1:0 y 17:3) para dar el intermediario deseado como un sólido (746 mg, 70%). CG-EM m/z: 122 (M^+).

Diclorohidrato de 2-Aminometil-3-fluoropiridina: Se disuelve 2-ciano-3-fluoropiridina (300 mg, 2.457 mmol) en etanol absoluto (12 mL). Se agrega 10% Pd/C (93 mg) y HCl concentrado (0.614 mL, 7.37 mmol). Se hidrogena a 40 psi (28.12 kg/cm^2) durante la noche. Se filtra a través de Celite® y se concentra in vacuo para dar el compuesto del título como un sólido (440 mg, 90%). EM (ES+) m/z: 127 $(M+H)^+$.

Preparación 105

Diclorohidrato de 2-aminometil-6-fluoropiridina

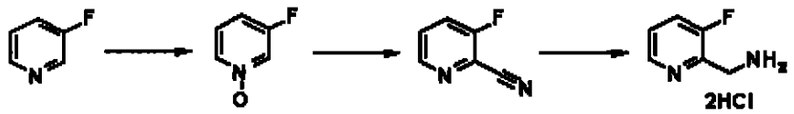


2-Ciano-6-fluoropiridina: Se disuelve 2,6-difluoropiridina (12 g, 104.2 mmol) en DMSO anhidro (5 mL). Se agrega una solución de cianuro de sodio (1.3 g, 26.53 mmol) en DMSO (60

recipiente y se purga el recipiente con nitrógeno. Se filtra la mezcla de reacción para remover el níquel Raney®, se lava con etanol y se concentra in vacuo. Se purifica por cromatografía SCX para dar el compuesto del título (560 mg, 55%). EM (ES+) m/z: 177 $(M+H)^+$.

Preparación 104

Diclorohidrato de 2-aminometil-6-fluoropiridina



3-Fluoropiridina-N-óxido: Se disuelve 3-fluoropiridina (2.5 g, 25.749 mmol) en DCM anhidro (75 mL). Se agrega m-CPBA (70% de suspensión, 12.696 g, 51.499 mmol) y se agita a temperatura ambiente durante la noche. Se lava la mezcla de reacción con $NaHCO_3$ acuoso saturado, se seca la fase orgánica sobre Na_2SO_4, se filtra, y se concentra in vacuo. Se purifica por cromatografía en gel de sílice eluido con DCM y DCM/metanol (97:3) para obtener el intermediario deseado como un sólido (1.413 g, 49%). EM (ES+) m/z: 115 $(M+H)^+$.

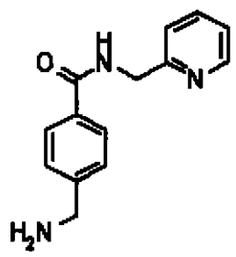
2-Ciano-3-fluoropiridina: Se disuelve 3-fluoropiridina-N-óxido (1.0 g, 8.687 mmol) en acetonitrilo anhidro (100 mL). Se agrega trietilamina (1.319 g, 1.82 mL, 13.031 mmol), trimetilsililcianuro (3.447 g, 4.63 mL, 34.749 mmol) y se

mL) durante 12 h al usar una bomba de jeringa. Se calienta la mezcla a 100°C durante la noche. Se enfría a temperatura ambiente, se diluye con EtOAc (500 mL), y se lava con salmuera. Se seca la fase orgánica sobre Na_2SO_4, se filtra, y se concentra in vacuo. Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (1:0 y 4:1) para dar el intermediario deseado como un sólido (723 mg, 22%). CG-EM m/z: 122 (M^+).

Diclorohidrato de 2-Aminometil-6-fluoropiridina: Se disuelve 2-ciano-6-fluoropiridina (300 mg, 2.46 mmol) en etanol absoluto (12 mL). Se agrega 10% Pd/C (93 mg) y HCl concentrado (0.614 mL, 7.37 mmol). Se hidrogena a 40 psi (28.12 kg/cm^2) durante la noche. Se filtra a través de Celite® y se concentra para dar el compuesto del título como un sólido (356 mg, 73%). EM (ES+) m/z: 127 $(M+H)^+$.

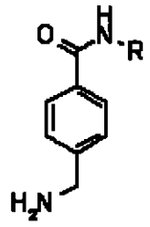
Preparación 106

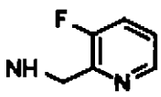
4-Aminometil-N-(piridin-2-il-metil)-benzamida

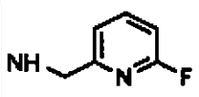
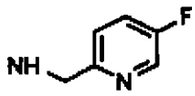
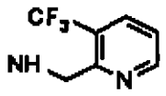
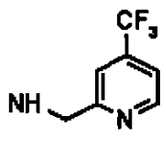
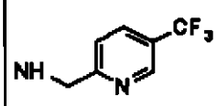


Se usa el Procedimiento general 6-2, al usar 2-(aminometil)piridina (181 mg, 0.172 mL, 1.67 mmol) y ácido 4-(tert-butoxicarbonilamino-metil)-benzoico (420 mg, 1.67 mmol) para dar el compuesto del título como un sólido (427 mg, 100 %). EM (ES+) m/z: 242 $(M+H)^+$.

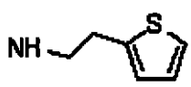
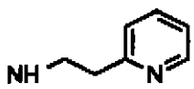
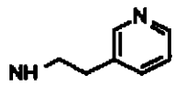
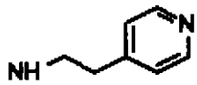
Los compuestos de las preparaciones 107-117 pueden prepararse esencialmente como se describen en la Preparación 106 al usar ácido 4-(tert-butoxicarbonilamino-metil)-benzoico y la amina apropiada. Los datos de rendimiento general y EM (ES+) se muestran en la Tabla a continuación.



Prep.	NHR	Compuesto	Rendimiento (%)	EM (ES+) o CG-EM
107		4-Aminometil-N-(tiofen-2-il-metil)-benzamida	100	247 $(M+H)^+$
108		4-Aminometil-N-(3-fluoro-piridin-2-ilmetil)-benzamida	58	259 $(M)^+$

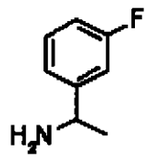
Prep.	NHR	Compuesto	Rendimiento (%)	EM (ES+) o CG-EM
109		4-Aminometil-N-(6-fluoro-piridin-2-ilmetil)-benzamida	98	259 $(M)^+$
110		4-Aminometil-N-(5-fluoro-piridin-2-ilmetil)-benzamida	67	259 $(M)^+$
111		4-Aminometil-N-(3-trifluorometil-piridin-2-ilmetil)-benzamida	62	310 (M+H) ±
112		4-Aminometil-N-(4-trifluorometil-piridin-2-ilmetil)-benzamida	76	309 $(M)^+$
113		4-Aminometil-N-(5-trifluorometil-piridin-2-ilmetil)-benzamida	65	310 (M+H) ±

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Prep.	NHR	Compuesto	Rendimiento (%)	EM (ES+) o CG-EM
114		4-Aminometil-N-(2-tiofen-2-il-etil)-benzamida	100	261 (M+H)+
115		4-Aminometil-N-(2-piridin-2-il-etil)-benzamida	81	256 (M+H)±
116		4-Aminometil-N-(2-piridin-3-il-etil)-benzamida	97	256 (M+H)±
117		4-Aminometil-N-(2-piridin-4-il-etil)-benzamida	96	256 (M+H)±

Preparación 118

(±)-1-(3-Fluorofenil)etilamina

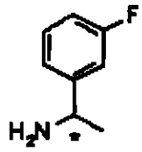


Se agrega cianoborohidruro de sodio (452 mg, 7.2 mmol) a una solución de 3-fluoroacetofenona (500 mg, 3.6 mmol) y acetato de amonio (2.8 g, 36 mmol) en metanol (11 mL). Se

agita la mezcla durante 96 h a temperatura ambiente bajo una atmósfera de nitrógeno. Se ajusta hasta pH 2 con cloruro de hidrógeno 2M en dietil éter. Se concentra la mezcla espesa in vacuo, se diluye el residuo con DCM y se lava con NaOH acuoso 5N seguido por $NaHCO_3$ acuoso saturado. Se seca la capa orgánica, se concentra in vacuo para la mitad del volumen, y se carga la solución en una columna SCX (una columna se prelava con metanol seguido por DCM, luego se eluye con amoniaco 2M en metanol). Se concentran las fracciones para la mitad del volumen para remover el amoniaco, se agrega exceso de cloruro de hidrógeno 2M en dietil éter y se concentra para obtener la sal de clorohidrato (mezcla 70:30 del compuesto del título y dímero). Se purifica por cromatografía en gel de sílice eluido con DCM/amoniaco 2M en metanol (20:1) para obtener el compuesto del título (323 mg, 51%). EM (ES+) m/z: 140 $(M+H)^+$.

Preparación 119

1-(3-Fluorofenil)etilamina, isómero 2



Se prepara el matraz equipado con condensador, agitador mecánico y embudo de adición. Se agrega 3-fluoroacetofenona (25 g, 0.18 mol) y ácido fórmico (4.2 g, 0.09 mol) por medio

del embudo de adición a un matraz que contiene formamida (32.6 g, 0.72 mol) a 140°C durante 15 min, y luego se calienta la mezcla a 160°C. Se agrega ácido formico sucesivamente (4.2 g, 0.5 equiv.) por medio de un embudo de adición al matraz cada hora durante 4 h mientras se mantiene la temperatura de reacción a 160°C. Se enfría la mezcla de reacción, se extrae con tolueno (3 x 100 mL), y se concentra la capa orgánica in vacuo. Se agrega HCl acuoso (37%, 40 mL) al residuo y se calienta hasta reflujo durante 2 h. Se enfría a temperatura ambiente y se lava la mezcla acuosa con tolueno (2 x 100 mL), luego se basifica la mezcla acuosa con NaOH acuoso 5N (120 mL). Se extrae la mezcla básica con EtOAc (3 x 100 mL), se secan los extractos orgánicos combinados sobre Na_2SO_4 y se filtra. Se acidifica el filtrado con cloruro de hidrógeno 2M en dietil éter a pH 2 y se concentra in vacuo hasta un sólido. Se suspendió el sólido en dietil éter, se filtra y se lava con dietil éter. Se seca el sólido en un horno al vacío a 50°C para obtener clorohidrato de (±)-1-(3-fluorofenil)etilamina (21.5 g, 68%). EM (ES+) m/z: 140 $(M+H)^+$.

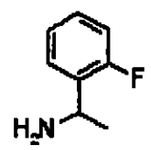
Se disuelve clorohidrato de (±)-1-(3-fluorofenil)etilamina (42.5 g, 0.24 mol) en THF (520 mL) y $NaHCO_3$ acuoso saturado (430 mL). Se agrega di-tert-butil-dicarbonato (69 g, 0.31 mol) y se agita durante 16 h a

temperatura ambiente. Se separa la capa orgánica, se diluye con EtOAc (300 mL) y se lava con NaOH acuoso 2N (1 x 400 mL) y agua (2 x 200 mL). Se concentra la capa orgánica in vacuo. Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (9:1) para obtener éster de tert-butilo del ácido (±)-N-[1-(3-fluorofenil)etil]-carbámico (56 g, 97%). CG-EM m/z: 183 [$(M-C_4H_9)^+$].

Se separa la mezcla racémica de éster de tert-butilo del ácido (±)-N-[1-(3-fluorofenil)etil]-carbámico por una cromatografía quieral de fase normal (Chiralcel OD 8 x 34 cm, se eluye con 95:5, heptano/isopropanol). Al usar el Procedimiento general 1-4, que desprotege al isómero deseado [20.7 g, >95% ee (Chiralcel OD, 4.6 x 250 mm, se eluye: 95:5 heptano/isopropanol con 0.2% DMEA, 1.0 mL/min)] para obtener el compuesto del título (9.4 g, 78%). EM (ES+) m/z: 140 $(M+H)^+$.

Preparación 120

(±)-1-(2-Fluorofenil)etilamina

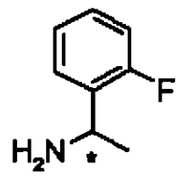


Se agrega cianoborohidruro de sodio (1.8 g, 29 mmol) a una solución de 2-fluoro-acetofenona (2.0 g, 14.5 mmol) y acetato de amonio (11.2 g, 145 mmol) en metanol (45 mL). Se

agita la mezcla durante 20 h a temperatura ambiente bajo una atmósfera de nitrógeno. Se ajusta la mezcla a pH 1 con cloruro de hidrógeno 2M en dietil éter. Se concentra la mezcla espesa in vacuo, se diluye el residuo con DCM y se lava con NaOH acuoso 5N. Se seca la capa orgánica, se concentra cuidadosamente, como la amina es volátil, bajo presión reducida a una tercera parte del volumen, y se carga el material en una columna SCX (columna pre-lavada con metanol, seguido por DCM, se eluye con amoniaco 2M en metanol). Se concentra la fracción para la mitad del volumen para remover el amoniaco, luego se agrega exceso cloruro de hidrógeno 2M en dietil éter y se concentra para obtener la sal de clorohidrato. Se purifica por cromatografía en gel de sílice eluido con DCM/amoniaco 2M en metanol (20:1) para obtener el compuesto del título (280 mg, 13%). EM (ES+) m/z: 140 $(M+H)^+$.

Preparación 121

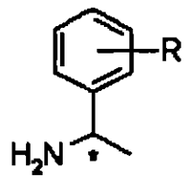
1-(2-Fluorofenil)etilamina, Isómero 1



Se usa un método similar al Procedimiento general 6-3, al usar 2-fluoroacetofenona (1.4 g, 9.9 mmol) y (R)-(+)-2-metil-2-propanosulfinamida (1.0 g, 8.2 mmol). Se purifica por

cromatografía en gel de sílice eluido con hexano/EtOAc/amoniaco 2M en metanol (90:9:1 hasta 50:45:5). Se agrega cloruro de hidrógeno 4M en dioxano para obtener el compuesto del título como el clorohidrato (600 mg, 35%). EM (ES+) m/z: 140 $(M+H)^+$. Se disuelve el clorohidrato en una solución acuosa de carbonato de cesio (1.5 equiv.) y se extrae con tolueno para obtener la base libre.

Los compuestos de las preparaciones 122-141 pueden prepararse esencialmente como se describen en la Preparación 121 al usar (R)-(+)-2-metil-2-propanosulfinamida o (S)-(-)-2-metil-2-propansulfinamida y la acetofenona adecuada. Datos de rendimiento general y espectro de masas se muestran en la Tabla a continuación.



Prep.	R	Compuesto	Rendimiento (%)	EM (ES+) o CG-EM
122	3-CN	1-(3-Cianofenil)etilamina, Isómero 1	37	130 $(M+H-NH_3)^+$
123	3-CN	1-(3-Cianofenil)etilamina, Isómero 2	49	130 $(M+H-NH_3)^+$

Prep.	R	Compuesto	Rendimiento (%)	EM (ES+) o CG-EM
124	4-CN	1-(4-Cianofenil)etilamina, Isómero 1	49	130 $(M+H-NH_3)^+$
125	4-CN	1-(4-Cianofenil)etilamina, Isómero 2	49	130 $(M+H-NH_3)^+$
126	2-Cl	1-(2-Clorofenil)etilamina, Isómero 1	25	156 $(M+H)^+$
127	3-Cl	1-(3-Clorofenil)etilamina, Isómero 1	68	156 $(M+H)^+$
128	3-CF_3	1-(3-Trifluorometilfenil)-etilamina, Isómero 1	40	190 $(M+H)^+$
129	4-CF_3	1-(4-Trifluorometilfenil)-etilamina, Isómero 2	70	190 $(M+H)^+$

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Prep.	R	Compuesto	Rendimiento (%)	EM (ES+) o CG-EM
130	3-Cl,4-F	1-(3-Cloro-4-fluorofenil)-etilamina, Isómero 1	66	174 $(M+H)^+$
131	3-Cl-4-F	1-(3-Cloro-4-fluorofenil)-etilamina, Isómero 2	68	174 $(M+H)^+$
132	2,3-diF	1-(2,3-Difluorofenil)-etilamina, Isómero 1	20	141 $(M+H-NH_3)^+$
133	2,3-diF	1-(2,3-Difluorofenil)-etilamina, Isómero 2	45	141 $(M+H-NH_3)^+$
134	2,4-diF	1-(2,4-Difluorofenil)-etilamina, Isómero 1	58	158 $(M+H)^+$

Prep.	R	Compuesto	Rendimiento (%)	EM (ES+) o CG-EM
135	2,4-diF	1-(2,4-Difluorofenil)-etilamina, Isómero_2	49	158 $(M+H)^+$
136	3,5-diF	1-(3,5-Difluorofenil)-etilamina, Isómero_1	26	158 $(M+H)^+$
137	3,5-diF	1-(3,5-Difluorofenil)-etilamina, Isómero_2	83	158 $(M+H)^+$
138	3,4-diF	1-(3,4-Difluorofenil)-etilamina, Isómero_1	67	158 $(M+H)^+$
139	3,4-diF	1-(3,4-Difluorofenil)-etilamina, Isómero_2	77	158 $(M+H)^+$

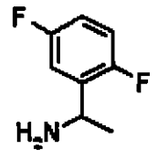
B46

Prep.	R	Compuesto	Rendimiento (%)	EM (ES+) o CG-EM
140	3,4,5-triF	1-(3,4,5-Trifluorofenil)-etilamina, Isómero 2	20	176 $(M+H)^+$
141	3,5-diCF_3	1-(3,5-bis-trifluorometilfenil)-etilamina, Isómero 2	49	258 $(M+H)^+$
142	2-OCF_3	1-(2-Trifluorometoxifenil)-etilamina, Isómero 2	47	ND
143	2-Me	1-(2-Metil)-etilamina, Isómero 1	13	136 (M^+)

ND = No se determina

Preparación 144

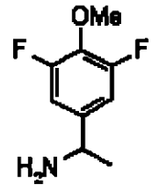
(±)-1-(2,5-Difluorofenil)etilamina



Se hace una mezcla espesa de 2',5'-difluoroacetofenona (0.9 g, 5.76 mmol), acetato de amonio (4.44 g, 57.5 mmol) y cianoborohidruro de sodio (755 mg, 12 mmol) en metanol anhidro (25 mL) y se agita durante 18 h a temperatura ambiente. Se acidifica con HCl acuoso 5N (5 mL), se diluye, se extrae con éter etílico (3 x 150 mL), se basifica la capa acuosa con NaOH acuoso 5N, se extrae con DCM (3 x 75 mL), se lava la capa orgánica con salmuera, se seca sobre $MgSO_4$, se filtran y se concentran in vacuo. Se purifica por cromatografía SCX para dar una mezcla de (±)-1-(2,5-difluorofenil)etilamina y bis-[1-(±)-2,5-difluorofenil)etil]-amina (total 400 mg, peso crudo). EM (ES+) m/z: 158 $(M+H)^+$ y m/z: 298 $(M+H)^+$.

Preparación 145

(±)-1-(3,5-Difluoro-4-metoxifenil)etilamina

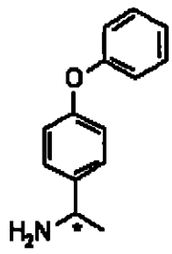


Se hace la mezcla espesa de 3',5'-difluoro-4'-metoxiacetofenona (1.0 g, 5.0 mmol), acetato de amonio (4.14 g, 50 mmol) y cianoborohidruro de sodio (630 mg, 20 mmol) en

metanol anhidro (35 mL) y se agita durante 18 h a temperatura ambiente. Se acidifica con HCl acuoso 1N (5 mL), se diluye, se extrae con éter etílico (3 x 150 mL), se basifica acuoso con NaOH acuoso 1N, se extrae con DCM (3 x 50 mL), se lavan los extractos orgánicos con salmuera, se secan sobre $MgSO_4$, se filtran y se concentran in vacuo. Se purifica por cromatografía SCX para dar el compuesto del título crudo como un aceite amarillo (380 mg).

Preparaciones 146 y 147

1-(4-Fenoxifenil)-etilamina, Isómero 1 y Isómero 2

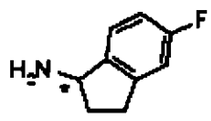


Se mezcla 4-fenoxiacetofenona (5.3 g, 25 mmol), acetato de amonio (14.5 g, 187.5 mmol) y cianoborohidruro de sodio (3.2 g, 50 mmol) en metanol anhidro (200 mL). Se agita durante 18 h a temperatura ambiente. Se acidifica con HCl acuoso 1N (10 mL), se diluye, se extrae con éter etílico (3 x 150 mL), se seca sobre $MgSO_4$, se filtran y se concentran in vacuo. Se purifica por cromatografía en gel de sílice eluido secuencialmente con hexano/EtOAc (4:1, 1:1 y 0:1) y EtOAc/metanol (1:1) para dar (±)-1-(4-fenoxifenil)-etilamina (1.6 g, 30%). Se disuelve el racemato (1.1 g, 5.2 mmol) en DCM (100 mL), se agrega

trietilamina (1.6mL, 11.4 mmol) seguido por di-tert-butil-dicarbonato (1.7 g, 7.8 mmol). Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (9:1) para dar éster de tert-butilo del ácido (±)-α-metil-(4'-fenoxi)-bencilamino]carbámico como un sólido completamente blanco (1.3 mg, 81%). Se separa por medio de cromatografía quiral (heptano/isopropanol/DMEA 95:5:0.2, 4.6 x 250 mm Chiralpak AD, 1 mL/min, UV detector a 260 nm) para dar éster de tert-butilo del ácido [α-metil-(4'-fenoxi)bencilamino]carbámico, isómero 1 (315 mg, quiral CLAR: t_R = 7.35 min; 99.1% ee) y éster de tert-butilo del ácido [α-metil-(4'-fenoxi)bencil-aminocarbámico, isómero 2 (400 mg, quiral CLAR: t_R = 8.7 min; 97.2% ee). Se disuelve éster de tert-butilo del ácido [α-metil-(4'-fenoxi)bencilamino]carbámico isómero 1 o isómero 2 en DCM/ácido trifluoroacético (1:1, 20 mL) para dar, después el solvente de evaporación y cromatografía sobre columna SCX, 1-(4-fenoxifenil)-etilamina, isómero 1 (Preparación 146) y 1-(4-fenoxifenil)-etilamina, isómero 2 (Preparación 147). EM (ES+) m/z: 214 $(M+H)^+$.

Preparación 148

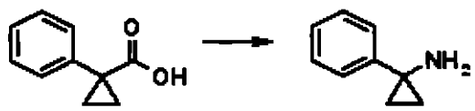
(5-Fluoro-indan-1-il)amina, Isómero 1



Se usa un método similar al Procedimiento general 6-3 para reaccionar 5-fluoro-indan-1-ona (1.5 g, 9.9 mmol) y (R)-(+)-2-metil-2-propanosulfinamida (1.0 g, 8.3 mmol). Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (5:2). Se agrega cloruro de hidrógeno 4M en dioxano para obtener el compuesto del título como el clorohidrato (254 mg, 16%). EM (ES+) m/z: 152 $(M+H)^+$. Se disuelve el clorohidrato en una solución acuosa de carbonato de cesio (1.5 equiv.) y se extrae con tolueno para obtener la base libre.

Preparación 149

1-Fenil-ciclopropilamina

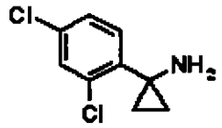


Se disuelve ácido 1-fenil-ciclopropancarboxílico (2.5 g, 15.4 mmol) en una mezcla de ácido sulfúrico (12.5 mL) y DCM (25 mL). Se agrega azida de sodio (2.3 g, 35.4 mmol) por porciones pequeñas a temperatura ambiente. Se calienta la mezcla de reacción a 50°C durante 8 h, se enfría a 0°C y lentamente se agrega NaOH acuoso 2M hasta pH 11. Se extrae la mezcla de reacción con DCM (3 x 100 mL), se combinan los extractos orgánicos y se secan sobre Na_2SO_4 anhidro. Se evapora el solvente y se purifica por cromatografía en gel de sílice eluido con DCM y DCM/amoniaco 2M en metanol (9:1) para

obtener el compuesto del título como un aceite café (1.1 g, 54%). EM (ES+) m/z: 134 $(M+H)^+$.

Preparación 150

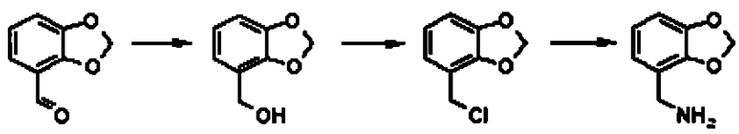
1-(2,4-Diclorofenil)-ciclopropilamina



Se usa un método similar a la Preparación 149, al usar ácido 1-(2,4-diclorofenil)-ciclopropancarboxílico (3.5 g, 15.4 mmol), para obtener el compuesto del título como un aceite amarillo (1.0 g, 32%). EM (ES+) m/z: 203 $(M+H)^+$.

Preparación 151

4-Metilamino-benzo[1,3]dioxol



Benzo[1,3]dioxol-4-il-metanol: Se disuelve benzo[1,3]dioxol-4-carbaldehído (2.0 g, 13.3 mmol) en THF anhidro (30 mL) y se trata con borohidruro de sodio (0.5 g, 13.3 mmol) a 0°C. Se agita la mezcla de reacción durante 30 min a temperatura ambiente y se apaga con agua (30 mL). Se extrae la mezcla de reacción con DCM (3 x 10 mL), se combinan los extractos orgánicos y se secan sobre Na_2SO_4 amhidro. Se elimina el

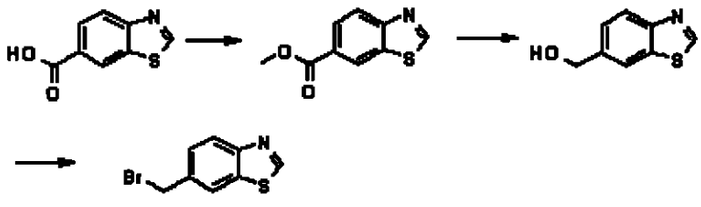
solvente para obtener el intermediario deseado como un aceite incoloro (1.9 g, 94%).

4-Clorometil-benzo[1,3]dioxol: Se disuelve benzo[1,3]dioxol-4-il-metanol (1.9 g, 12.5 mmol) en cloruro de tionilo (3 mL, 41.1 mmol) y se pone a reflujo la mezcla de reacción durante 1 h. Se concentra in vacuo para obtener el intermediario deseado como un aceite amarillo (1.9 g, 91%) que se usa sin purificación adicional. CG-EM m/z: 170 (M^+).

4-Metilamino-benzo[1,3]dioxol: Se disuelve 4-clorometil-benzo[1,3]dioxol (1.9 g, 11.1 mmol) en metanol (5 mL), se enfría la solución a 0°C y se satura con amoniaco anhidro durante 15 min. Se mantiene la mezcla de reacción a 0°C durante 18 h. Se evapora el solvente y se purifica por cromatografía SCX para obtener el compuesto del título como un aceite amarillo (0.6 g, 36%). CG-EM m/z: 151 (M^+).

Preparación 152

6-Bromometil-benzotiazol



Éster de metilo del ácido benzotiazol-6-carboxílico: Se agrega 1-metil-3-nitro-1-nitrosoguanidina (5.0 g, 33.9 mmol) a una mezcla de dietil éter (20 mL) y NaOH acuoso 1N (20 mL) a temperatura ambiente. Se separa la capa orgánica y se agrega lentamente a una solución de ácido benzotiazol-6-carboxílico (1.0 g, 5.58 mmol) en THF (50 mL) a 0°C. Se evapora el solvente para obtener el intermediario deseado como un sólido amarillo (1.1 g, 100%). EM (ES+) m/z: 194 $(M+H)^+$.

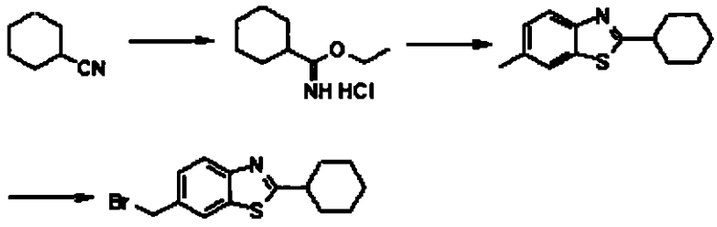
Benzotiazol-6-il-metanol: Se agrega lentamente una solución de éster de metilo del ácido benzotiazol-6-carboxílico (0.5 g, 2.59 mmol) en THF anhidro (10 mL) a una suspensión de hidruro de aluminio de litio (0.1 g, 2.85 mmol) en THF anhidro (20 mL) a -10°C y se agita durante 20 min a -10°C. Se trata la mezcla de reacción con NaOH acuoso 2N hasta que el precipitado de partida granular se forma y se filtra a través de una almohadilla de Celite®. Se evapora el solvente y se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (1:0, 9:1, 4:1, 7:3, 3:2 y 1:1) para obtener el intermediario deseado como un aceite amarillo (0.4 g, 99%). EM (ES+) m/z: 166 $(M+H)^+$.

6-Bromometil-benzotiazol: Se disuelve benzotiazol-6-il-metanol (0.4 g, 2.55 mmol) en dietil éter (10 mL) y se agrega lentamente una solución de tribromuro de fosforo (0.7 g, 2.55

mmol) en dietil éter (5 mL). Se agita la mezcla de reacción durante 2 h a temperatura ambiente, se lava con salmuera, se seca la fase orgánica sobre Na_2SO_4 anhidro, se evapora el solvente y se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (1:0, 9:1 y 4:1) para obtener el compuesto del título como un sólido blanco (0.5 g, 86%). EM (ES+) m/z: 229 $(M+H)^+$.

Preparación 153

6-Bromometil-2-ciclohexil-benzotiazol



éster de etilo del ácido ciclohexanocarboximídico, clorohidrato: Se combina ciclohexanocarbonitrilo (1.0 g, 9.20 mmol), etanol (0.4 g, 9.20 mmol) y cloruro de hidrógeno 4N en dioxano (8 mL) y se agita la mezcla de reacción durante 17 h a temperatura ambiente. Se evapora el solvente y se tritura el residuo con dietil éter para obtener el intermediario deseado como un sólido blanco (1.4 g, 80%).

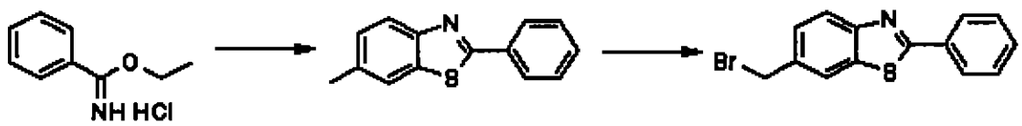
2-Ciclohexil-6-metil-benzotiazol: Se combina sal de zinc 2-amino-5-metil-bencenotiol (1.0 g, 2.91 mmol, se prepara como en Synth. Commun. 1980, 10, 167-173), clorohidrato de éster

de etilo del ácido ciclohexanocarboximídico (1.1 g, 5.82 mmol), metanol (20 mL) y se puso a reflujo la mezcla de reacción durante 17 h. Se evapora el solvente y se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (1:0 y 9:1) para obtener el intermediario deseado como un sólido blanco (1.15 g, 85%).

6-Bromometil-2-ciclohexil-benzotiazol: Se combina 2-bencil-6-metil-benzotiazol (0.6 g, 2.42 mmol), NBS (0.5 g, 2.54 mmol), AIBN (40 mg, 0.24 mmol), tetracloruro de carbono (10 mL) y se puso a reflujo durante 3 h. Se enfría la mezcla de reacción a temperatura ambiente, se diluye con cloroformo y se lava con agua. Se secan los extractos orgánicos sobre Na_2SO_4 anhidro, se concentra in vacuo y se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (1:0 y 9:1) para obtener el compuesto del título como un sólido blanco (0.4 g, 53%). EM (ES+) m/z: 311 $(M+H)^+$.

Preparación 154

6-Bromometil-2-fenil-benzotiazol



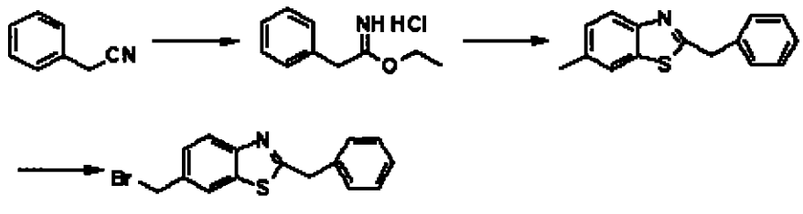
6-Metil-2-fenil-benzotiazol: Se combina sal de zinc de 2-amino-5-metil-bencenotiol (1.0 g, 2.91 mmol, se prepara como

se describe en Synth. Commun. 1980, 10, 167-173), clorohidrato de benzimidato de etilo (1.1 g, 5.82 mmol), metanol (20 mL), y se puso a reflujo la mezcla de reacción durante 17 h. Se evapora el solvente y se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (1:0 y 9:1) para obtener el intermediario deseado como un sólido blanco (1.1 g, 85%). EM (ES+) m/z: 226 $(M+H)^+$.

6-Bromometil-2-fenil-benzotiazol: Se combina 6-metil-2-fenil-benzotiazol (0.2 g, 0.98 mmol), NBS (0.2 g, 1.02 mmol), AIBN (20 mg, 0.10 mmol), tetracloruro de carbono (5 mL) y se puso a reflujo durante 3 h. Se enfría la mezcla de reacción a temperatura ambiente, se diluye con cloroformo y se lava con agua. Se secan los extractos orgánicos sobre Na_2SO_4 anhidro, se concentra y se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (1:0, 9:1, 8:2 y 7:3) para obtener el compuesto del título como un sólido blanco (0.2 g, 69%).

Preparación 155

2-Bencil-6-bromometil-benzotiazol



éster de etilo del ácido 2-Fenil-acetimídico, clorohidrato: Se combina cianuro de bencilo (1.0 g, 8.50 mmol), etanol (0.4 g, 8.50 mmol) y cloruro de hidrógeno 4N en dioxano (8 mL) y se agita la mezcla de reacción a temperatura ambiente durante 17 h. Se evapora el solvente y se tritura el residuo con dietil éter para obtener el intermediario deseado como un sólido blanco (1.7 g, 100%).

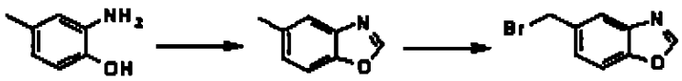
2-Bencil-6-metil-benzotiazol: Se combina sal de zinc de 2-amino-5-metil-bencenotiol (1.0 g, 2.91 mmol, se prepara como se describe en Synth. Commun. 1980, 10, 167-173), clorohidrato de éster de etilo del ácido 2-fenil-acetimidico (1.16 g, 5.82 mmol), metanol (20 mL) y se puso a reflujo la mezcla de reacción durante 17 h. Se evapora el solvente y se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (1:0 y 9:1) para obtener el intermediario deseado como un sólido blanco (1.0 g, 72%). EM (ES+) m/z: 240 $(M+H)^+$.

2-Bencil-6-bromometil-benzotiazol: Se combina 2-bencil-6-metil-benzotiazol (0.6 g, 2.51 mmol), NBS (0.5 g, 2.63 mmol), AIBN (40 mg, 0.25 mmol), tetracloruro de carbono (10 mL) y se puso a reflujo durante 3 h. Se enfría la mezcla de reacción a temperatura ambiente, se diluye con cloroformo y se lava con agua. Se secan los extractos orgánicos combinados sobre Na_2SO_4

anhidro, se evapora el solvente y se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (1:0 y 9:1) para obtener el compuesto del título como un sólido blanco (0.2 g, 69%). EM (ES+) m/z: 319 $(M+H)^+$.

Preparación 156

5-Bromometil-benzoxazol



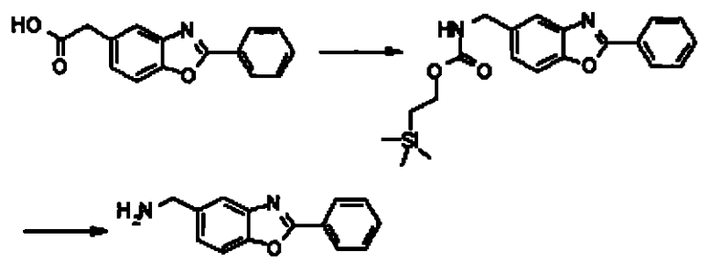
5-Metil-benzoxazol: Se combina 2-amino-4-metil-fenol (1.0 g, 8.12 mmol), cloruro de [(dimetilaminometilen-aminometilen)dimetilamonio (reactivo de Gold) (1.6 g, 9.91 mmol), 1,4-dioxano anhidro (25 mL) y se puso a reflujo durante 17 h. Se enfría la mezcla de reacción a temperatura ambiente, se evapora el solvente y se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (9:1) para obtener el intermediario deseado como un aceite amarillo (0.7 g, 65%).

5-Bromometil-benzoxazol: Se combina 5-metil-benzoxazol (0.5 g, 3.75 mmol), NBS (0.7 g, 3.93 mmol), AIBN (60 mg, 0.37 mmol), cloroformo (10 mL) y se puso a reflujo durante 1 h. Se enfría la mezcla de reacción a temperatura ambiente, se diluye con cloroformo y se lava con agua. Se secan los extractos orgánicos sobre Na_2SO_4 anhidro, se evapora el

solvente y se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (1:0, 9:1, 4:1 y 7:3) para obtener el compuesto del título como un sólido blanco (0.1 g, 13%).

Preparación 157

5-Metilamino-2-fenil-benzoxazol

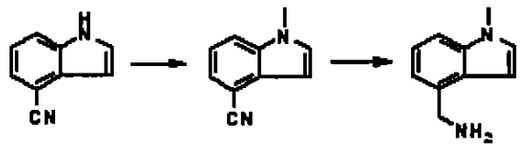


Éster de 2-trimetilsilanil-etilo del ácido 2-(Fenil-benzoxazol-5-ilmetil)-carbámico: Se combina ácido (2-fenil-benzoxazol-5-il)-acético (1.0 g, 3.95 mmol), trietilamina (0.5 g, 4.34 mmol), y tolueno anhidro (20 mL), se calienta a reflujo y lentamente se agrega azida de difenilfosforilo (1.2 g, 4.15 mmol) en tolueno anhidro (8 mL). Se continua a reflujo durante 3 h, Se enfría a temperatura ambiente, se agrega 2-trimetilsililetanol (0.9 g, 7.89 mmol) a la mezcla de reacción y se continua a reflujo durante 3 h. Se evapora el solvente y se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (1:0, 9:1, 4:1 y 7:3) para obtener el intermediario deseado como un sólido amarillo (0.4 g, 26%).

5-Metilamino-2-fenil-benzoxazol: Se disuelve éster de 2-trimetilsilanil-etilo del ácido (2-fenil-benzoxazol-5-il-metil)-carbámico (0.4, 0.99 mmol) en THF anhidro (5 mL) y se trata con floruro de tetrabutilamonio 1M en THF (1.5 mL, 1.54 mmol). Se calienta la mezcla a reflujo durante 30 min, se evapora el solvente y se purifica por cromatografía SCX para obtener el compuesto del título como un aceite amarillo (0.1 g, 27%).

Preparación 158

4-Aminometil-1-metilindol



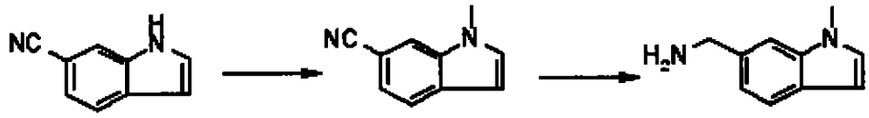
1-Metilindol-4-carbonitrilo: Se agrega lentamente una solución de indol-4-carbonitrilo (1.0 g, 7.04 mmol) en DMF anhidro (5 mL) a una suspensión de hidruro de sodio (60% dispersion en aceite mineral, 0.6 g, 8.64 mmol) en DMF anhidro (2 mL) a 0°C y se calienta la mezcla de reacción a temperatura ambiente. Se agrega yodometano (0.7 mL, 10.6 mmol) y se agita la reacción durante 1 h a temperatura ambiente. Se diluye la mezcla de reacción con NH_4OH acuoso 1M (30 mL) y se extrae con dietil éter (3 x 10 mL). Se combinan los extractos orgánicos, se secan sobre Na_2SO_4 anhidro, se concentran in vacuo y se purifican por cromatografía en gel

de sílice eluido con hexano/EtOAc (1:0, 9:1, 4:1 y 7:3) para obtener el intermediario deseado como un aceite amarillo (1.0 g, 87%). CG-EM m/z: 156 (M^+).

4-Aminometil-1-metilindol: Se disuelve 1-metilindol-4-carbonitrilo (1.0 g, 6.18 mmol) en THF anhidro (10 mL) y se agrega lentamente a hidruro de aluminio de litio 1M en THF (12.4 mL, 12.37 mmol) a temperatura ambiente. Se calienta la mezcla de reacción a 50°C durante 17 h y se enfría a temperatura ambiente. Se apaga la mezcla de reacción con agua hasta que un precipitado de partida granular se forma y se filtra a través de una almohadilla de Celite®. Se evapora el solvente y se purifica por cromatografía SCX para obtener el compuesto del título como un aceite amarillo (0.9 g, 91%). CG-EM m/z: 160 (M^+).

Preparación 159

6-Aminometil-1-metilindol



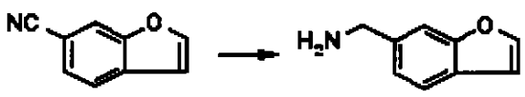
1-Metilindol-6-carbonitrilo: Se agrega lentamente una solución de indol-6-carbonitrilo (1.0 g, 7.04 mmol) en DMF anhidro (5 mL) a una suspensión de hidruro de sodio (60% dispersion en aceite mineral, 0.6 g, 14.1 mmol) en DMF

anhidro (2 mL) a 0°C y se calienta la mezcla de reacción a temperatura ambiente. Se agrega yodometano (0.7 mL, 1.06 mmol) y se agita la mezcla de reacción durante 1 h a temperatura ambiente. Se diluye la mezcla de reacción con NH_4OH acuoso 1M (30 mL) y se extrae con dietil éter (3 x 10 mL). Se combinan las capas orgánicas, se secan sobre Na_2SO_4 anhidro, se elimina el solvente y se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (1:0, 9:1, 4:1 y 7:3) para obtener el intermediario deseado como un aceite amarillo (1.0 g, 87%). EM (ES+) m/z: 156 $(M+H)^+$.

6-Aminometil-1-metilindol: Se disuelve 1-metilindol-6-carbonitrilo (0.97 g, 6.18 mmol) en THF anhidro (10 mL) y se agrega lentamente a hidruro de aluminio de litio 1M en THF (1.24 mL, 1.24 mmol) a temperatura ambiente. Se calienta la mezcla de reacción a 50°C durante 17 h y se enfría a temperatura ambiente. Se apaga la mezcla de reacción con agua hasta que un precipitado de partida granular se forma y se filtra a través de una almohadilla de Celite®. Se evapora el solvente y se purifica por cromatografía SCX para obtener el compuesto del título como un aceite amarillo (0.9 g, 91%). CG-EM m/z: 160 (M^+).

Preparación 160

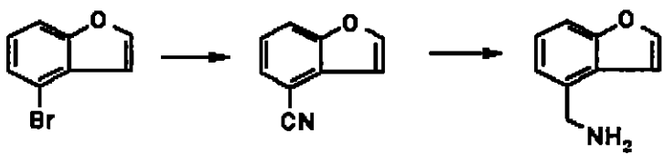
6-Aminometil-benzofurano



Se disuelve benzofuran-6-carbonitrilo (0.5 g, 3.28 mmol) en THF anhidro (10 mL) y se agrega lentamente a hidruro de aluminio de litio 1M en THF (6.56 mL, 6.56 mmol) a temperatura ambiente. Se calienta la mezcla de reacción a 50°C durante 17 h y se enfría a temperatura ambiente. Se apaga la mezcla de reacción con agua hasta que un precipitado de partida granular se forma y se filtra a través de una almohadilla de Celite®. Se evapora el solvente y se purifica por cromatografía SCX para obtener el compuesto del título como un aceite amarillo (0.4 g, 79%).

Preparación 161

4-Aminometil-benzofurano



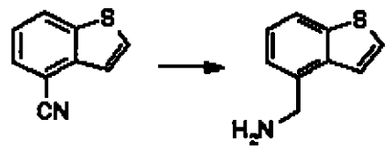
Benzofuran-4-carbonitrilo: Se combina 4-bromo-benzofurano (1.0 g, 5.07 mmol), cianuro de cobre (I) (0.9 g, 10.2 mmol), DMF anhidro (16 mL) y se puso a reflujo durante 17 h. Se enfría la mezcla de reacción a temperatura ambiente, se trata con 50% (p/p) etilendiamina acuosa (25 mL). Se extrae la

mezcla de reacción con dietil éter (3 x 15 mL), se combinan los extractos orgánicos, se lavan con salmuera (15 mL) y se secan sobre Na_2SO_4 anhidro. Se evapora el solvente y se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (1:0, 9:1 y 4:1) para obtener el intermediario deseado como un aceite incoloro (0.3 g, 39%).

4-Aminometil-benzofurano: Se disuelve benzofuran-4-carbonitrilo (0.3 g, 1.96 mmol) en THF anhidro (5 mL) y se agrega lentamente a hidruro de aluminio de litio 1M en THF (3.91 mL, 3.91 mmol) a temperatura ambiente. Se calienta la mezcla de reacción a 50°C durante 5 h y se enfría a temperatura ambiente. Se apaga la mezcla de reacción con agua hasta que un precipitado de partida granular se forma y se filtra a través de una almohadilla de Celite®. Se evapora el solvente y se purifica por cromatografía SCX para obtener el compuesto del título como un aceite café (0.4 g, 79%). CG-EM m/z: 147 (M^+).

Preparación 162

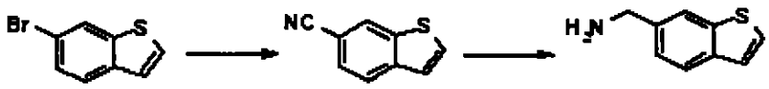
4-Aminometil-benzo[b]tiofeno



Se agrega hidruro de aluminio de litio (solución 1M en THF, 7.5 mL) a benzo[b]tiofen-4-carbonitrilo (se prepara como se describe en WO 0168653) (0.6 g, 3.8 mmol) a 0°C en THF (38 mL). después 17 h a temperatura ambiente, se enfría a 0°C y se agrega secuencialmente agua (1.89 mL), NaOH acuoso 2N (1.89 mL) y agua (2.69 mL). Se filtran los sólidos y se evapora el filtrado para obtener la amina cruda. Se purifica por cromatografía SCX. Se enjuaga la columna con metanol, se agrega una solución de la amina cruda en metanol, se lava la columna con metanol y luego se eluye con amoniaco 1N en metanol. Se concentra para dar el compuesto del título (0.57 g, 93%). CG-EM m/z: 163 (M^+).

Preparación 163

6-Aminometil-benzo[b]tiofeno



Benzo[b]tiofen-6-carbonitrilo: Se calienta cianuro de cobre (I) (0.84 g, 9.4 mmol) y 6-bromobenzo[b]tiofeno (se prepara como se describe en WO 01/23381) (1.0 g, 4.7 mmol) a 160°C durante 13 h. Se enfría la mezcla a 0°C, se agrega 33% de etilendiamina acuoso (20 mL) y se diluye con éter. Se lava lamezcla orgánica con salmuera, se seca sobre Na_2SO_4 y se evapora. Se purifica por cromatografía en gel de sílice

eluido con EtOAc/hexano (0:1 hasta 1:3) para dar el intermediario deseado (0.58 g, 78%). CG-EM m/z: 159 (M^+).

6-Aminometil-benzo[b]tiofeno: Se agrega hidruro de aluminio de litio 1M en THF (7.3 mL) a benzo[b]tiofeno-6-carbonitrilo (0.6 g, 3.6 mmol) a 0°C en THF (36 mL). Después de 15 h a temperatura ambiente, se enfría a 0°C y se agrega secuencialmente agua (1.82 mL), NaOH acuoso 2N (1.82 mL) y agua (2.60 mL). Se filtra el sólido y se evapora el filtrado para obtener la amina cruda. Se purifica por cromatografía SCX. Se enjuaga la columna con metanol, se agrega una solución de la amina cruda en metanol, se lava la columna con metanol y luego se eluye con amoniaco 1N en metanol. Se concentra in vacuo para dar el compuesto del título (0.55 g, 92%).

Preparación 164

8-Bromometil-quinolina



Se combina 8-metil-quinolina (1.0 g, 6.99 mmol), NBS (1.3 g, 7.13 mmol), peróxido de benzoílo (6.0 mg, 0.03 mmol), tetracloruro de carbono (30 mL) y se puso a reflujo durante 17 h. Se enfría la mezcla de reacción a temperatura ambiente y se evapora el solvente. Se disuelve el residuo en

cloroformo (30 mL), se lava la solución orgánica con $NaHCO_3$ acuoso saturado (2 x 10 mL), salmuera (10 mL) y se seca sobre Na_2SO_4 anhidro. Se evapora el solvente y se purifica por cromatografía en gel de sílice eluido con DCM para obtener el compuesto del título como un sólido blanco (1.3 g, 83%). EM (ES+) m/z: 223 $(M+H)^+$.

Preparación 165

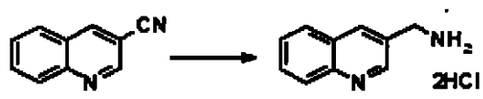
2-Aminometil-quinolina



Se combina quinolin-2-carbonitrilo (0.2 g, 1.29 mmol), níquel Raney® 3201 (mezcla espesa en agua, 0.05 g), amoniaco 2N en metanol (10 mL) y se hidrogena a 50 psi (3.515 kg/cm^2) durante 15 min. Se filtra la mezcla de reacción a través de una almohadilla de Celite®, se elimina el solvente y se purifica por cromatografía SCX para obtener el compuesto del título como un aceite amarillo (0.2 g, 98%). EM (ES+) m/z: 159 $(M+H)^+$.

Preparación 166

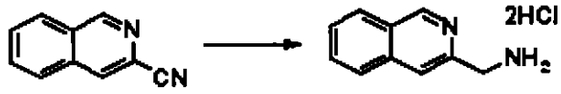
Diclorohidrato de 3-aminometil-quinolina



Se combina quinolin-3-carbonitrilo (1.0 g, 6.49 mmol), 10% Pd/C (0.2 g), 5% TFA en metanol (100 mL) y se hidrogena a 30 psi (2.1409 kg/cm^2) durante 2 h. Se filtra la mezcla de reacción a través de una almohadilla de Celite® y se evapora el solvente. Se disuelve el residuo en etanol (10 mL), se trata con cloruro de hidrógeno 1N en dietil éter (5 mL) y se permite a la mezcla reposar a 5°C durante 18 h. Se filtra el precipitado, se lava con etanol y se seca bajo vacío para obtener el compuesto del título como un sólido blanco (0.6 g, 53%).

Preparación 167

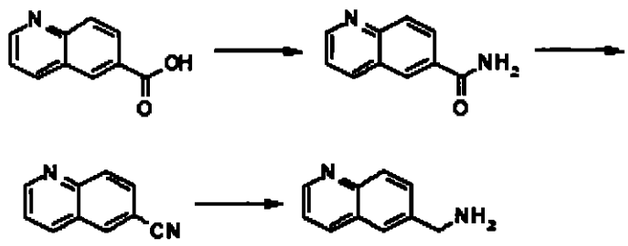
Diclorohidrato de 2-aminometil-isoquinolina



Se combina isoquinolin-3-carbonitrilo (1.0 g, 6.49 mmol), 10% Pd/C (0.2 g), 5% TFA en metanol (95 mL) y se hidrogena a 30 psi (2.109 kg/cm^2) durante 17 h. Se filtra la mezcla de reacción a través de una almohadilla de Celite y se evapora el solvente. Se disuelve el residuo en etanol (10 mL), se trata con cloruro de hidrógeno 1N en dietil éter (5 mL) y se permite reposar a 5°C durante 18 h. Se filtra el precipitado, se lava con etanol y se seca bajo vacío para obtener el compuesto del título como un sólido blanco (0.6 g, 55%).

Preparación 168

6-Aminometil-quinolina



6-Quinolinocarboxamida: Se combina ácido 6-quinolincarboxílico (2.0 g, 11.6 mmol), 1,1-carbonildiimidazol (3.8 g, 23.45 mmol) en DCM (50 mL) y se agita a temperatura ambiente durante 1 h. Se satura la mezcla de reacción con amoniaco anhidro y se continua para agitación durante 1 h. Se apaga la mezcla de reacción con agua (100 mL) y se extrae con cloroformo (3 x 50 mL). Se combinan los extractos orgánicos, se secan sobre Na_2SO_4 anhidro y se evapora el solvente para obtener el intermediario deseado como un sólido blanco (1.6 g, 78%).

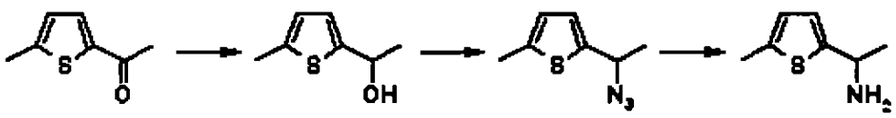
6-Quinolincarbonitrilo: Se disuelve 6-quinolincarboxamida (1.5 g, 8.95 mmol) en DCM (50 mL), se agrega trietilamina (2.7 g, 26.8 mmol) y se enfría la mezcla de reacción a 0°C. Se agrega anhídrido ácido trifluoroacético (2.4 g, 11.16 mmol) a la mezcla de reacción y se agita durante 10 min a 0°C. Se apaga la mezcla de reacción con agua (20 mL) y se separa la capa orgánica. Se extrae la capa acuosa con DCM (2

x 15 mL). Se combinan los extractos orgánicos y se secan sobre Na_2SO_4 anhidro. Se evapora el solvente para obtener el intermediario deseado como un sólido blanco (1.0 g, 73%). CG-EM m/z: 154 (M^+).

6-Aminometil-quinolina: Se combina 6-quinolincarbonitrilo (1.0 g, 6.49 mmol), níquel Raney® 3201 (mezcla espesa en agua, 0.2 g), amoniaco 2N en metanol (20 mL) y se hidrogena a 50 psi (3.515 kg/cm^2) durante 1 h. Se filtra la mezcla de reacción a través de una almohadilla de Celite®, se elimina el solvente y se purifica por cromatografía SCX para obtener el compuesto del título como un aceite amarillo (0.8 g, 78%).

Preparación 169

(±)-2-(1-Aminoetil)-5-metiltiofeno



(±)-2-(1-Hidroxietil)-5-metiltiofeno: Se agrega borohidruro de sodio (270 mg, 7.13 mmol) a una solución de 2-acetil-5-metiltiofeno (1.0 g, 7.13 mmol) en metanol (40 mL). Se agita la mezcla durante 1 h a temperatura ambiente. Se elimina el solvente in vacuo y se divide el residuo entre agua y DCM. Se separa la fase orgánica, se seca sobre Na_2SO_4, se filtra y se concentra para obtener el intermediario deseado como un

aceite (0.995 g, 98%) que se usa sin purificación adicional. CG-EM m/z 142 (M^+).

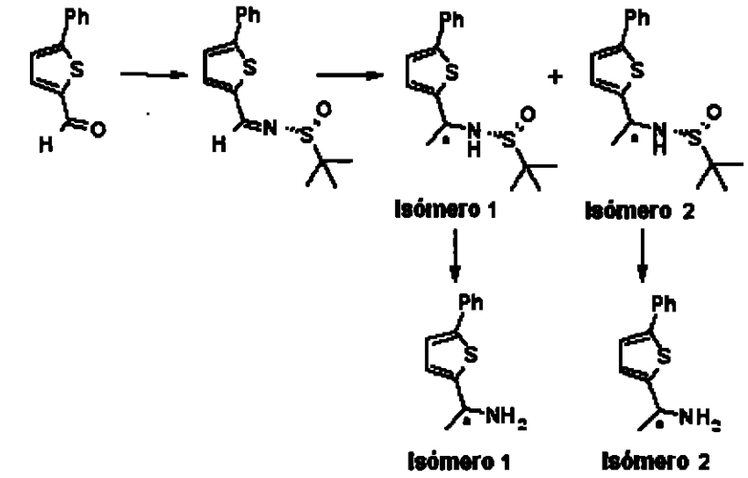
(±)-2-(1-Azidoetil)-5-metiltiofeno: Se agrega DBU (1.228 g, 1.2 mL, 8.07 mmol) a una solución de (±)-2-(1-hidroxietil)-5-metiltiofeno (0.955 g, 6.72 mmol) y azida difenilfosforilo (2.22 g, 1.74 mL, 8.07 mmol) en tolueno anhidro. Se agita a temperatura ambiente durante 18 h. Se diluye la mezcla con EtOAc y se lava con agua y HCl acuoso 0.5N. Se seca la fase orgánica sobre Na_2SO_4, se filtra y se concentra. Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (1:0 y 19:1) para obtener el intermediario deseado como un aceite (0.875 g, 78%). CG-EM m/z 167 (M^+).

(±)-2-(1-Aminoetil)-5-metiltiofeno: Se agrega hidruro de aluminio de litio (29 mg, 0.72 mmol) a una solución de (±)-2-(1-azidoetil)-5-metiltiofeno (100 mg, 0.59 mmol) en THF anhidro (5 mL). Se agita a temperatura ambiente durante la noche. Se trabaja la mezcla con EtOAc y agua. Se filtra la mezcla sobre Celite®. Se separa y se lava la fase orgánica con salmuera. Se seca sobre Na_2SO_4, se filtra y se concentra in vacuo. Se purifica por cromatografía SCX. Se enjuaga con DCM/metanol (1:1), se carga la mezcla cruda en metanol y se eluye secuencialmente con metanol y amoniaco 1N en metanol

para obtener el compuesto del título como un aceite (80 mg, 95%). CG-EM m/z 141 (M^+).

Preparaciones 170 y 171

1-(5-Fenil-tiofen-2-il)etilamina, Isómeros 1 y 2



N-[(5-Feniltiofen-2-il)-metilen]-2-metilpropanosulfinamida: A una solución de 5-fenil-2-tiofencarboxaldehído (1.25 g, 6.64 mmol) en THF anhidro (50 mL), se agrega etóxido de titanio (IV) (3.03 g, 2.78 mL, 13.28 mmol) y (R)-(+)-2-metil-2-propanosulfinamida (0.965 g, 7.968 mmol) bajo nitrógeno. Se calienta la reacción a 80°C durante la noche. Se enfría la mezcla a temperatura ambiente y se diluye con EtOAc. Se agrega agua y se filtra el precipitado resultante sobre Celite®. Se separa y se seca la fase orgánica sobre Na_2SO_4, se filtran y se concentran in vacuo para obtener el intermediario deseado como un sólido amarillo (1.93 g, 100% rendimiento) que se usan sin purificación.

N-[1-(5-Feniltiofen-2-il)etil]-2-metilpropanosulfinamida (Isómero 1) y N-[1-(5-feniltiofen-2-il)etil]-2-metilpropanosulfinamida (Isómero 2): Se agrega lentamente metillitio (8.1 mL, 12.92 mmol, solución en éter 1.6 M) a una solución de N-[(5-feniltiofen-2-il)-metilen]-2-metilpropanosulfinamida (1.883 g, 6.46 mmol) en THF anhidro (50 mL) a -40°C. Se calienta la reacción a -20°C y se agita durante 2 h. Se calienta a 0°C y se agita durante unas 2 horas adicionales. Se agrega NH_4Cl acuoso saturado y se extrae con EtOAc. Se seca la fase orgánica sobre Na_2SO_4, se filtra y se concentra in vacuo. Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (7:3 y 1:1) para obtener N-[1-(5-feniltiofen-2-il)etil]-2-metilpropanosulfinamida (Isómero 1) (575 mg, 30% rendimiento) y N-[1-(5-feniltiofen-2-il)etil]-2-metilpropanosulfinamida (Isómero 2) (847 mg, 44% rendimiento).

1-(5-Fenil-tiofen-2-il)etilamina (Isómero 1, Preparación 170) Se agrega cloruro de hidrógeno 4N en dioxano (0.837 mL, 3.349 mmol) a una solución agitada de N-[1-(5-feniltiofen-2-il)etil]-2-metilpropanosulfinamida (Isómero 1) (515 mg, 1.675 mmol) en metanol (8 mL) a temperatura ambiente. Se agita durante 2 h y se elimina el solvente in vacuo para obtener a sólido que se lava con éter etílico. Se disuelve el sólido en DCM y se lava con $NaHCO_3$ acuoso saturado. Se seca la fase

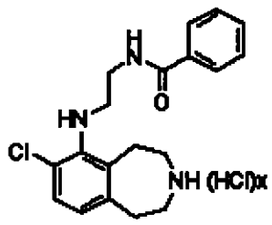
orgánica sobre Na_2SO_4, se filtra y se concentra in vacuo para obtener el intermediario deseado (236 mg, 69% rendimiento).

1-(5-Fenil-tiofen-2-il)etilamina (Isómero 2, Preparación 171)

Se agrega cloruro de hidrógeno 4N en dioxano (1.112 mL, 4.449 mmol) a una solución agitada de N-[1-(5-feniltiofen-2-il)etil]-2-metilpropanosulfinamida (Isómero 2) (684 mg, 2.225 mmol) en metanol (10 mL) a temperatura ambiente. Se agita durante 2 h y se elimina el solvente in vacuo para obtener un sólido que se lava con éter etílico. Se disuelve el sólido en DCM y se lava con $NaHCO_3$ acuoso saturado. Se seca la fase orgánica sobre Na_2SO_4, se filtra y se concentra in vacuo para obtener el intermediario deseado (347 mg, 77% rendimiento).

Ejemplo 49

Clorohidrato de 6-(2-Benzoilamino-etilamino)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina

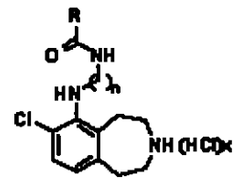


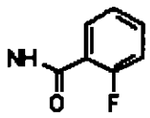
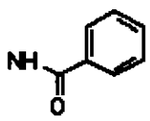
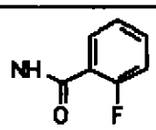
Se disuelve 6-(2-amino-etilamino)-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (70 mg, 0.208 mmol) en DCM (4 mL). Se agrega cloruro de benzoilo (24 µL, 0.208 mmol), y trietilamina (44 µL, 0.312 mmol) y se

agita a temperatura ambiente durante 24 h bajo atmósfera de nitrógeno. Se diluye con DCM y se agrega HCl acuoso 1M. Se extrajo la capa acuosa con DCM. Se seca la capa orgánica sobre $MgSO_4$ y se concentra in vacuo. Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (1:0, 7:3 y 1:1) para obtener 6-(2-benzoilamino-etilamino)-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina.

Se usa un método similar al Procedimiento general 1-1, al usar 6-(2-benzoilamino-etilamino)-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina, para dar la base libre del compuesto del título. Se usa un método similar al Procedimiento general 2-2 para dar el compuesto del título (77 mg, 90% en general). CLAR: t_R = 2.64 min (20-80% del solvente B en 7.5 min. Solvente A: agua, 0.1% TFA. Solvente B: acetonitrilo, 0.1% TFA. Columna: C18 Metachem, 5 micron, 4.6x50).

Ejemplos 50-52 pueden prepararse esencialmente como se describe en el Ejemplo 49 al usar 6-(2-amino-etilamino)-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina o 6-(3-amino-propilamino)-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina y el cloruro de benzoilo adecuado. Los datos de rendimiento general y EM (ES+) se muestran en la Tabla a continuación.

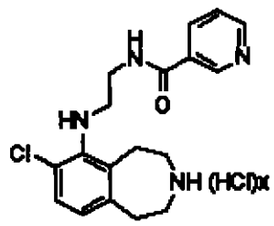


Ej.	NH-CO-R	n	Compuesto	Rendimiento (%)	EM (ES+) m/z
50		2	Clorohidrato de 7-Cloro-6-[2-(2-fluorobenzoilamino)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	40	362 $(M+H)^+$
51		3	Clorohidrato de 6-(3-Benzoilamino-propilamino)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina	90	ND
52		3	Clorohidrato de 7-Cloro-6-[3-(2-fluorobenzoilamino)-propilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	40	376 $(M+H)^+$

ND = No se determina

Ejemplo 53

Clorohidrato de 7-Cloro-6-{2-[(piridina-3-carbonil)-amino]-etilamino}-2,3,4,5-tetrahidro-1H-benzo[d]azepina



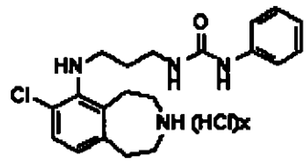
Se disuelve ácido nicotínico (28.2 mg, 0.23 mmol) en DCM (3 mL). Se agrega EDC (40 mg, 0.208 mmol), HOBT (28.1 mg, 0.2081mmol) y se agita a temperatura ambiente durante 10 min. Se agrega 6-(2-amino-etilamino)-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (70 mg, 0.208 mmol) y se agita a temperatura ambiente durante 10 hr. Se diluye con DCM, se agrega agua y se extrae la capa acuosa 3 veces con DCM. Se lavan los extractos orgánicos combinados con NaOH acuoso 1N, y salmuera. Se seca la capa orgánica sobre $MgSO_4$, se concentra in vacuo y se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (1:0, 1:1, 3:7 y 1:9) para obtener 7-cloro-6-{2-[(piridina-3-carbonil)-amino]-etilamino}-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina.

Se usa un método similar al Procedimiento general 1-1, al usar 7-cloro-6-{2-[(piridina-3-carbonil)-amino]-etilamino}-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina, para dar la base libre del compuesto del

título. Se usa un método similar al Procedimiento general 2-2 para dar el compuesto del título como un sólido (92 mg, 98%). CLAR: t_R= 1.38 min (20-80% del Solvente B en 7.5 min. Solvente A: agua, 0.1% TFA. Solvente B: acetonitrilo, 0.1% TFA. Columna: C18 Metachem, 5 micron, 4.6x50).

Ejemplo 54

Clorohidrato de 7-Cloro-6-[3-(3-fenil-ureido)-propilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina

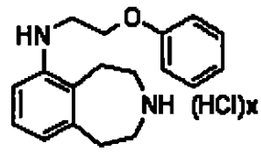


Se combina fenil isocianato (15 µL, 0.137 mmol) y 6-(3-amino-propilamino)-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (48 mg, 0.137 mmol) en DCM y se agita durante 16 h. Se concentra, se agrega DCM, se filtra y se recolecta el sólido para obtener 7-cloro-6-[3-(3-fenil-ureido)-propilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (18 mg, 28%).

Se usa un método similar al Procedimiento general 1-1, al usar 7-cloro-6-[3-(3-fenil-ureido)-propilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina, para dar la base libre del compuesto del título. Se usa un método similar al Procedimiento general 2-2 para dar el compuesto del título (14 mg, 23%). EM (ES+) m/z: 373 $(M+H)^+$.

Ejemplo 55

Clorohidrato de 6-(2-Fenoxi-etilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

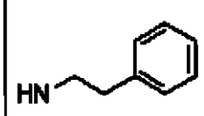
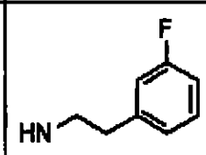
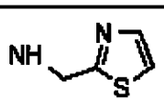


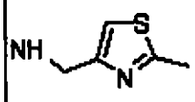
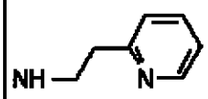
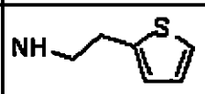
Se usa un método similar al Procedimiento general 5-1, al usar 3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (100 mg, 0.23 mmol) y fenoxietilamina (63 mg, 0.4 mmol) para dar, después cromatografía en gel de sílice eluido con hexano/EtOAc (85:15) seguido por cromatografía SCX, 6-(2-fenoxi-etilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite amarillo. EM (ES+) m/z: 379 $(M+H)^+$.

Se usa un método similar al Procedimiento general 1-1 para desproteger 6-(2-fenoxi-etilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (75 mg, 0.19 mmol). Se purifica por cromatografía SCX para dar la base libre del compuesto del título. Se usa un método similar al Procedimiento general 2-2 para dar el compuesto del título como un sólido blanco. EM (ES+) m/z: 283 $(M+H)^+$.

Ejemplos 56-61 pueden prepararse esencialmente como se describe en el Ejemplo 55 al usar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-

tetrahidro-1H-benzo[d]azepina y la amina apropiada. Los datos de rendimiento para la Etapa 1 (Procedimiento general 5-1) y EM (ES+) se muestran en la Tabla a continuación.

Ej.	NH-R	Compuesto	Rendimiento (%)	EM (ES+) m/z
56		Clorohidrato de 7-Cloro-6-fenetilamino-2,3,4,5-tetrahidro-1H-benzo[d]azepina	47	301 $(M+H)^+$
57		Clorohidrato de 7-Cloro-6-(3-fluoro-fenetilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	55	319 $(M+H)^+$
58		Clorohidrato 7-Cloro-6-[(tiazol-2-il)metilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	21	294 $(M+H)^+$

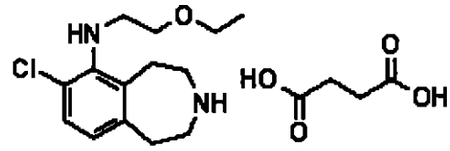
Ej.	NH-R	Compuesto	Rendimiento (%)	EM (ES+) m/z
59		Clorohidrato 7-Cloro-6-[(2-metil-tiazol-4-il)metilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	16	308 $(M+H)^+$
60		Clorohidrato de 7-Cloro-6-(2-piridin-2-il-etilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	86	302 $(M+H)^+$
61		Clorohidrato de 7-Cloro-6-(2-tiofen-2-il-etilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	78	ND

ND = No se determina

882

Ejemplo 62

Succinato de 7-Cloro-6-[(2-etoxietil)amino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina

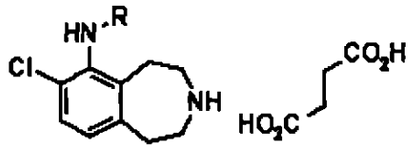


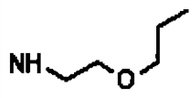
Se usa un método similar al Procedimiento general 5-1, al usar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (200 mg, 0.47 mmol) y 2-etoxietil amina (105 µL, 1.0 mmol) para dar, después cromatografía en gel de sílice eluido con hexano/EtOAc (95:5) y se Cromatografía SCX adicional, 7-cloro-6-[(2-etoxietil)amino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (32 mg, 19%). EM (ES+) m/z: 365 $(M+H)^+$.

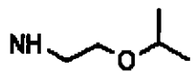
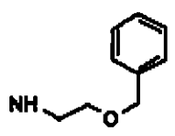
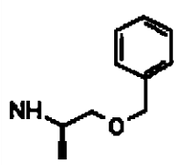
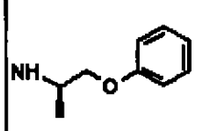
Se usa un método similar al Procedimiento general 1-1 para desproteger 7-cloro-6-[(2-etoxietil)amino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (30 mg, 0.08 mmol). Se purifica por cromatografía SCX para dar la base libre del compuesto del título. Se usa un método similar al Procedimiento general 2-1 para dar el compuesto del título como un aceite (23.8 mg, 75% durante 2 etapas). EM (ES+) m/z: 269 $(M+H)^+$.

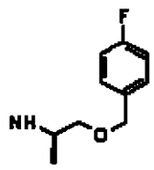
883

Ejemplos 63-68 pueden prepararse esencialmente como se describe en el Ejemplo 62 al usar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina y la amina apropiada. Los datos de rendimiento durante la Etapa 1 (Procedimiento general 5-1), rotaciones ópticas y EM (ES+) se muestran en la Tabla a continuación.



Ej.	NH-R	Compuesto	Rendimiento (%)	EM (ES+) m/z.	$[\alpha]^{20}_D$ (c, solvente)
63		Succinato de 7-Cloro-6-[2-(1-propoxi)etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	57	283 $(M+H)^+$	-

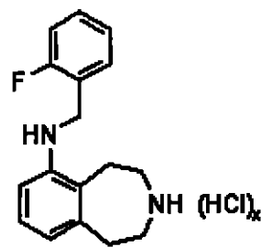
64		Succinato de 7-Cloro-6-[2-(2-propoxi)etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	75	283 $(M+H)^+$	-
65		Succinato de 6-(2-Benciloxi-etilamino)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina	37	331 $(M+H)^+$	-
66		Succinato de (R)-6-(2-Benciloxi-1-metil-etilamino)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina	15	345 $(M+H)^+$	ND
67		Succinato de (R)-6-(2-Fenoxi-1-metil-etilamino)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina	15	331 $(M+H)^+$	+54.7° (c 0.5, CH_3OH)

Ej.	NH-R	Compuesto	Rendimiento (%)	EM (ES+) m/z.	$[\alpha]^{20}_D$ (c, solvente)
68		Succinato (R)-6-[2-(4-Fluoro benciloxi)-1-metil-etilamino]-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina	69	363 $(M+H)^+$	+22.6° (c 0.5, CH_3OH)

ND = No se determina

Ejemplo 69

Clorohidrato de 6-(2-Fluorobencilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

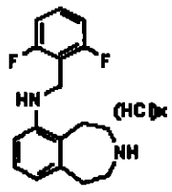


Se usa un método similar al Procedimiento general 5-1, al usar 3-(2,2,2-trifluoroacetil)-6-trifluorometilsulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (100 mg, 0.26 mmol) y 2-fluorobencilamina (88

µL, 0.77 mmol) para dar, después cromatografía en gel de sílice eluido con hexano/EtOAc (9:1), 6-(2-fluorobencilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite amarillo (45 mg, 48%). EM (ES+) m/z: 367 $(M+H)^+$.

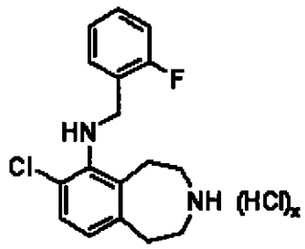
Se usa un método similar al Procedimiento general 1-1 para desproteger 6-(2-fluorobencilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (40 mg, 0.11 mmol). Se purifica por cromatografía SCX para dar la base libre del compuesto del título como un aceite amarillo (28 mg, 94 %). Se usa un método similar al Procedimiento general 2-2 para dar el compuesto del título como un solido completamente blanco (29 mg, 95%). EM (ES+) m/z: 271 $(M+H)^+$.

El ejemplo 70 puede prepararse esencialmente como se describe en el Ejemplo 69 al usar 3-(2,2,2-trifluoroacetil)-6-trifluorometilsulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 2,6-difluorobencilamina. Los datos de rendimiento durante la Etapa 1 (Procedimiento general 5-1) y EM (ES+) se muestran en la Tabla a continuación.

Ej.	Estructura	Compuesto	Rendimiento (%)	EM (ES+) m/z
70		Clorohidrato de 6-(2,6-Difluorobencilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	69	289 $(M+H)^+$

Ejemplo 71

Clorohidrato de 7-Cloro-6-(2-fluorobencilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

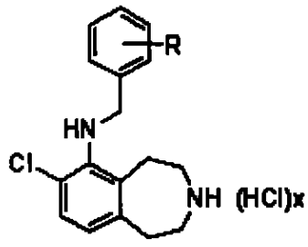


Se usa un método similar al Procedimiento general 5-1 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 2-fluorobencil amina. Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (9:1 y 4:1) para dar 7-cloro-6-(2-fluorobencilamino)-3-(2,2,2-

trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un sólido amarillo. EM (ES+) m/z: 401 $(M+H)^+$.

Se usa un método similar al Procedimiento general 1-1 para desproteger 7-cloro-6-(2-fluorobencilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina. Se purifica por cromatografía SCX para dar la base libre del compuesto del título como un aceite amarillo. Se usa un método similar al Procedimiento general 2-2 para dar el compuesto del título como un sólido amarillo ligero. EM (ES+) m/z: 305 $(M+H)^+$.

Ejemplos 72-80 pueden prepararse esencialmente como se describe en el Ejemplo 71 al usar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina y la amina apropiada. EM (ES+) data se muestran en la Tabla a continuación.

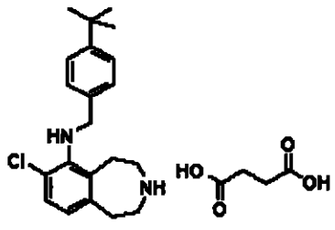


Ej.	R	Compuesto	EM (ES+) m/z
72	3-F	Clorohidrato de 7-Cloro-6-(3-fluorobencilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	305 $(M+H)^+$
73	4-F	Clorohidrato de 7-Cloro-6-(4-fluorobencilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	305 $(M+H)^+$
74	2,3-diF	Clorohidrato de 7-Cloro-6-(2,3-difluorobencilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	323 $(M+H)^+$
75	3,4-diF	Clorohidrato de 7-Cloro-6-(3,4-difluorobencilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	323 $(M+H)^+$
76	3,5-diF	Clorohidrato de 7-Cloro-6-(3,5-difluorobencilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	323 $(M+H)^+$
77	3,4,5-triF	Clorohidrato de 7-Cloro-6-(3,4,5-trifluorobencilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	341 $(M+H)^+$

Ej.	R	Compuesto	EM (ES+) m/z
78	3-CF_3	Clorohidrato de 7-Cloro-6-(3-trifluorometil-bencilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	355 $(M+H)^+$
79	3,5-diCF_3	Clorohidrato de 7-Cloro-6-[3,5-bis(trifluorometil) bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	423 $(M+H)^+$
80	4-$O(CH_2)_2N(CH_3)_2$	Clorohidrato de 7-Cloro-6-{4-[2-(N,N-dimetilamino)etoxi] bencilamino}-2,3,4,5-tetrahidro-1H-benzo[d]azepina	374 $(M+H)^+$

Ejemplo 81

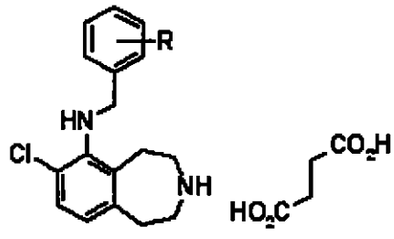
Succinato de 6-(4-tert-Butilbencilamino)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al Procedimiento general 5-1 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (300 mg, 0.7 mmol) con 4-(tert-butil)bencil amina (375 µL, 2.1 mmol). Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (95:5) seguido por cromatografía SCX para dar 6-(4-tert-butilbencilamino)-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite incoloro (240 mg, 78%). EM (ES+) m/z: 439 $(M+H)^+$.

Se usa un método similar al Procedimiento general 1-1 para desproteger 6-(4-tert-butilbencilamino)-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (235 mg, 0.54 mmol). Se purifica por cromatografía SCX para dar la base libre del compuesto del título (161 mg, 87%). Se usa un método similar al Procedimiento general 2-1 para dar el compuesto del título como una goma completamente blanca (190 mg, 88%). EM (ES+) m/z: 343 $(M+H)^+$.

Ejemplos 82-88 pueden prepararse esencialmente como se describe en el Ejemplo 81 al usar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina y la amina apropiada. EM (ES+) data se muestran en la Tabla a continuación.

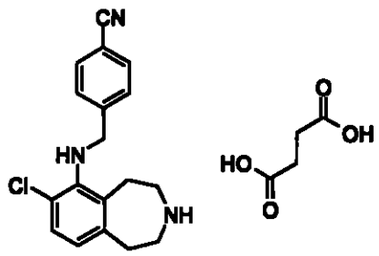


Ej.	R	Compuesto	EM (ES+) m/z
82	3-t-Bu	Succinato de 6-(3-tert-Butilbencilamino)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina	343 $(M+H)^+$
83	4-OCF_3	Succinato de 7-Cloro-6-(4-trifluorometoxi-bencilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	371 $(M+H)^+$
84	4-F,3-CF_3	Succinato de 7-Cloro-6-[(4-fluoro-3-trifluorometil)bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	373 $(M+H)^+$
85	4-F,3-OCH_3	Succinato de 7-Cloro-6-[(4-fluoro-3-metoxi)bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	321 $(M+H)^+$

86	4-Ph	Succinato de 7-Cloro-6-(4-fenilbencilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	363 $(M+H)^+$
87	4-OPh	Succinato de 7-Cloro-6-(4-fenoxi-bencilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	379 $(M+H)^+$
88	4-SO_2CH_3	Succinato de 7-Cloro-6-(4-metanosulfonil-bencilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	365 $(M+H)^+$

Ejemplo 89

Succinato de 7-Cloro-6-(4-cianobencilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



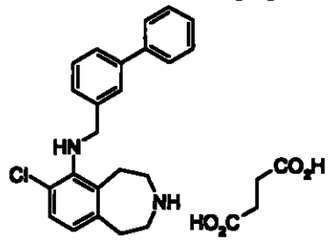
Se usa un método similar al Procedimiento general 5-1 al hacer reaccionar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi -2,3,4,5-tetrahidro-1H-benzo[d]azepina (504 mg, 1.2 mmol), 4-cianobencilamina (476 mg, 3.6 mmol), acetato de

paladio (II) (29 mg, 0.1 mmol), BINAP (148 mg, 0.2 mmol) y carbonato de cesio (540 mg, 1.7 mmol) en tolueno (5 mL). Se purifica por cromatografía en gel de sílice eluido con isohexano/EtOAc (1:0 hasta 1:1) para dar 7-cloro-6-(4-cianobencilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como una goma blanca (108 mg, 22%). EM (ES+) m/z: 408 $(M+H)^+$.

Se usa un método similar al Procedimiento general 1-2 para desproteger 7-cloro-6-(4-cianobencilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (98 mg, 0.2 mmol). Purificación por cromatografía líquida preparativa eluida con un gradiente de agua/acetonitrilo (19:1 hasta 1:19) para dar la base libre del compuesto del título (31 mg, 42%). EM (ES+) m/z: 312 $(M+H)^+$. Se usa un método similar al Procedimiento general 2-1, al usar 7-cloro-6-(4-cianobencilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (31 mg, 0.1 mmol) para dar el compuesto del título como un sólido beige (41 mg, 95%). EM (ES+) m/z: 312 $(M+H)^+$.

Ejemplo 90

Succinato de 7-Cloro-6-(3-fenil-bencilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



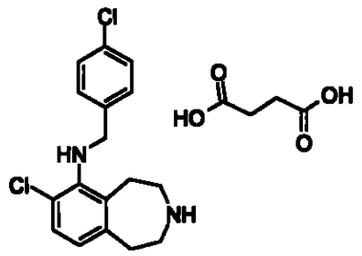
Se usa un método similar al Procedimiento general 5-3 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (0.3 g, 0.706 mmol) con 3-fenil-bencilamina (0.388 g, 2.117 mmol) al usar acetato de paladio (II) (32 mg, 0.141 mmol), tris(dibencilidenacetona)dipaladio(0) (65 mg, 0.070 mmol), BINAP (264 mg, 0.424 mmol) y carbonato de cesio (460 mg, 1.412 mmol) en tolueno (12 mL). Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (1:0, 19:1) para dar 7-cloro-6-(3-fenil-bencilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite (0.257 g, 79%). EM (ES+) m/z: 459 $(M+H)^+$.

Se usa un método similar al Procedimiento general 1-2, al usar 7-cloro-6-(3-fenil-bencilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (237 mg, 0.516 mmol), para dar la base libre del compuesto del título como un aceite (188 mg, 100%) que se usa sin purificación adicional.

Se usa un método similar al Procedimiento general 2-1, al usar 7-cloro-6-(3-fenil-bencilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (188 mg, 0.518 mmol) para dar el compuesto del título como un sólido blanco (191 mg, 77%). EM (ES+) m/z: 363 $(M+H)^+$.

Ejemplo 91

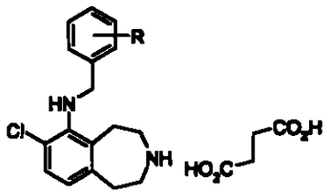
Succinato de 7-Cloro-6-(4-clorobencilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al Procedimiento general 5-3 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (700 mg, 1.6 mmol) con 4-clorobencilamina (354 mg, 2.5 mmol). Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (1:0 y 9:1) y luego Cromatografía SCX para dar 7-cloro-6-(4-clorobencilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (459 mg, 69%). EM (ES+) m/z: 417 $(M+H)^+$.

Se usa un método similar al Procedimiento general 1-1 para desproteger 7-cloro-6-[1-(4-clorobencilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina. Se purifica por cromatografía en gel de sílice eluido con DCM/amoniaco 2M en metanol (95:5) para dar la base libre del compuesto del título. EM (ES+) m/z: 321 $(M+H)^+$. Se usa un método similar al Procedimiento general 2-1 para obtener el compuesto del título.

Los ejemplos 92-98 pueden prepararse esencialmente como se describe en el Ejemplo 91 al usar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina y la amina apropiada. Los rendimientos para la etapa 1 (Procedimiento general 5-3) y los datos EM (ES+) se muestran en la Tabla a continuación.

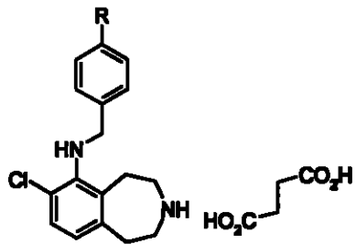


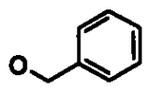
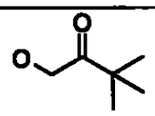
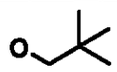
Ej.	R	Compuesto	Rendimiento (%)	EM (ES+) m/z
92	3-Cl	Succinato de 7-Cloro-6-(3-clorobencilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	45	321 $(M+H)^+$
93	3-Cl,4-F	Succinato de 7-Cloro-6-(3-cloro-4-fluoro-bencilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	90	339 $(M+H)^+$

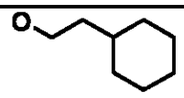
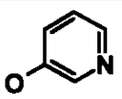
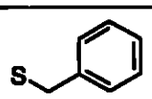
94	2-Cl,4-F	Succinato de 7-Cloro-6-(2-cloro-4-fluoro-bencilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	75	339 $(M+H)^+$
95	3-OCH_3	Succinato de 7-Cloro-6-(3-metoxi-bencilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	84	316 $(M+H)^+$
96	2-F,4-CH_3	Succinato de 7-Cloro-6-(2-fluoro-4-metil-bencilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	53	319 $(M+H)^+$

97	3-OCF_3	Succinato de 7-Cloro-6-(3-trifluorometoxi-bencilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	85	371 $(M+H)^+$
98	3-Cl,4-OCH_3	Succinato de 7-Cloro-6-(3-cloro-4-metoxi-bencilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	100	351 $(M+H)^+$

Los ejemplos 99-106 pueden prepararse esencialmente como se describe en el Ejemplo 91 al usar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina y la amina apropiada. Los rendimientos para la etapa 1 (Procedimiento general 5-3) y Los datos EM (ES+) se muestran en la tabla a continuación.

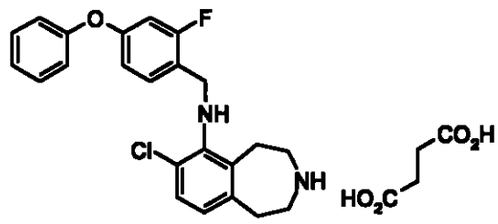


Ej.	R	Compuesto	Rendimiento (%)	EM (ES+) m/z
99		Succinato de 7-Cloro-6-(4-benciloxi-bencilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	87	393 (M+H)+
100		Succinato de 7-Cloro-6-[4-(3,3-dimetil-2-oxo-butoxi)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	20	401 (M+H)+
101		Succinato de 7-Cloro-6-[4-(2,2-dimetilpropoxi)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	23	373 (M+H)+

102		Succinato de 7-Cloro-6-[4-(2-ciclohexiletoxi)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	61	413 (M+H)+
103		Succinato de 7-Cloro-6-[4-(1H-pirazol-1-il)bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	36	353 (M+H)+
104		Succinato de 7-Cloro-6-[4-(piridin-3-iloxi)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	42	380 (M+H)+
105		Succinato de 6-(4-Benziltio-bencilamino)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina	21	409 (M+H)+

Ejemplo 106

Succinato de 7-Cloro-6-(2-fluoro-4-fenoxi-bencilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



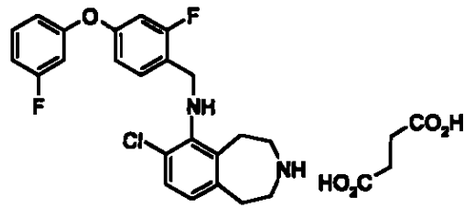
Al usar un método similar al procedimiento general 5-3, se acopla 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (1.1 g, 2.5 mmol) con 2-fluoro-4-fenoxi-bencilamina (550 mg, 2.5 mmol). Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (9:1) y luego Cromatografía SCX para obtener 7-cloro-6-(2-fluoro-4-fenoxi-bencilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina. EM (ES+) m/z: 493 $(M+H)^+$.

Se usa un método similar al Procedimiento general 1-1 para desproteger 7-cloro-6-(2-fluoro-4-fenoxi-bencilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina. Se purifica por cromatografía en gel de sílice eluido con DCM/amoniaco 2M en metanol (95:5) para dar la base libre del compuesto del título (468 mg, 47% en general). EM (ES+) m/z: 397 $(M+H)^+$. Se usa un método similar

al procedimiento general 2-1 para obtener el compuesto del título.

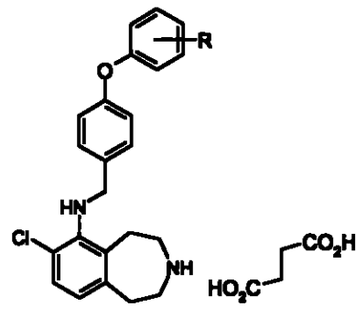
Ejemplo 107

Succinato de 7-Cloro-6-[2-fluoro-4-(3'-fluorofenoxi)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al Ejemplo 106, al usar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (426 mg, 1.0 mmol) y 2-fluoro-4-(3'-fluorofenoxi)-bencilamina (340 mg, 1.4 mmol) para dar la base libre del compuesto del título (162 mg, 39%). EM (ES+) m/z: 415 $(M+H)^+$. Se usa un método similar al Procedimiento general 2-1 para obtener el compuesto del título.

Los ejemplos 108-121 pueden prepararse esencialmente como se describen en el Ejemplo 107 al usar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina y la amina apropiada. Los rendimientos para la etapa 1 (Procedimiento general 5-3) y Los datos EM (ES+) se muestran en la Tabla a continuación.



Ej.	R	Compuesto	Rendimiento (%)	EM (ES+) m/z
108	2-F	Succinato de 7-Cloro-6-[4-(2'-fluorofenoxi)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	44	397 $(M+H)^+$
109	3-F	Succinato de 7-Cloro-6-[4-(3'-fluorofenoxi)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	23	397 $(M+H)^+$
110	4-F	Succinato de 7-Cloro-6-[4-(4'-fluorofenoxi)-bencilamino]-2,3,4,5-tetrahidro-1H-	50	397 $(M+H)^+$

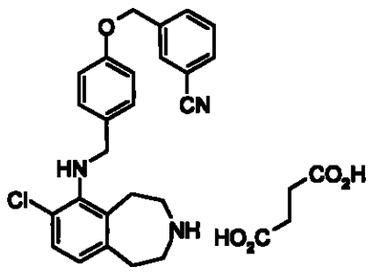
		benzo[d]azepina		
111	3-Cl	Succinato de 7-Cloro-6-[4-(3'-clorofenoxi)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	45	413 $(M+H)^+$
112	3,5-diF	Succinato de 7-Cloro-6-[4-(3',5'-difluorofenoxi)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	36	415 $(M+H)^+$
113	4-CH_3	Succinato de 7-Cloro-6-[4-(4'-metilfenoxi)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	54	393 $(M+H)^+$
114	3-CH_3	Succinato de 7-Cloro-6-[4-(3'-metilfenoxi)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	45	393 $(M+H)^+$
115	2-CH_3	Succinato de 7-Cloro-6-[4-(2'-metilfenoxi)-	54	393 $(M+H)^+$

		bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina		
116	3-^{i}Pr	Succinato de 7-Cloro-6-[4-(3'-isopropilfenoxi)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	49	421 $(M+H)^+$
117	2-^{i}Pr	Succinato de 7-Cloro-6-[4-(2'-isopropilfenoxi)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	40	421 $(M+H)^+$
118	2-CN	Succinato de 7-Cloro-6-[4-(2'-cianofenoxi)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	79	404 $(M+H)^+$
119	3-CN	Succinato de 7-Cloro-6-[4-(3'-cianofenoxi)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	37	404 $(M+H)^+$

120	2-CF_3	Succinato de 7-Cloro-6-[4-(2'-trifluorometil-fenoxi)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	30	447 $(M+H)^+$
121	3-CF_3	Succinato de 7-Cloro-6-[4-(3'-trifluorometil-fenoxi)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	37	447 $(M+H)^+$

Ejemplo 122

Succinato de 7-Cloro-6-[4-(3'-cianobenciloxi)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina

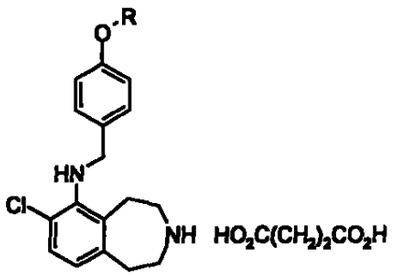


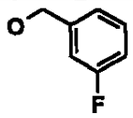
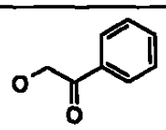
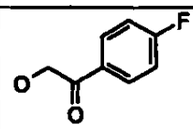
Se mezcla 7-cloro-6-(4-hidroxi-bencilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (150 mg, 0.38 mmol), bromuro de 3-cianobencilo (90 mg, 0.46 mmol),

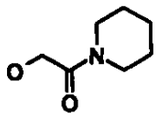
carbonato de potasio en polvo (105 mg, 0.76 mmol), yoduro de potasio en polvo (6.6 mg, 0.04 mmol) y acetona (30 mL). Se agita y se calienta hasta reflujo bajo nitrógeno durante 16 hr. Se diluye con acetona, se filtra, se concentra in vacuo y se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (1:0 y 4:1) para obtener 7-cloro-6-[4-(3'-cianobenciloxi)-bencilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (72.4 mg, 37%). EM (ES+) m/z 514 $(M+H)^+$.

Se usa un método similar al Procedimiento general 1-1 para desproteger 7-cloro-6-[4-(3'-cianobenciloxi)-bencilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina. Se purifica por cromatografía en gel de sílice eluido con DCM/amoniaco 2M en metanol (95:5) para dar la base libre del compuesto del título (42 mg, 71%). EM (ES+) m/z: 418 $(M+H)^+$. Se usa un método similar al Procedimiento general 2-1 para obtener el compuesto del título.

Los ejemplos 123-126 pueden prepararse esencialmente como se describen en el Ejemplo 122 al usar 7-cloro-6-(4-hidroxi-bencilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina y el bromuro apropiado. Los datos de rendimiento generales y EM (ES+) se muestran en la Tabla a continuación.

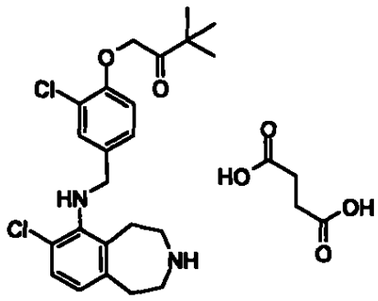


Ej.	O-R	Compuesto	Rendimiento (%)	EM (ES+) m/z
123		Succinato de 7-Cloro-6-[4-(3'-fluorobenciloxi)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	75	411 $(M+H)^+$
124		Succinato de 7-Cloro-6-[4-(2-oxo-2-fenil-etoxi)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	45	421 $(M+H)^+$
125		Succinato de 7-Cloro-6-[4-(2-oxo-2-(4-fluorofenil)-etoxi)-	17	439 $(M+H)^+$

		bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina		
126		Succinato de 7-Cloro-6-[4-(2-oxo-2-piperidin-1-il-etoxi)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	44	428 $(M+H)^+$

Ejemplo 127

Succinato de 7-Cloro-6-[3-cloro-4-(3,3-dimetil-2-oxo-butoxi)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



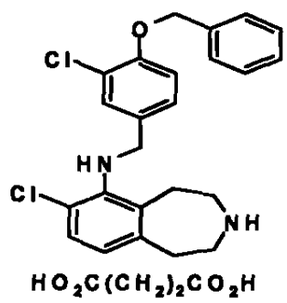
Se usa un método similar al Procedimiento general 4-1 al hacer reaccionar 7-cloro-6-(3-cloro-4-hidroxi-bencilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (438 mg, 1.01 mmol) y 1-bromopinacolona (217 mg, 1.21 mmol). Se purifica por

cromatografía en gel de sílice eluido con EtOAc/hexano (1:4) para dar 7-cloro-6-[3-cloro-4-(3,3-dimetil-2-oxo-butoxi)-bencilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite incoloro (441 mg, 82%). EM (ES+) m/z: 531 $(M+H)^+$.

Se usa un método similar al Procedimiento general 1-1 para desproteger 7-cloro-6-[3-cloro-4-(3,3-dimetil-2-oxo-butoxi)-bencilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (441 mg, 0.83 mmol). Se purifica por cromatografía en gel de sílice eluido con DCM/amoniaco 2M en metanol (93:7) para dar la base libre del compuesto del título (278 mg, 95%). EM (ES+) m/z: 435 $(M+H)^+$. Se usa un método similar al Procedimiento general 2-1 para dar el compuesto del título.

Ejemplo 128

Succinato de 7-Cloro-6-(3-cloro-4-benciloxi-bencilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



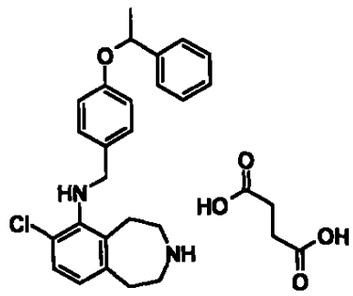
$HO_2C(CH_2)_2CO_2H$

El compuesto del título puede prepararse esencialmente como se describe en el Ejemplo 127, al usar 7-cloro-6-(3-cloro-4-hidroxi-bencilamino)-3-(2,2,2-trifluoroacetil)-

2,3,4,5-tetrahidro-1H-benzo[d]azepina y bromuro de bencilo (64%). EM (ES+) m/z: 427 $(M+H)^+$.

Ejemplo 129

Succinato de (±)-7-Cloro-6-[4-(1-fenil-etoxi)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



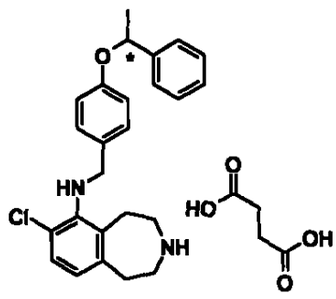
Se usa un método similar al Procedimiento general 5-3, para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (851 mg, 2.0 mmol) y (±)-4-(1-fenil-etoxi)-bencilamina (721 mg, 2.6 mmol). Se purifica por cromatografía en gel de sílice eluido con EtOAc/hexano (1:8) para dar (±)-7-cloro-6-[4-(1-fenil-etoxi)-bencilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (702 mg, 69%). EM (ES+) m/z: 503 $(M+H)^+$.

Se usa un método similar al Procedimiento general 1-1 para desproteger (±)-7-cloro-6-[4-(1-fenil-etoxi)-bencilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (702 mg, 1.40 mmol). Se purifica por

cromatografía en gel de sílice eluido con DCM/amoniaco 2M en metanol (92:8) para dar la base libre del compuesto del título (368 mg, 65 %). EM (ES+) m/z: 407 $(M+H)^+$. Se usa un método similar al Procedimiento general 2-1 para obtener el compuesto del título.

Ejemplos 130 y 131

Succinato de (-)-7-Cloro-6-[4-(1-fenil-etoxi)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina y Succinato de (+)-7-Cloro-6-[4-(1-fenil-etoxi)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



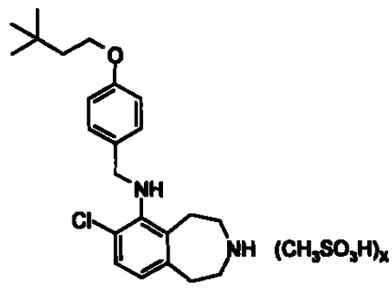
Se separan los dos enantiómeros del ejemplo 129 por CLAR quiral [Chiralcel OJ-H column, acetonitrilo/metanol (20:80) con 0.2% DMEA; relación de flujo 1 mL/min; Isómero 1: t_R=5.0 min, Isómero 2: t_R=6.5 min].

Se usa un método similar al Procedimiento general 2-1 para preparar el succinato de cada enantiómero: Succinato de (-)-7-cloro-6-[4-(1-fenil-etoxi)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina, $[\alpha]^{20}_D$ -17.4° (c 0.5, CH_3OH), y Succinato de (+)-7-cloro-6-[4-(1-fenil-etoxi)-bencilamino]-

2,3,4,5-tetrahidro-1H-benzo[d]azepina, $[\alpha]^{20}_D$ +18.2° (c 0.5, CH_3OH).

Ejemplo 132

Mesilato de 7-Cloro-6-[4-(3,3-dimetilbutoxi)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



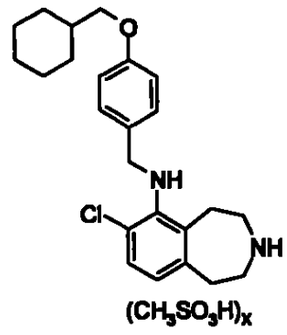
Se usa un método similar al Procedimiento general 5-3 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (426 mg, 1.0 mmol) y 4-(3,3-dimetilbutoxi)-bencilamina (325 mg, 1.5 mmol). Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (1:0 y 9:1) y luego Cromatografía SCX para obtener 7-cloro-6-[4-(3,3-dimetilbutoxi)-bencilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina. EM (ES+) m/z: 483 $(M+H)^+$.

Se usa un método similar al Procedimiento general 1-1 para desproteger 7-cloro-6-[4-(3,3-dimetilbutoxi)-bencilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-

benzo[d]azepina. Se purifica por cromatografía en gel de sílice eluido con DCM/amoniaco 2M en metanol (95:5) para dar la base libre del compuesto del título (161 mg, 42% en general). EM (ES+) m/z: 387 $(M+H)^+$. Se usa un método similar al Procedimiento general 2-4 para obtener el compuesto del título.

Ejemplo 133

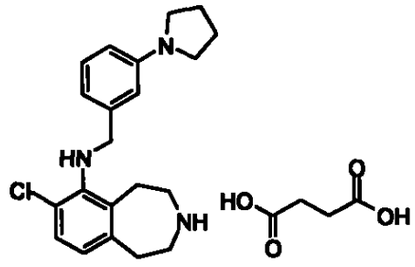
Mesilato de 7-Cloro-6-(4-ciclohexilmetoxi-bencilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



El compuesto del título puede prepararse esencialmente como se describe en el Ejemplo 132, al usar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 4-ciclohexilmetoxi-bencilamina (27% rendimiento, EM (ES+) m/z 399 $(M+H)^+$).

Ejemplo 134

Succinato de 7-Cloro-6-(3-pirrolidinil-bencilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



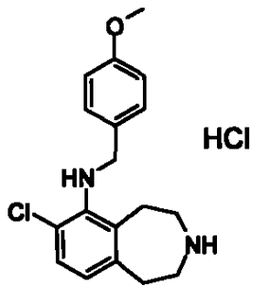
Se usa un método similar al Procedimiento general 5-1, al usar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (300 mg, 0.7 mmol) y 3-(pyrrolidin-1-il)bencilamina (300 mg, 1.7 mmol) para dar, después de cromatografía en gel de sílice eluido con hexano/EtOAc (19:1, 9:1, 4:1 y 3:2), 7-cloro-6-(3-pirrolidinil-bencilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite amarillo (195 mg, 62%). EM (ES+) m/z: 452 $(M+H)^+$.

Se usa un método similar al Procedimiento general 1-1 para desproteger 7-cloro-6-(3-pirrolidinil-bencilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (195 mg, 0.43 mmol). Se purifica por cromatografía SCX para dar la base libre del compuesto del título (136 mg, 89%). Se usa un método similar al Procedimiento general 2-1, al usar 7-cloro-6-(3-

pirrolidinil-bencilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (130 mg, 0.37 mmol), para dar el compuesto del título como una goma blanca opaca (111 mg, 61%). EM (ES+) m/z: 356 $(M+H)^+$.

Ejemplo 135

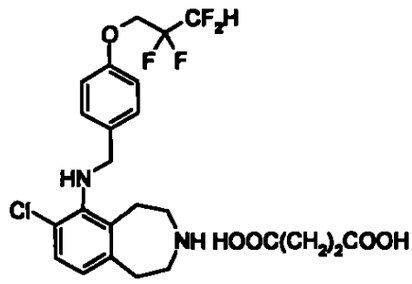
Clorohidrato de 6-(4-Metoxibencilamino)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al procedimiento general 1-1, al usar 6-(4-metoxibencilamino)-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (0.1 g, 0.24 mmol) para dar la base libre del compuesto del título. Se usa un método similar al procedimiento general 2-2 para dar el compuesto del título (75 mg, 80%). EMAR calculado para $C_{18}H_{21}ClN_2O$ 317.1421, encontrado 317.1410.

Ejemplo 136

Succinato de 7-Cloro-6-[4-(2,2,3,3-tetrafluoropropoxi)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina

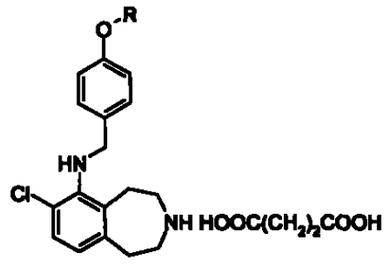


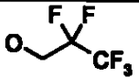
Se usa un método similar al Procedimiento general 5-2 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (500 mg, 1.2 mmol) con 4-(2,2,3,3-tetrafluoropropoxi)-bencilamina (835 mg, 3.5 mmol) en tolueno (10 mL). Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (10:1, 5:1 y 3:1) seguido por cromatografía SCX [se pre-lava la columna con metanol seguido por DCM, se carga el material disuelto en DCM, luego se eluye con DCM/amoniaco 2M en metanol (1:1) y se concentra in vacuo] para obtener 7-cloro-6-[4-(2,2,3,3-tetrafluoropropoxi)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (600 mg, 99%).

Se usa un método similar al procedimiento general 1-3 para desproteger 7-cloro-6-[4-(2,2,3,3-tetrafluoropropoxi)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (600 mg, 1.2 mmol). Se purifica por cromatografía en gel de sílice eluido con DCM/amoniaco 2M en metanol (99:1 hasta 90:10) para dar la base libre del compuesto del título. Se usa un método

similar al Procedimiento general 2-1 para dar el compuesto del título (390 mg, 62 %). EM (ES+) m/z: 417 $(M+H)^+$.

Los ejemplos 137-138 pueden prepararse esencialmente como se describen en el Ejemplo 136 al usar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina y la amina apropiada. Los datos de rendimiento general y EM (ES+) se muestran en la Tabla a continuación.

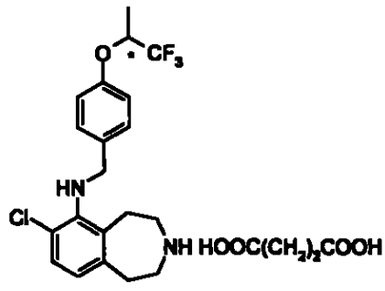


Ej.	O-R	Compuesto	Rendimiento (%)	EM (ES+) m/z
137		Succinato de 7-Cloro-6-[4-(2,2,3,3,3-pentafluoropropoxi)-	45	435 $(M+H)^+$

		bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina		
138		Succinato de 7-Cloro-6-[4-(2,2,2-trifluoro-1,2-dimetil-etoxi)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	66	413 (M+H)+

Ejemplos 139 y 140

Succinato de (-)-7-Cloro-6-[4-(2,2,2-trifluoro-1-metil-etoxi)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina y Succinato de (+)-7-Cloro-6-[4-(2,2,2-trifluoro-1-metil-etoxi)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al procedimiento general 5-2 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (500 mg, 1.2 mmol) con (±)-4-(2,2,2-trifluoro-1-metil-etoxi)-bencilamina (515 mg, 2.3 mmol) en

tolueno (10 mL). Se purifica cromatografía en gel de sílice eluido con hexano/EtOAc (10:1, 5:1 y 3:1) seguido por cromatografía SCX [se pre-lava la columna con metanol seguido por DCM, se carga material disuelto en DCM, luego se eluye con DCM/amoniaco 2M en metanol (1:1) y se concentra in vacuo] para dar (±)-7-cloro-6-[4-(2,2,2-trifluoro-1-metil-etoxi)-bencilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (530 mg, 90%). CG-EM m/z: 494 (M^+).

Se usa un método similar al Procedimiento general 1-3 para desproteger (±)-7-cloro-6-[4-(2,2,2-trifluoro-1-metil-etoxi)-bencilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (520 mg, 1.1 mmol). Se purifica por cromatografía en gel de sílice eluido con DCM/amoniaco 2M en metanol (99:1 hasta 90:10) para dar (±)-7-cloro-6-[4-(2,2,2-trifluoro-1-metil-etoxi)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina. Se usa un método similar al procedimiento general 2-1 para obtener Succinato de (±)-7-cloro-6-[4-(2,2,2-trifluoro-1-metil-etoxi)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina.

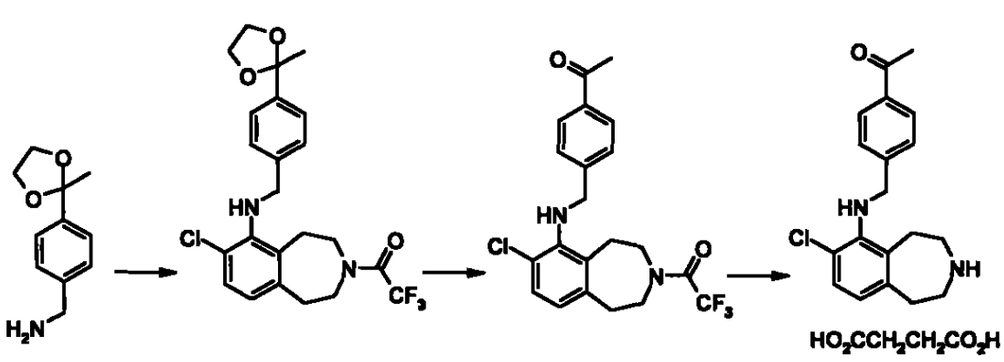
Se separan los dos enantiómeros de succinato de (±)-7-cloro-6-[4-(2,2,2-trifluoro-1-metil-etoxi)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina por cromatografía quiral de fase normal (Chiralpak AD 8x30 cm, elute con 85:15 heptano/3A etanol con 0.2% DMEA).

Se usa un método similar al Procedimiento general 2-1 para obtener Succinato de (-)-7-cloro-6-[4-(2,2,2-trifluoro-1-metil-etoxi)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina [137 mg, 71% recuperación, 98% ee (Chiralpak AD, 4.6x150 mm, eluyente: 85:15 heptano/isopropanol con 0.2% DMEA, 0.6 mL/min)]. EM (ES+) m/z: 399 $(M+H)^+$. $[\alpha]^{20}_D$ -7.9° (c 0.5, MeOH).

Se usa un método similar al Procedimiento general 2-1 para obtener Succinato de (+)-7-cloro-6-[4-(2,2,2-trifluoro-1-metil-etoxi)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina [133 mg, 69% recuperación, 97% ee (Chiralpak AD, 4.6x150 mm, eluyente: 85:15 heptano/isopropanol con 0.2% DMEA, 0.6 mL/min)]. EM (ES+) m/z: 399 $(M+H)^+$. $[\alpha]^{20}_D$ +9.2° (c 0.5, MeOH).

Ejemplo 141

Succinato de 6-(4-acetil-bencilamino)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al Procedimiento general 5-3 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (200 mg, 0.47 mmol) con 4-(2-metil-[1,3]dioxolan-2-il)-bencilamina (preparado por seguir el procedimiento descrito en J. Med. Chem. 1978, 21, 507) (182 mg, 0.94 mmol). Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (1:0, 19:1 y 9:1) para dar 6-{4-(2-metil-[1,3]dioxolan-2-il)bencilamino}-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite (150 mg, 68%). CG-EM m/z 468 (M^+).

Se disuelve 6-{4-(2-metil-[1,3]dioxolan-2-il)bencilamino}-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (150 mg, 0.32 mmol) en metanol (5 mL) y se agrega HCl acuoso 1N (1 mL). Se agita la solución a temperatura ambiente durante 2 h. Se elimina el solvente, se disuelve el residuo en DCM y se lava con $NaHCO_3$ acuoso saturado. La fase orgánica se seca sobre Na_2SO_4, se filtra y se concentra. Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (1:0, 9:1, 17:3 y 4:1) para obtener 6-(4-acetil-bencilamino)-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-

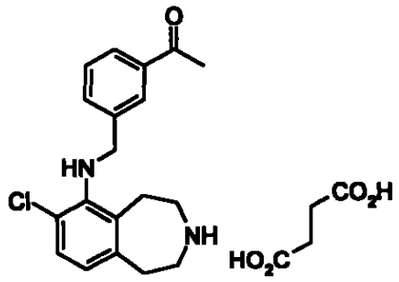
tetrahidro-1H-benzo[d]azepina como un aceite (107 mg, 79%). CG-EM m/z 424 (M^+).

Se usa un método similar al Procedimiento general 1-2, al usar 6-(4-acetil-bencilamino)-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (100 mg, 0.23 mmol), para dar la base libre del compuesto del título como un aceite (76 mg, 99%) que se usa sin purificación adicional.

Se usa un método similar al Procedimiento general 2-1, al usar 6-(4-acetil-bencilamino)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina (76 mg, 0.23 mmol), para dar el compuesto del título como un sólido blanco (102 mg, 97%). EM (ES+) m/z: 329 $(M+H)^+$.

Ejemplo 142

Succinato de 6-(3-Acetilbencilamino)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina

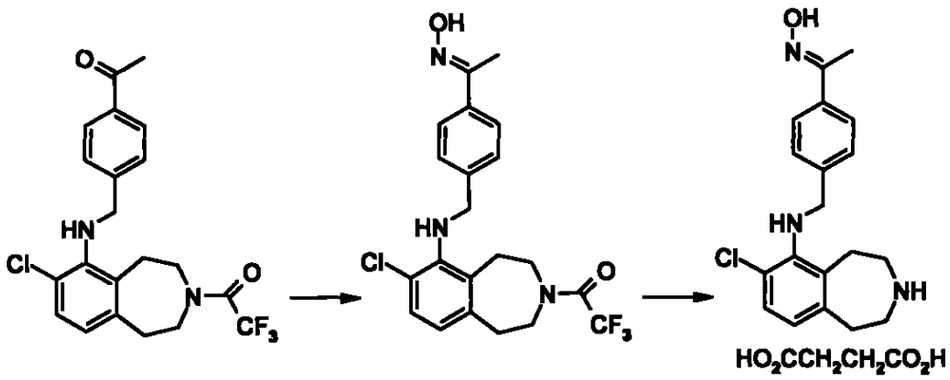


Se usa un método similar al Ejemplo 141, al usar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 3-(2-metil-[1,3]dioxolan-2-il)-bencilamina (preparado por seguir el procedimiento

descrito en J. Med. Chem. 2000, 43, 3315), para dar el compuesto del título como un sólido. EM (ES+) m/z: 329 $(M+H)^+$.

Ejemplo 143

Succinato de 7-Cloro-6-[4-(1-hidroxiiminoetil)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se agrega clorohidrato de hidroxilamina (19 mg, 0.27 mmol) y piridina (0.04 mL, 0.54 mmol) a una solución de 6-(4-acetilbencilamino)-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (115 mg, 0.27 mmol) en etanol (10 mL). Se calienta la mezcla reflujo durante 2 h. Se elimina el solvente in vacuo y se divide el residuo entre DCM y HCl acuoso 0.1N. La fase orgánica se seca sobre Na_2SO_4, se filtra y se concentra. Se disuelve el aceite en la cantidad minima de éter y se agrega hexano al precipitado sólido. Se filtra para obtener 7-cloro-6-[4-(1-hidroxiiminoetil)-bencilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

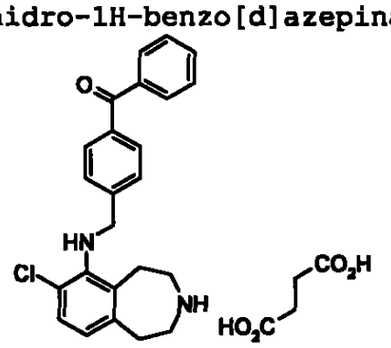
como un sólido (112 mg, 94%) que se usa sin purificación adicional. EM (ES+) m/z: 440 $(M+H)^+$.

Se usa un método similar al Procedimiento general 1-2, al usar 7-cloro-6-[4-(1-hidroxiiminoetil)-bencilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (100 mg, 0.23 mmol), para dar 7-cloro-6-[4-(1-hidroxiiminoetil)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite (61 mg, 78%) que se usa sin purificación adicional.

Se usa un método similar al Procedimiento general 2-1, al usar 7-cloro-6-[4-(1-hidroxiiminoetil)bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina(58 mg, 0.17 mmol) para dar el compuesto del título como un sólido blanco (68 mg, 87%). EM (ES+) m/z: 344 $(M+H)^+$.

Ejemplo 144

Succinato de 6-(4-Benzoil-bencilamino)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al Procedimiento general 5-3 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-

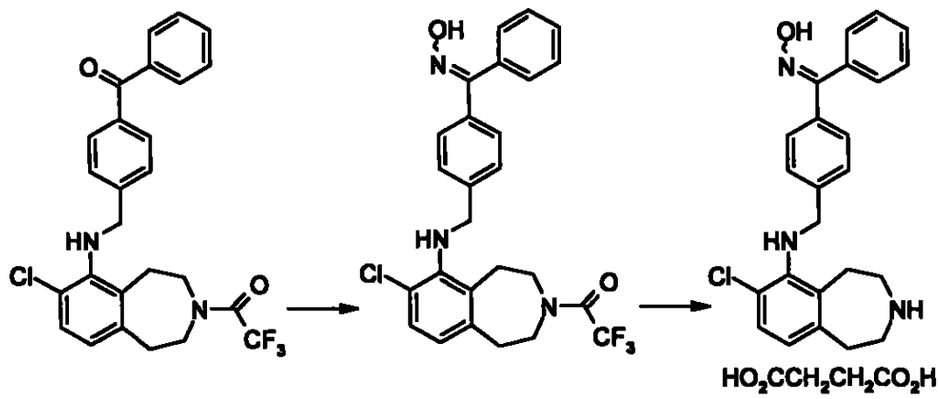
benzo[d]azepina (272 mg, 0.64 mmol) con 4-(aminometil)benzofenona (preparado por seguir el procedimiento descrito en J. Biol. Chem. 1993, 268 (19), 14230) (270 mg, 1.3 mmol). Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (1:0, 9:1, 17:3 y 4:1) para dar 6-(4-benzoil-bencilamino)-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite (300 mg, 96%).

Se usa un método similar al Procedimiento general 1-2, al usar 6-(4-benzoil-bencilamino)-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (80 mg, 0.16 mmol), para dar 6-(4-benzoil-bencilamino)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite (47 mg, 73%) que se usa sin purificación adicional.

Se usa un método similar al Procedimiento general 2-1, al usar (4-benzoil-bencilamino)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina (45 mg, 0.11 mmol), para dar el compuesto del título como un sólido blanco (37 mg, 63%). EM (ES+) m/z: 391 $(M+H)^+$.

Ejemplo 145

Succinato de 7-Cloro-6-[4-(1-hidroxiiminobencil)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se agrega clorohidrato de hidroxilamina (52 mg, 0.75 mmol) y piridina (0.1 mL) a una solución de 6-(4-benzoil-bencilamino)-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (91 mg, 0.19 mmol) en etanol (10 mL). Se calienta la mezcla a reflujo durante la noche. Se elimina el solvente in vacuo y se divide el residuo entre DCM y HCl acuoso 0.1N. La fase orgánica se seca sobre Na_2SO_4, se filtra y se concentra. Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (1:0, 4:1 y 3:1) para dar 7-cloro-6-[4-(1-hidroxiiminobencil)-bencilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como una mezcla de E/Z isómeros (93 mg, 99%).

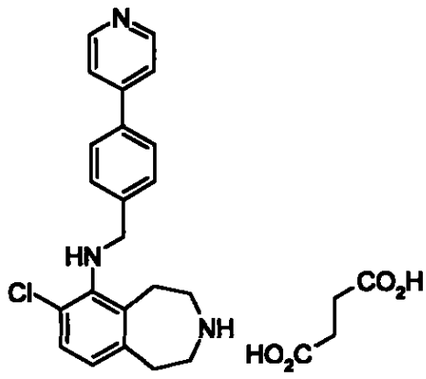
Se usa un método similar al Procedimiento general 1-2, al usar 7-cloro-6-[4-(1-hidroxiiminobencil)bencilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (97 mg, 0.19 mmol), para dar 7-cloro-6-[4-(1-hidroxiiminobencil)-bencilamino]-2,3,4,5-tetrahidro-1H-

benzo[d]azepina como un aceite (68 mg, 87%) que se usa sin purificación adicional.

Se usa un método similar al Procedimiento general 2-1, al usar 7-cloro-6-[4-(1-hidroxiiminobencil)bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina (65 mg, 0.16 mmol), para dar el compuesto del título como un sólido blanco (67 mg, 80%). EM (ES+) m/z: 406 $(M+H)^+$.

Ejemplo 146

Succinato de 7-Cloro-6-[4-(piridin-4-il)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina

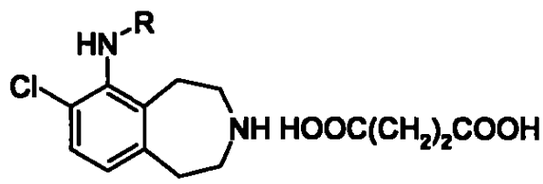


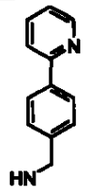
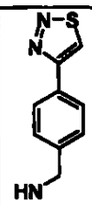
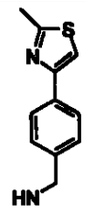
Se usa un método similar al Procedimiento general 5-3, al usar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (178 mg, 0.426 mmol) y una solución de 4-(piridin-4-il)-bencilamina (116 mg, 0.63 mmol) en THF/tolueno (1:1, 8 mL). Se purifica por cromatografía en

gel de sílice eluido con hexano/EtOAc (1:0, 7:3 y 1:1) para dar 7-cloro-6-[4-(4-piridin-4-il)-bencilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite (120 mg, 63%). EM (ES+) m/z: 460 $(M+H)^+$.

Se usa un método similar al Procedimiento general 1-2, al usar 7-cloro-6-[4-(piridin-4-il)-bencilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (153 mg, 0.33 mmol), para dar 7-cloro-6-[4-(piridin-4-il)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite (110 mg, 91%) que se usa sin purificación adicional. Se usa un método similar al Procedimiento general 2-1, al usar 7-cloro-6-[4-(piridin-4-il)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina (105 mg, 0.289 mmol) para dar el compuesto del título como un sólido blanco (123 mg, 88%). EM (ES+) m/z: 364 $(M+H)^+$.

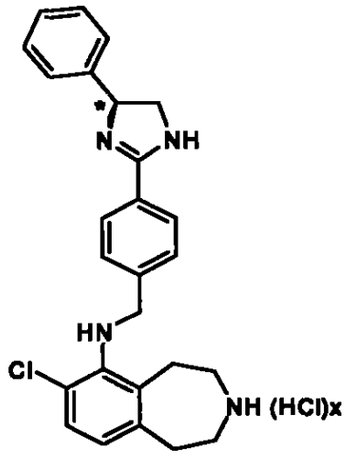
Los ejemplos 147-149 pueden prepararse esencialmente como se describe en el Ejemplo 146 al usar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina y la amina apropiada. Los datos de rendimiento generales y EM (ES+) se muestran en la Tabla a continuación.



Ej.	NH-R	Compuesto	Rendimiento (%)	EM (ES+) m/z
147		Succinato de 7-Cloro-6-[4-(piridin-2-il)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	32	364 $(M+H)^+$
148		Succinato de 7-Cloro-6-[4-(1,2,3-tiadiazol-4-il)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	23	371 $(M+H)^+$
149		Succinato de 7-Cloro-6-[4-(2-metiltiazol-4-il)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	22	384 $(M+H)^+$

Ejemplo 150

Clorohidrato de (-)-7-Cloro-6-[4-(4-fenil-4,5-dihidro-1H-imidazol-2-il)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina

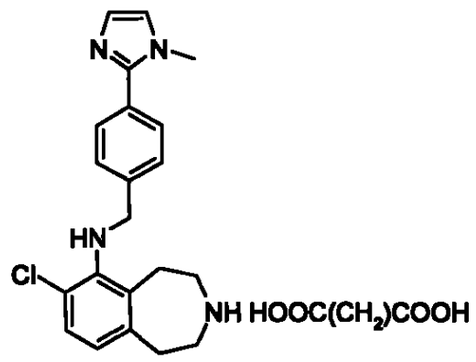


Se mezcla 7-cloro-6-(4-cianobencilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (200mg, 0.49 mmol, 1.0 equiv.), 1-(R)-fenil-etano-1,2-diamina (600 mg, 4.4 mmol, preparado como se describe en J. Org. Chem. 1997, 62, 3586) y monohidrato del ácido p-toluensulfónico (102 mg, 0.53 mmol) en un tubo sellado equipado con un agitador magnético. Se calienta la mezcla a 200°C durante 16 h. Se enfría la mezcla a temperatura ambiente. Se diluye con DCM (50 mL) y se lava con $NaHCO_3$ acuoso saturado (10 mL). Se colecta la fracción orgánica y se concentra in vacuo. Se purifica por cromatografía en gel de sílice eluido con DCM/amoniaco 2M en metanol (98:2 hasta 80:20).

Se usa un método similar al Procedimiento general 2-3 para dar el compuesto del título como el clorohidrato. Se usa CLAR de fase inversa [Columna: Simetría C18, 10x300 mm, flujo = 25 mL/min, agua con 0.1% TFA/Acetonitrilo (9:1 hasta 2:3)] seguido por cromatografía SCX para obtener la base libre del compuesto del título. Se usa un método similar al Procedimiento general 2-3 para obtener el compuesto del título (38 mg, 16%). EM (ES+) m/z: 431 $(M+H)^+$. $[\alpha]^{20}_D$ -20° (c 0.5, MeOH).

Ejemplo 151

Succinato de 7-Cloro-6-[4-(1-metil-1H-imidazol-2-il)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



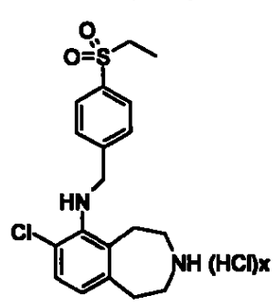
Se usa un método similar al Procedimiento general 5-2 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (455 mg, 1.1 mmol) con 4-(1-metil-1H-imidazol-2-il)-bencilamina (240 mg, 1.3 mmol) en tolueno (8

mL). Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (10:1, 5:1 y 3:1) seguido por cromatografía SCX [se pre-lava la columna con metanol seguido por DCM, se carga material disuelto en DCM, luego se eluye con DCM/amoniaco 2M en metanol (1:1) y se concentra in vacuo] para obtener 7-cloro-6-[4-(1-metil-1H-imidazol-2-il)-bencilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (429 mg, 93%). EM (ES+) m/z: 463 $(M+H)^+$.

Se usa un método similar al Procedimiento general 1-3 para desproteger 7-cloro-6-[4-(1-metil-1H-imidazol-2-il)-bencilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina. Se purifica por cromatografía en gel de sílice eluido con DCM/amoniaco 2M en metanol (99:1 hasta 90:10) para dar la base libre del compuesto del título. Se usa un método similar al Procedimiento general 2-1 para dar el compuesto del título (350 mg, 73 %). EM (ES+) m/z: 367 $(M+H)^+$.

Ejemplo 152

Clorohidrato de 7-Cloro-6-(4-etansulfonil-bencilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

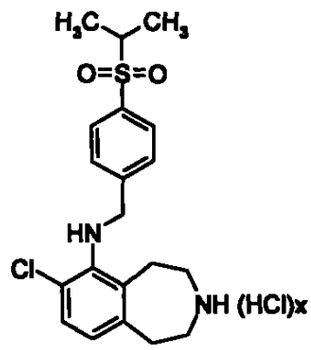


Se usa un método similar al Procedimiento general 5-2, al usar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (0.2 g, 0.35 mmol) y 4-etansulfonil-bencilamina (0.2 g, 1.06 mmol) para dar 7-cloro-6-(4-etansulfonil-bencilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite incoloro.

Se usa un método similar al Procedimiento general 1-1 para obtener la base libre del compuesto del título como un aceite amarillo. Se usa un método similar al Procedimiento general 2-2 para formar la sal de clorohidrato. Se purifica por CLAR preparativa de fase inversa (Zorbax SB-Fenil 21.2x250 mm, 5 micron, 22 mL/min de 0.1% HCl en agua/acetonitrilo (9:1 hasta 1:1) durante 30 min, detector a 230 nm) para obtener el compuesto del título como un sólido blanco (57 mg, 36%). EM (ES+) m/z: 379 $(M+H)^+$.

Ejemplo 153

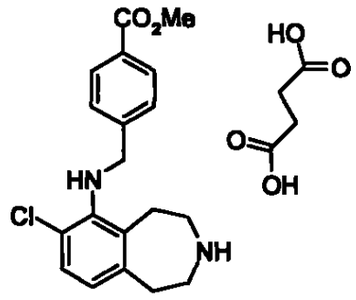
Clorohidrato de 7-Cloro-6-[4-(2-propanosulfonil)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



El compuesto del título puede prepararse esencialmente como se describe en el Ejemplo 152, al usar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 4-(2-propanosulfonil)-bencilamina (11% rendimiento, EM (ES+) m/z 393 $(M+H)^+$).

Ejemplo 154

Succinato de 7-Cloro-6-(4-metoxicarbonil-bencilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



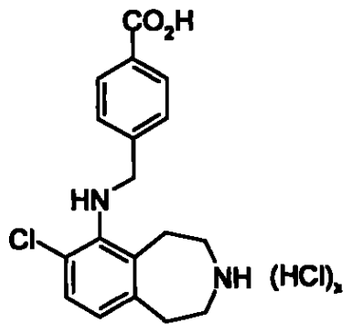
Se trata clorohidrato de éster de metilo del ácido 4-aminometil-benzoico (0.2 g, 0.71 mmol) con K_2CO_3 (1.0 g, 0.71 mmol) en una mezcla de tolueno/agua (1:1, 2 mL). Se separa la capa orgánica, se seca sobre Na_2SO_4 anhidro y se usa como una solución de tolueno para la siguiente etapa. Se usa un método similar al Procedimiento general 5-2, al usar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (0.1 g, 0.24 mmol) y éster de metilo del ácido 4-aminometil-benzoico (0.2 g, 0.71 mmol) para dar 7-cloro-6-(4-metoxicarbonil-bencilamino)-3-(2,2,2-

trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite incoloro.

Se usa un método similar al Procedimiento general 1-1 para obtener la base libre del compuesto del título como un aceite amarillo. Se usa un método similar al Procedimiento general 2-1 para obtener el compuesto del título como un sólido blanco (20 mg, 18%). EM (ES+) m/z: 345 $(M+H)^+$.

Ejemplo 155

Clorohidrato de 6-(4-Carboxi-bencilamino)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina

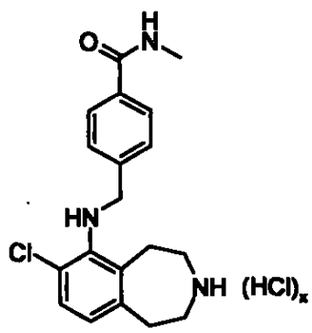


Se combina 7-cloro-6-(4-metoxicarbonil-bencilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (70 mg, 0.16 mmol), carbonato de potasio (0.87 g, 6.3 mmol), metanol (2 mL), agua (2 mL) y se calienta a 50°C durante 3 h. Se purifica por cromatografía SCX para obtener 6-(4-Carboxi-bencilamino)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite amarillo.

Se usa un método similar al Procedimiento general 2-2 para formar la sal de clorohidrato. Se purifica por CLAR preparativa de fase inversa [Zorbax SB-Fenil 21.2x250 mm, 5 micron, 22 mL/min de 0.1% HCl en agua/acetonitrilo (9:1 hasta 1:1) durante 30 min, detector a 230 nm] para obtener el compuesto del título como un sólido blanco (30 mg, 46%). EM (ES+) m/z: 331 $(M+H)^+$.

Ejemplo 156

Clorohidrato de 7-Cloro-6-(4-metilcarbamoil-bencilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

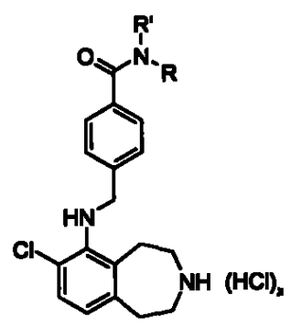


Se combina 3-(tert-butoxicarbonil)-6-(4-Carboxi-bencilamino)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina (0.1 g, 0.3 mmol), clorohidrato de metilamina (31 mg, 0.46 mmol), trietilamina (0.1 g, 0.9 mmol), HATU (0.2 g, 0.5 mmol), DMF anhidro (3 mL) y se agita a temperatura ambiente durante 17 h. Se divide la mezcla de reacción entre salmuera (5 mL) y dietil éter (5 mL), se separa la capa orgánica y se seca sobre Na_2SO_4 anhidro. Se evapora el solvente para obtener

3-(tert-butoxicarbonil)-7-cloro-6-(4-metilcarbamoil-bencilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite amarillo (0.1 g, 93%). EM (ES+) m/z: 344 $(M+H-Boc)^+$.

Se usa un método similar al Procedimiento general 1-5 y se purifica el residuo por cromatografía SCX para obtener la base libre del compuesto del título como un aceite amarillo. Se usa un método similar al Procedimiento general 2-2 para formar la sal de clorohidrato. Se purifica por CLAR preparativa de fase inversa [Zorbax SB-Fenil 21.2x250 mm, 5 micron, 22 mL/min de 0.1% HCl en agua/acetonitrilo (9:1 hasta 1:1) durante 30 min, detector a 230 nm] para obtener el compuesto del título como un sólido blanco (0.9 g, 65%). EM (ES+) m/z: 344 $(M+H)^+$.

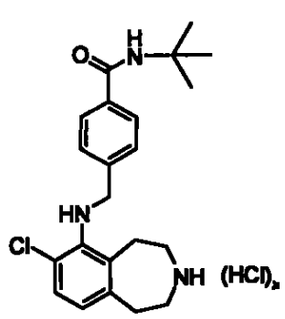
Los ejemplos 157-158 pueden prepararse esencialmente como se describen en el Ejemplo 156 al usar 3-(tert-butoxicarbonil)-6-(4-Carboxi-bencilamino)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina y la amina apropiada. Los datos de rendimiento general y EM (ES+) se muestran en la Tabla a continuación.



Ej.	R	R'	Compuesto	Rendimiento (%)	EM (ES+) m/z
157	Me	Me	Clorohidrato de 7-Cloro-6-(4-dimetilcarbamoil-bencilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	51	358 $(M+H)^+$
158	i-Pr	H	Clorohidrato de 7-Cloro-6-(4-isopropilcarbamoil-bencilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	56	372 $(M+H)^+$

Ejemplo 159

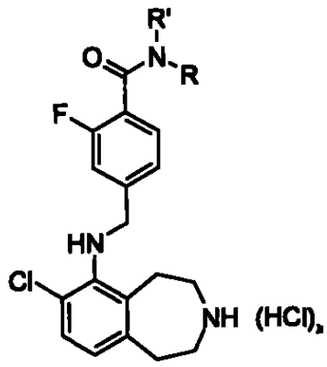
Clorohidrato de 6-(4-tert-Butilcarbamoil-bencilamino)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al Procedimiento general 5-2, al usar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (0.2 g, 0.35 mmol) y 4-aminometil-N-tert-butil-benzamida (0.2 g, 1.06 mmol), para dar 6-(4-tert-butilcarbamoil-bencilamino)-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite incoloro.

Se usa un método similar al Procedimiento general 1-1 para obtener la base libre del compuesto del título como un aceite amarillo. Se usa un método similar al Procedimiento general 2-2 para formar la sal de clorohidrato y se purifica por CLAR preparativa de fase inversa [Zorbax SB-Fenil 21.2x250 mm, 5 micron, 22 mL/min de 0.1% HCl en agua/acetonitrilo (9:1 hasta 1:1) durante 30 min, detector a 230 nm] para obtener el compuesto del título como un sólido blanco (65 mg, 41%). EM (ES+) m/z: 386 $(M+H)^+$.

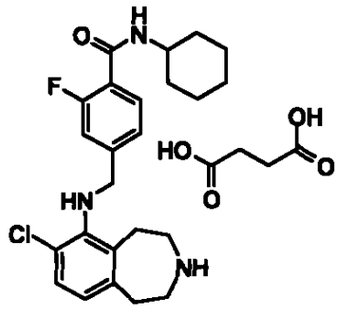
Los ejemplos 160-161 pueden prepararse esencialmente como se describe en el Ejemplo 159 al usar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina y la amina apropiada. Los datos de rendimiento general y EM (ES+) se muestran en la Tabla a continuación.



Ej.	R	R'	Compuesto	Rendimiento (%)	EM (ES+) m/z
160	t-Bu	Me	Clorohidrato de 6-(4-tert-Butilcarbamoil-3-fluoro-bencilamino)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina	48	404 $(M+H)^+$
161	n-Pr	Me	Clorohidrato de 7-Cloro-6-[3-fluoro-4-(N-metil-N-Propil-carbamoil)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	48	404 $(M+H)^+$

Ejemplo 162

Succinato de 7-Cloro-6-[4-(ciclohexilaminocarbonil-)3-fluoro-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al Procedimiento general 5-2 al hacer reaccionar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (500 mg, 1.17 mmol) con 4-aminometil-N-ciclohexil-2-fluoro-benzamida (441 mg, 1.76 mmol). Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (20:1, 10:1, 7:1 y 5:1) para dar 7-cloro-6-[4-(ciclohexilaminocarbonil-)3-fluoro-bencilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite.

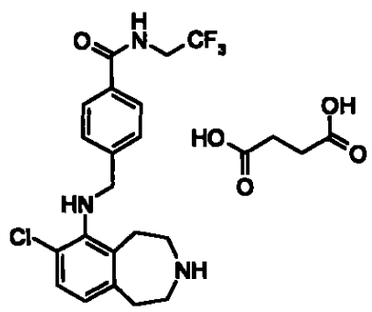
Se usa un método similar al Procedimiento general 1-3 y se purifica por cromatografía en gel de sílice eluido con DCM/amoniaco 2M en metanol (1:0, 20:1. 10:1 y 7:1) seguido por CLAR de fase inversa semi-preparativa [columna SymmetryPrep C18, 7 □m, 19x300 mm eluida con acetonitrilo/0.1

% ácido trifluoroacético en agua (1:9 hasta 8:2) a 20 mL/min] y Cromatografía SCX para dar la base libre del compuesto del título.

Se usa un método similar al Procedimiento general 2-1 para dar el compuesto del título como un sólido amarillo (97 mg, 15%). EM (ES+) m/z: 430 $(M+H)^+$.

Ejemplo 163

Succinato de 7-Cloro-6-[4-(2,2,2-trifluoroetilaminocarbonil)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina

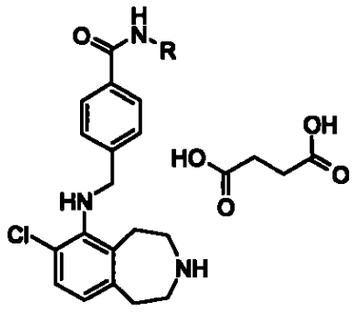


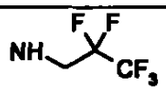
Se usa un método similar al Procedimiento general 5-2 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (250 mg, 0.59 mmol) con 4-aminometil-N-(2,2,2-trifluoroetil)-benzamida (273 mg, 1.17 mmol). Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (20:1, 10:1, 7:1 y 5:1) para dar 7-cloro-3-(2,2,2-trifluoroacetil)-6-[4-(2,2,2-trifluoroetil-

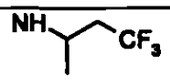
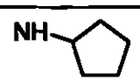
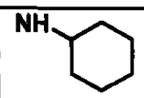
aminocarbonil)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite.

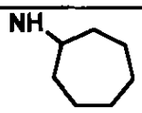
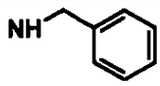
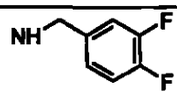
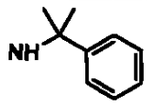
Se usa un método similar al Procedimiento general 1-3 y se purifica por cromatografía en gel de sílice eluido con DCM/amoniaco 2M en metanol (1:0, 20:1. 10:1 y 7:1) para dar la base libre del compuesto del título. Se usa un método similar al Procedimiento general 2-1 para dar el compuesto del título como un sólido blanco (191 mg, 61%). EM (ES+) m/z: 412 $(M+H)^+$.

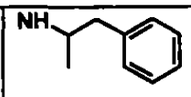
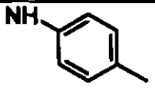
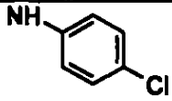
Los ejemplos 164-177 pueden prepararse esencialmente como se describe en el Ejemplo 163 al usar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina y la amina apropiada. Los datos de rendimiento general y EM (ES+) se muestran en la Tabla a continuación.

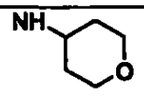


Ej.	NH-R	Compuesto	Rendimiento (%)	EM (ES+) m/z
164		Succinato de 7-Cloro-6-[4-(3,3,3-trifluoro-propilaminocarbonil)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	38	426 (M+H)+
165		Succinato de 7-Cloro-6-[4-(2,2,3,3,3-pentafluoro-propilaminocarbonil)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	41	462 (M+H)+
166		Succinato de (±)-7-Cloro-6-[4-(2,2,2-trifluoro-1-metil-etilaminocarbonil)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	46	426 (M+H)+

167		Succinato de (±)-7-Cloro-6-[4-(1-metil-3,3,3-trifluoro-propilaminocarbonil)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	28	440 (M+H)+
168		Succinato de 7-Cloro-6-[4-(ciclopentilaminocarbonil)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	55	398 (M+H)+
169		Succinato de 7-Cloro-6-[4-(ciclohexilaminocarbonil)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	82	412 (M+H)+

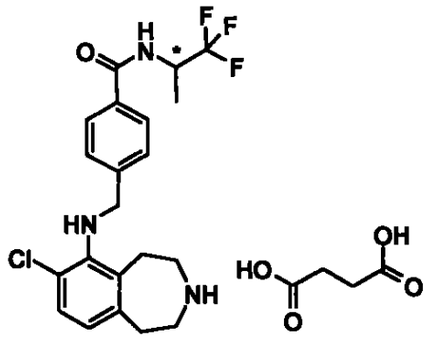
170		Succinato de 7-Cloro-6-[4-(cicloheptilcarbamoil)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	65	426 (M+H)+
171		Succinato de 6-[4-(Bencilaminocarbonil)-bencilamino]-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina	33	420 (M+H)+
172		Succinato de 7-Cloro-6-[4-(3,4-difluoro-bencilaminocarbonil)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	55	456 (M+H)+
173		Succinato de 7-Cloro-6-[4-(1-metil-1-fenil-etilaminocarbonil)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	12	448 (M+H)+

174		Succinato de (±)-7-Cloro-6-[4-(1-metil-2-fenil-etilaminocarbonil)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	36	448 (M+H)+
175		Succinato de 7-Cloro-6-[4-(p-toluilaminocarbonil)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	60	420 (M+H)+
176		Succinato de 7-Cloro-6-[4-(4-cloro-fenilaminocarbonil)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	28	440 (M+H)+

177		Succinato de 7-Cloro-6-[4-(tetrahidro-piran-4-il-aminocarbonil)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	13	414 (M+H)+

Ejemplos 178 y 179

Succinato de (-)-7-Cloro-6-[4-(2,2,2-trifluoro-1-metil-etilaminocarbonil)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina y Succinato de (+)-7-Cloro-6-[4-(2,2,2-trifluoro-1-metil-etilaminocarbonil)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se disuelve (±)-7-cloro-6-[4-(2,2,2-trifluoro-1-metil-etilaminocarbonil)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina (472 mg, 1.11 mmol) en DCM (50 mL) y se agrega di-tert-butil-dicarbonato (300 mg, 1.34 mmol) y una solución de carbonato de sodio (2 g) en agua (50 mL). Se

agita la reacción a temperatura ambiente durante 2 h luego se diluye con DCM, se lava con agua, se seca sobre Na_2SO_4, se filtra y se concentra. Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (10:1, 5:1 y 3:1) para dar (±)-3-tert-butoxicarbonil-7-cloro-6-[4-(2,2,2-trifluoro-1-metil-etilaminocarbonil)-bencilamino]-2,3,4,5-tetrahidro-benzo[d]azepina (330 mg, 57%).

Se separan los dos enantiómeros por CLAR quiral [Columna Chiralpak AD, 8x30 cm, eluida con 0.2% DMEA en heptano/isopropanol (9:1)].

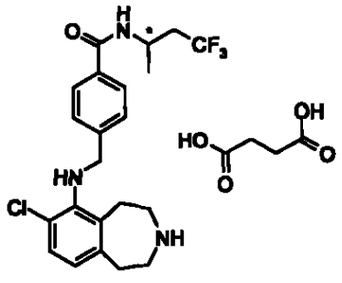
Se usa un método similar al Procedimiento general 1-5 para desproteger el primer compuesto eluyente y se purifica por cromatografía SCX para dar (-)-7-cloro-6-[4-(2,2,2-trifluoro-1-metil-etilaminocarbonil)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina. Se usa un método similar al Procedimiento general 2-1 para dar succinato de (-)-7-cloro-6-[4-(2,2,2-trifluoro-1-metil-etilaminocarbonil)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un sólido blanco (50 mg, 15%). EM (ES+) m/z: 426 $(M+H)^+$; $[\alpha]^{20}_D$ - 3.3° (c 0.5, CH_3OH).

Se usa un método similar al Procedimiento general 1-5 para desproteger el compuesto eluyente segundo y se purifica por cromatografía SCX para dar (+)-7-cloro-6-[4-(2,2,2-trifluoro-1-metil-etilaminocarbonil)-bencilamino]-2,3,4,5-

tetrahidro-1H-benzo[d]azepina. Se usa un método similar al Procedimiento general 2-1 para dar succinato de (+)-7-cloro-6-[4-(2,2,2-trifluoro-1-metil-etilaminocarbonil)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un sólido blanco (55 mg, 16%). EM (ES+) m/z: 426 $(M+H)^+$; $[\alpha]^{20}_D$ +4.4° (c 0.5, CH_3OH).

Ejemplos 180 y 181

Succinato de (+)-7-Cloro-6-[4-(1-metil-3,3,3-trifluoro-propilaminocarbonil)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina y Succinato de (-)-7-Cloro-6-[4-(1-metil-3,3,3-trifluoro-propilaminocarbonil)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se disuelve (±)-7-cloro-3-(2,2,2-trifluoroacetil)-6-[4-(1-metil-3,3,3-trifluoro-propilaminocarbonil)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina (985 mg, 2.24 mmol) en DCM (50 mL) y se agrega di-tert-butil-dicarbonato (605 mg, 3.36 mmol) y una solución de carbonato de sodio (2 g) en agua

(50 mL). Se agita la mezcla a temperatura ambiente durante 1 h luego se diluye con DCM, se lava con agua, se seca sobre Na_2SO_4, se filtra y se concentra. Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (10:1, 5:1 y 3:1) para dar (±)-3-tert-butoxicarbonil-7-cloro-6-[4-(1-metil-3,3,3-trifluoro-propilaminocarbonil)-bencilamino]-2,3,4,5-tetrahidro-benzo[d]azepina.

Se separan los dos enantiómeros por CLAR quiral [Columna Chiralpak AD, 8x30 cm, eluido con heptano/isopropanol/0.2% DMEA en metanol (90:5:5)].

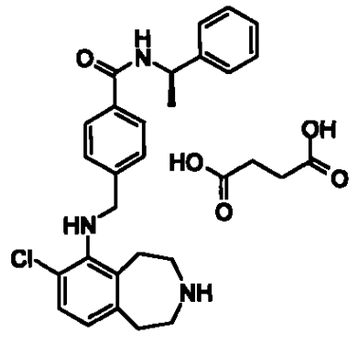
Se usa un método similar al Procedimiento general 1-5 para desproteger el primer compuesto eluyente y se purifica por cromatografía SCX para dar (+)-7-cloro-6-[4-(1-metil-3,3,3-trifluoro-propilaminocarbonil)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina. Se usa un método similar al Procedimiento general 2-1 para dar succinato de (+)-7-cloro-6-[4-(1-metil-3,3,3-trifluoro-propilaminocarbonil)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un sólido blanco (186 mg, 15%). EM (ES+) m/z: 440 $(M+H)^+$; $[\alpha]^{20}_D$ +6.5° (c 0.5, CH_3OH).

Se usa un método similar al Procedimiento general 1-5 para desproteger el segundo compuesto eluyente y se purifica por cromatografía SCX para dar (-)-7-cloro-6-[4-(1-metil-3,3,3-trifluoro-propilaminocarbonil)-bencilamino]-2,3,4,5-

tetrahidro-1H-benzo[d]azepina. Se usa un método similar al Procedimiento general 2-1 para dar succinato de (-)-7-cloro-6-[4-(1-metil-3,3,3-trifluoro-propilaminocarbonil)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un sólido blanco (191 mg, 15%). EM (ES+) m/z: 440 $(M+H)^+$; $[\alpha]^{20}_D$ -5.2° (c 0.5, CH_3OH).

Ejemplo 182

Succinato de (R)-(+)-7-Cloro-6-[4-(1-fenil-etilaminocarbonil)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



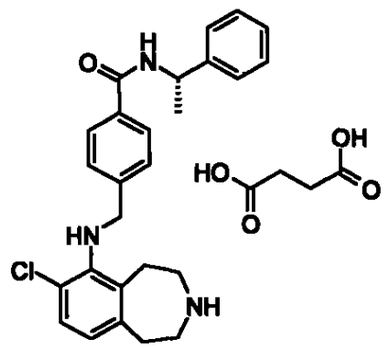
Se usa un método similar al Procedimiento general 5-2 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (250 mg, 0.59 mmol) con (R)-4-aminometil-N-(1-fenil-etil)-benzamida (298 mg, 1.17 mmol) en tolueno (15 mL). Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (20:1, 10:1, 7:1 y 5:1) para dar (R)-(+)-7-cloro-6-[4-(1-fenil-etilcaminocarbonil)-bencilamino]-3-

(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite.

Se usa un método similar al Procedimiento general 1-3 y se purifica por cromatografía en gel de sílice eluido con DCM/amoniaco 2M en metanol (1:0, 20:1. 10:1 y 7:1) para dar la base libre del compuesto del título. Se usa un método similar al Procedimiento general 2-1 para dar el compuesto del título como un sólido amarillo (158 mg, 49%). EM (ES+) m/z: 434 $(M+H)^+$; $[\alpha]^{20}_D$ +18.7° (c 0.5, CH_3OH).

Ejemplo 183

Succinato de (S)-(-)-7-Cloro-6-[4-(1-fenil-etilaminocarbonil)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina

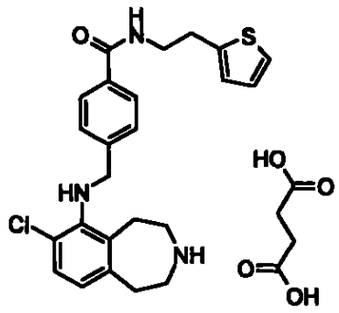


Se usa un método similar al Ejemplo 182, al usar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (250 mg, 0.59 mmol) y (S)-4-aminometil-N-(1-fenil-etil)-benzamida (298 mg, 1.17

mmol) para dar el compuesto del título como un sólido blanco (95 mg, 29%). EM (ES+) m/z: 434 $(M+H)^+$; $[\alpha]^{20}_D$ -20.1° (c 0.5, CH_3OH).

Ejemplo 184

Succinato de 7-Cloro-6-{4-[(2-tiofen-2-il-etil)-carbamoil]-bencilamino}-2,3,4,5-tetrahidro-1H-benzo[d]azepina



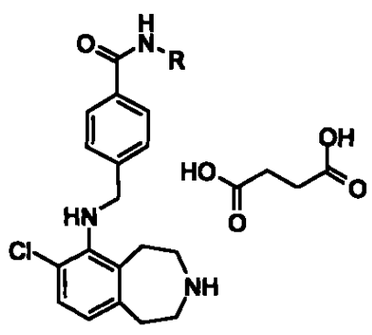
Se usa un método similar al Procedimiento general 5-3, para hacer reaccionar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (250 mg, 0.588 mmol) con 4-aminometil-N-(2-tiofen-2-il-etil)-benzamida (306 mg, 1.176 mmol) al usar acetato de paladio (II) (26 mg, 0.118 mmol), tris(dibencilidenacetona)dipaladio(0) (53 mg, 0.059 mmol), BINAP (220 mg, 0.353 mmol) y carbonato de cesio (383 mg, 1.176 mmol) en dioxano (6 mL). Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (1:0, 7:3 y 1:1) para dar 7-cloro-6-{4-[(2-tiofen-2-il-etil)-carbamoil]-bencilamino}-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-

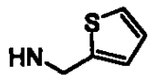
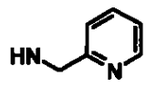
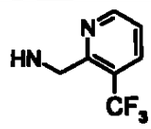
benzo[d]azepina como un aceite (233 mg, 91%). EM (ES+) m/z: 535 $(M+H)^+$.

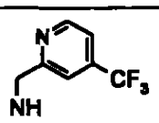
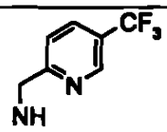
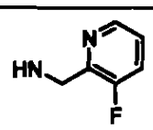
Se usa un método similar al Procedimiento general 1-2, al usar 7-cloro-6-{4-[(2-tiofen-2-il-etil)-carbamoil]-bencilamino}-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (223 mg, 0.416 mmol), para dar 7-cloro-6-{4-[(2-tiofen-2-il-etil)-carbamoil]-bencilamino}-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite (145 mg, 79%) que se usa sin purificación adicional.

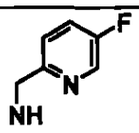
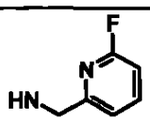
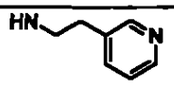
Se usa un método similar al Procedimiento general 2-1, al usar 7-cloro-6-{4-[(2-tiofen-2-il-etil)-carbamoil]-bencilamino}-2,3,4,5-tetrahidro-1H-benzo[d]azepina (145 mg, 0.330 mmol), para dar el compuesto del título como un sólido (123 mg, 67%). EM (ES+) m/z: 440 $(M+H)^+$.

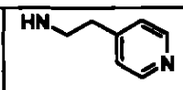
Los ejemplos 185-194 pueden prepararse esencialmente como se describen en el Ejemplo 184 al usar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina y la amina apropiada. Los datos de rendimiento general y EM (ES+) se muestran en la Tabla a continuación.



Ej.	NH-R	Compuesto	Rendimiento (%)	EM (ES+) m/z
185		Succinato de 7-Cloro-6-{4-[(tiofen-2-ilmetil)-carbamoil]-bencilamino}-2,3,4,5-tetrahidro-1H-benzo[d]azepina	46	426 $(M+H)^+$
186		Succinato de 7-Cloro-6-{4-[(piridin-2-ilmetil)-carbamoil]-bencilamino}-2,3,4,5-tetrahidro-1H-benzo[d]azepina	49	421 $(M+H)^+$
187		Succinato de 7-Cloro-6-{4-[(3-trifluorometil-piridin-2-ilmetil)-carbamoil]-bencilamino}-2,3,4,5-tetrahidro-1H-benzo[d]azepina	39	489 $(M+H)^+$

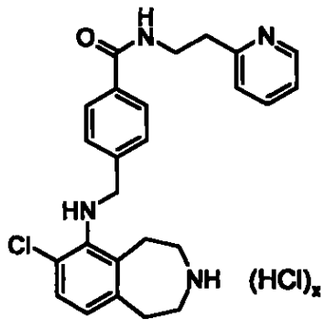
188		Succinato de 7-Cloro-6-{4-[(4-trifluorometil-piridin-2-ilmetil)-carbamoil]-bencilamino}-2,3,4,5-tetrahidro-1H-benzo[d]azepina	26	489 (M+H)$^+$
189		Succinato de 7-Cloro-6-{4-[(5-trifluorometil-piridin-2-ilmetil)-carbamoil]-bencilamino}-2,3,4,5-tetrahidro-1H-benzo[d]azepina	29	489 (M+H)$^+$
190		Succinato de 7-Cloro-6-{4-[(3-fluoro-piridin-2-ilmetil)-carbamoil]-bencilamino}-2,3,4,5-tetrahidro-1H-benzo[d]azepina	37	439 (M+H)$^+$

191		Succinato de 7-Cloro-6-{4-[(5-fluoro-piridin-2-ilmetil)-carbamoil]-bencilamino}-2,3,4,5-tetrahidro-1H-benzo[d]azepina	51	439 (M+H)$^+$
192		Succinato de 7-Cloro-6-{4-[(6-fluoro-piridin-2-ilmetil)-carbamoil]-bencilamino}-2,3,4,5-tetrahidro-1H-benzo[d]azepina	54	439 (M+H)$^+$
193		Succinato de 7-Cloro-6-[4-(2-piridin-3-il-etilcarbamoil)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	46	435 (M+H)$^+$

194		Succinato de 7-Cloro-6-[4-(2-piridin-4-il-etilcarbamoil)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	27	435 $(M+H)^+$

Ejemplo 195

Clorohidrato de 7-Cloro-6-[4-(2-piridin-2-il-etilcarbamoil)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al Procedimiento general 5-3 al hacer reaccionar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (200 mg, 0.471 mmol) y 4-aminometil-N-(2-piridin-2-il-etil)-benzamida (241 mg, 0.942 mmol) al usar acetato de paladio (II) (21 mg,

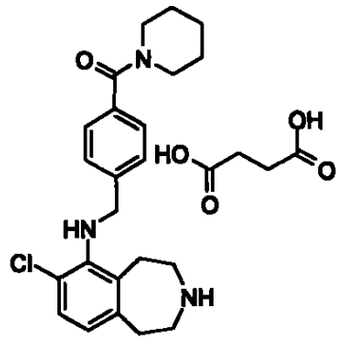
0.094 mmol), tris(dibencilidenacetona)dipaladio(0) (43 mg, 0.047 mmol), BINAP (176 mg, 0.283 mmol) y carbonato de cesio (307 mg, 0.942 mmol) en dioxano (5 mL). Se purifica por cromatografía en gel de sílice eluido con hexano y hexano/EtOAc/DCM/metanol (7:1:1:1) para dar 7-cloro-6-[4-(2-piridin-2-il-etilcarbamoil)-bencilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite (107 mg, 43%). EM (ES+) m/z: 531 $(M+H)^+$.

Se usa un método similar al Procedimiento general 1-2, al usar 7-cloro-6-[4-(2-piridin-2-il-etilcarbamoil)-bencilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (107 mg, 0.202 mmol), para dar 7-cloro-6-[4-(2-piridin-2-il-etilcarbamoil)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite (85 mg, 97%) que se usa sin purificación adicional.

Se usa un método similar al Procedimiento general 2-2, al usar 7-cloro-6-[4-(2-piridin-2-il-etilcarbamoil)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina (85 mg, 0.195 mmol), para dar el compuesto del título como un sólido (103 mg, 97 %). EM (ES+) m/z: 435 $(M+H)^+$.

Ejemplo 196

Succinato de 7-Cloro-6-[4-(piperidina-1-carbonil)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



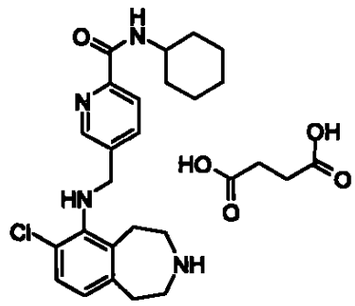
Al usar un método similar al procedimiento general 5-2, para hacer reaccionar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (500 mg, 1.17 mmol) con 4-(piperidin-1- ilcarbonil)-bencilamina (308 mg, 1.41 mmol). Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (20:1, 10:1, 7:1 y 5:1) para dar 7-cloro-6-[4-(piperidina-1-carbonil)-bencilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite.

Se usa un método similar al Procedimiento general 1-3 y se purifica por cromatografía en gel de sílice eluido con DCM/amoniaco 2M en metanol (1:0, 20:1. 10:1 y 7:1) para dar la base libre del compuesto del título. Se usa un método similar al Procedimiento general 2-1 para dar

el compuesto del titulo como un sólido amarillo (284 mg, 47%). EM (ES+) m/z: 398 $(M+H)^+$.

Ejemplo 197

Succinato de 7-Cloro-6-[2-(ciclohexilaminocarbonil-piridin-5-ilmetil)-amino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



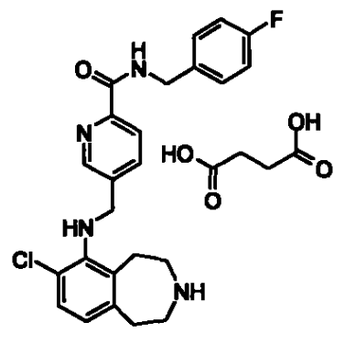
Se usa un método similar al Procedimiento general 5-2 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (348 mg, 0.82 mmol) con ciclohexilamida del ácido 5-aminometil-piridina-2-carboxílico (200 mg, 0.86 mmol). Se purifica por cromatografía en gel de sílice eluido con hexano/EtOAc (20:1, 10:1, 7:1 y 5:1) para dar 7-cloro-6-[2-(ciclohexilaminocarbonil-piridin-5-ilmetil)-amino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como aceite.

Se usa un método similar al Procedimiento general 1-3 y se purifica por cromatografía en gel de sílice eluido con DCM/amoniaco 2M en metanol (1:0, 20:1. 10:1 y 7:1) para dar la base libre del compuesto del título.

Se usa un método similar al Procedimiento general 2-1 para dar el compuesto del título como un sólido amarillo (147 mg, 34%). EM (ES+) m/z: 413 $(M+H)^+$.

Ejemplo 198

Succinato de 7-Cloro-6-[2-(4-fluoro-bencilaminocarbonil)-piridin-5-ilmetil]-amino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina

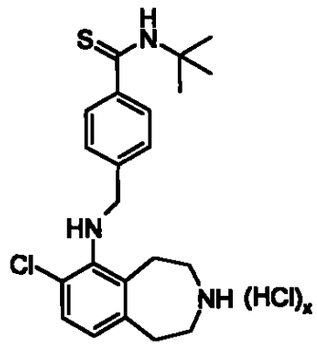


El compuesto del título puede prepararse esencialmente como se describe en el Ejemplo 197, al usar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 4-fluoro-bencilamida del ácido 5-

aminometil-piridina-2-Carboxílico (28% rendimiento, EM (ES+) m/z 439).

Ejemplo 199

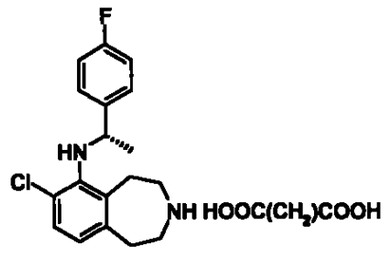
Clorohidrato de 7-Cloro-6-(4-tert-butilthiocarbamoil-bencilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se combina 6-(4-tert-butilcarbamoil-bencilamino)-7-cloro-2,3,4,5-tetrahidro-1H-benzo-[d]azepina (0.3 g, 0.67 mmol), 2,4-bis(4-metoxifenil)-1,3-ditia-2,4-difosfetano-2,4-disulfuro (reactivo de Lawesson) (0.3, g, 0.67 mmol) y 1,4-dioxano anhidro (10 mL) en un tubo sellado y se calienta a 100°C durante 5 h. Se enfría la mezcla de reacción a temperatura ambiente, se evapora el solvente y se purifica el residuo por SCX.

Ejemplo 200

Succinato de (S)-(-)-7-Cloro-6-[1-(4-fluorofenil)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina

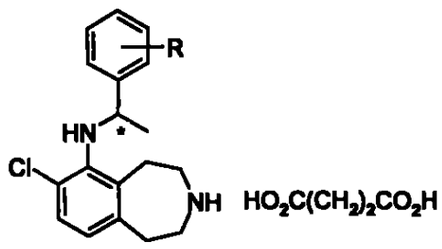


Se usa un método similar al procedimiento general 5-2 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (7.0g, 16.4mmol) con (S)-1-(4-fluorofenil)etilamina (6.9 g, 49.3 mmol) en tolueno (175 mL). Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (9:1 hasta 1:1) seguido por cromatografía SCX [columna de pre-lavado con metanol seguido por DCM, cargado de material disuelto en DCM, luego eluido con DCM/amoniaco 2M en metanol (1:1) y concentrado in vacuo] para dar 7-cloro-6-[1-(S)-(4-fluorofenil)-etilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (3.96 g, 58%). GC-EM m/z: 414 (M^+).

Se usa un método similar al procedimiento general 1-3 para desproteger 7-cloro-6-[1-(S)-(4-fluorofenil)-etilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (3.92 g, 9.5 mmol) y purificación por cromatografía en gel de sílice eluyendo con DCM/amoniaco 2M en metanol (99:1 hasta

80:20) para dar la base libre del compuesto del título. Se usa un método similar al procedimiento general 2-1 y se cristaliza el sólido a partir de etanol y metil-t-butil éter. Se filtra y se seca el sólido en un horno al vacío a 60°C durante la noche para obtener el compuesto del título (3.4 g, 83 %). EM (ES+) m/z: 319 $(M+H)^+$; $[\alpha]^{20}_D$ -102.8° (c 0.5, MeOH).

Los ejemplos 201-209 pueden prepararse esencialmente como se describe en el ejemplo 200 al usar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina y la amina apropiada. Los rendimientos para la etapa 1 (Procedimiento general 5-2), rotación óptica y datos EM (ES+) se muestran en la tabla a continuación.



Ej.	R	Compuesto	Rendimiento (%)	$[\alpha]^{20}_D$ (c, solvente)	EM

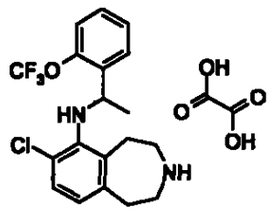
201	4-F	Succinato de (R)-(+)-7-Cloro-6-[1-(4-fluorofenil)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	69	+89.2° (c 0.5, MeOH)	319 (M+H)+
202	2-F	Succinato de (+)-7-Cloro-6-[1-(2-fluorofenil)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	62	+105° (c 0.5, MeOH)	319 (M+H)+
203	4-CN	Succinato de (+)-7-Cloro-6-[1-(4-cianofenil)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	60	+142.1° (c 0.5, MeOH)	326 (M+H)+
204	4-CN	Succinato de (-)-7-Cloro-6-[1-(4-cianofenil)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	52	-149.3° (c 0.5, MeOH)	326 (M+H)+

205	2,3-diF	Succinato de (+)-7-Cloro-6-[1-(2,3-difluorofenil)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	14	+99.3° (c 0.5, MeOH)	337 (M+H)+
206	2,3-diF	Succinato de (-)-7-Cloro-6-[1-(2,3-difluorofenil)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	80	-107.9° (c 0.5, MeOH)	337 (M+H)+
207	2,4-diF	Succinato de (+)-7-Cloro-6-[1-(2,4-difluorofenil)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	94	+101.4° (c 0.5, MeOH)	337 (M+H)+
208	2,4-diF	Succinato de (-)-7-Cloro-6-[1-(2,4-difluorofenil)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	96	-107.9° (c 0.5, MeOH)	337 (M+H)+

209	3,5-diCF$_3$	Succinato de (-)-7-Cloro-6-[1-(3,5-bis-trifluorometil-fenil)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	99	-93° (c 0.5, MeOH)	437 (M+H)$^+$

Ejemplo 210

Oxalato de (+)-7-Cloro-6-[(2-trifluorometoxi-fenil)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina

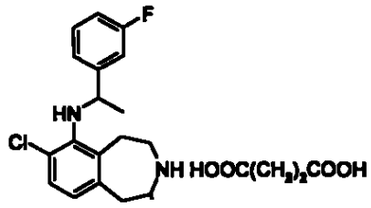


Se usa un método similar al procedimiento general 5-2 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (0.15 g, 0.35 mmol) con 1-(2-trifluorometoxifenil)-etilamina Isómero 2 a 90°C durante 15 h. Se usa un método similar al procedimiento general 1-2 y se purifica por CLAR preparativa de fase inversa para dar la base libre del compuesto del título. Se usa un método similar al procedimiento general 2-5 para dar el compuesto del título (27 mg, 16 %). CLAR t_R = 4.2 min (Chiralpak AD 4.6x150 mm, columna de 3 micrones, 1.0 mL/min de 94.8/5/0.2

heptano/etanol/dimetietilamina isocrática; detector es a 225 nm); EMAR calculado para $C_{19}H_{20}ClF_3N_2O$ 385.1294, encontrado 385.1285; $[\alpha]^{20}_D$ +95.4° (c 0.5, MeOH).

Ejemplo 211

Succinato de (±)-7-Cloro-6-[1-(3-fluorofenil)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



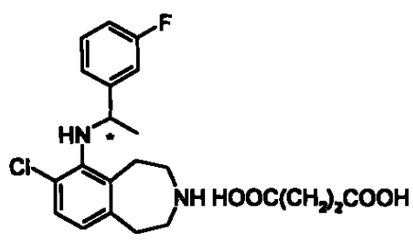
Se agrega acetato de paladio (II) (27 mg, 0.12 mmol), BINAP (146 mg, 0.24 mmol), carbonato de cesio(270 mg, 0.8 mmol) y (±)-1-(3-fluorofenil)-etilamina (230 mg, 1.6 mmol) a una solución de 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (250 mg, 0.6 mmol) en tolueno (9 mL). Se desgasifica la mezcla espesa y se llena con nitrógeno. Se calienta la mezcla a 95°C durante 16 h. Se agrega acetato de paladio (II) adicional (0.1 equiv.) y BINAP (0.2 equiv.) y se continua calentando la reacción durante una 24 horas adicionales. La mezcla fría, se diluye con EtOAc (50 mL) luego se filtra a través de Celite®. Se concentra el filtrado y se purifica por cromatografía en gel de sílice eluyendo con

hexano/EtOAc (9:1 hasta 1:1) seguido por cromatografía SCX para obtener (±)-7-cloro-6-[1-(3-fluorofenil)-etilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (138 mg, 56%). GC-EM m/z: 414 (M^+).

Se usa un método similar al procedimiento general 1-3 para desproteger (±)-7-cloro-6-[1-(3-fluorofenil)-etilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (132 mg, 0.3 mmol) y purificación por cromatografía en gel de sílice eluyendo con DCM/amoniaco 2M en metanol (99:1 hasta 90:10) para dar la base libre del compuesto del título. Se usa un método similar al procedimiento general 2-1 para dar el compuesto del título (98 mg, 70 %). EM (ES+) m/z: 319 $(M+H)^+$.

Ejemplo 212

Succinato de (+)-7-Cloro-6-[1-(3-fluorofenil)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



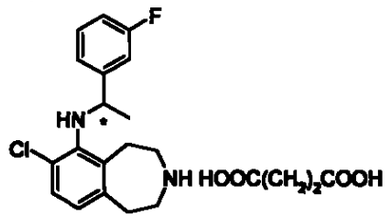
Se separaron los dos enantiómeros de succinato de (±)-7-cloro-6-[1-(3-fluorofenil)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina por cromatografía de fase normal (Chiralpak

AD 2x25 cm, eluida con 95:5 heptano/isopropanol con 0.2 % DMEA).

Se usa un método similar al procedimiento general 2-1 para obtener el compuesto del título [23 mg, 30% de recuperación, 99% ee (Chiralpak AD, 4.6x250 mm, eluyente: 95:5 heptano/isopropanol, con 0.2% DMEA, 1.0 mL/min)]. EM (ES+) m/z: 319 $(M+H)^+$; $[\alpha]^{20}_D$ +64° (c 0.5, MeOH).

Ejemplo 213

Succinato de (-)-7-Cloro-6-[1-(3-fluorofenil)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se agrega tris(dibencilidenacetona)dipaladio(0) (3.4 g, 3.8 mmol), BINAP (4.7 g, 7.5 mmol), carbonato de cesio (8.6 g, 26.3 mmol) y 1-(3-fluorofenil)-etilamina Isómero 2 (5.8 g, 41.3 mmol) a una solución de 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (8.0 g, 18.8 mmol) en tolueno (225 mL). Se desgasifica la mezcla espesa y se llena con nitrógeno. Se calienta la mezcla a 95°C durante 8 h. Se

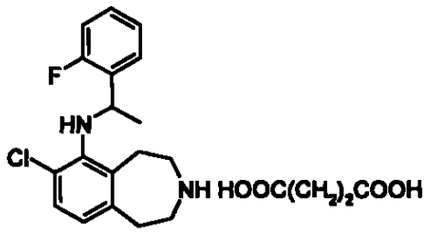
agrega tris(dibencilidenacetona)dipaladio(0) adicional (0.1 equiv.), y BINAP (0.2 equiv.). Se continua calentando la reacción durante 16 horas adicionales. La mezcla fría, se diluye con EtOAc (200 mL) luego se filtra a través de Celite®. Se concentra in vacuo y se purifica por cromatografía en gel de sílice eluyendo con hexano/EtOAc (9:1) seguido por cromatografía SCX para obtener 7-cloro-6-[1-(3-fluorofenil)-etilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (6.0 g, 78%). GC-EM m/z: 414 (M^+).

Se usa un método similar al procedimiento general 1-3 para desproteger 7-cloro-6-[1-(3-fluorofenil)-etilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (6.0 g, 14.4 mmol). Purificación por cromatografía en gel de sílice eluyendo con DCM/amoniaco 2M en metanol (99:1 hasta 90:10) para dar la base libre del compuesto del título. Se usa un método similar al procedimiento general 2-1 y se cristaliza el sólido a partir de etanol y metil-t-butil éter. Se filtra y se seca el sólido bajo vacío a 60°C durante la noche para obtener el compuesto del título [5.3 g, 84 % rendimiento, 99% ee (Chiralpak AD, 4.6x250 mm, eluyente: 95:5 heptano/EtOH, con 0.2% DMEA,

1.0 mL/min)]. EM (ES+) m/z: 319 $(M+H)^+$; $[\alpha]^{20}_D$ -90.6° (c 0.5, MeOH).

Ejemplo 214

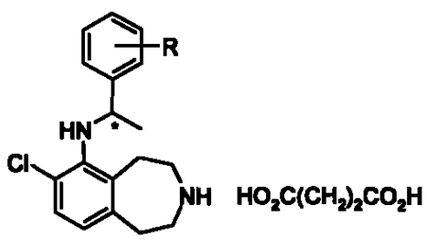
Succinato de (±)-7-Cloro-6-[1-(2-fluorofenil)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al procedimiento general 5-1 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (250 mg, 0.6 mmol) con (±)-1-(2-fluorofenil)-etilamina (206 mg, 1.5 mmol) en tolueno (5 mL). Se purifica el residuo por cromatografía en gel de sílice eluido con hexano/EtOAc (9:1 hasta 1:1) seguido por cromatografía SCX [columna de pre-lavado con metanol seguido por DCM, cargado de material disuelto en DCM, luego eluido con DCM/amoniaco 2M en metanol (1:1) y concentrado in vacuo] para obtener (±)-7-cloro-6-[1-(2-fluorofenil)-etilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (86 mg, 35%). GC-EM m/z: 414 (M^+).

Se usa un método similar al procedimiento general 1-3 para desproteger (±)-7-cloro-6-[1-(2-fluorofenil)-etilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (85 mg, 0.2 mmol) y purificación por cromatografía en gel de sílice eluyendo con DCM/amoniaco 2M en metanol (99:1 hasta 90:10) para dar la base libre del compuesto del título. Se usa un método similar al procedimiento general 2-1 para dar el compuesto del título (70 mg, 80 %). EM (ES+) m/z: 319 $(M+H)^+$.

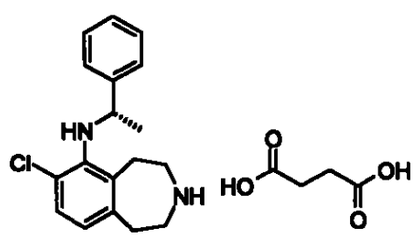
Los ejemplos 215-216 pueden prepararse esencialmente como se describe en el ejemplo 214 al usar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina y la amina apropiada. Los rendimientos para la etapa 1 (Procedimiento general 5-1), rotación óptica y Datos EM (ES+) se muestran en la tabla a continuación.



Ej.	R	Compuesto	Rendimiento (%)	$[\alpha]^{20}_D$ (c, solvente)	EM (ES+) m/z
215	3-CN	Succinato de (+)-7-Cloro-6-[1-(3-cianofenil)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	58	+100.7° (c 0.5, MeOH)	326 $(M+H)^+$
216	3-CN	Succinato de (-)-7-Cloro-6-[1-(3-cianofenil)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	90	-109.7° (c 0.5, MeOH)	326 $(M+H)^+$

Ejemplo 217

Succinato de (S)-(-)-7-Cloro-6-(1-fenil-etilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

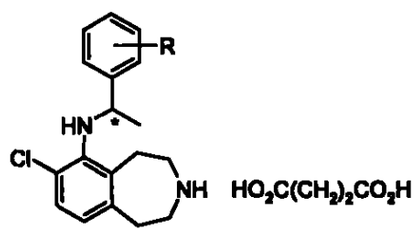


Se agrega acetato de paladio (II) (396 mg, 1.8 mmol), BINAP (2.2 g, 3.5 mmol), carbonato de cesio (8.0 g, 24.6 mmol), y 1S-(-)-metilbencilamina (6.4 g, 52.9 mmol) a una solución de 7-cloro-6-trifluorometansulfoniloxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (7.5 g, 17.6 mmol) en tolueno(173 ml). Se desgasifica la mezcla espesa y se llena con nitrógeno. Se calienta la mezcla a 95°C durante 16 h. GC/EM mostraron algunos materiales de partida que todavía se presentaron después de 16 h, también Se agrega acetato de paladio (II) adicional (0.1 equiv.), BINAP, y 1S-(-)-metilbencilamina (1.0 equiv.). Se continua calentando la reacción durante 24 horas adicionales. La mezcla fría, se diluye con EtOAc (250 ml) luego se filtra a través de Celite®. Se concentra in vacuo y se purifica por cromatografía en gel de sílice eluyendo con hexano/EtOAc/metanol (84:15:1) seguido por cromatografía SCX para dar (S)-7-cloro-6-(1-fenil-etilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (4.38 g, 63%). GC-EM m/z: 396 (M^+).

Se usa un método similar al procedimiento general 1-1 para desproteger (S)-7-cloro-6-(1-fenil-etilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-

benzo[d]azepina (4.3 g, 10.8 mmol). Purificación por cromatografía en gel de sílice eluyendo con DCM/amoniaco 2M en metanol (99/1 hasta 80/20) para dar la base libre del compuesto del título. Se usa un método similar al procedimiento general 2-1 y se cristaliza el sólido a partir de etanol y metil-t-butil éter. Se filtra y se seca el sólido en un horno al vacío a 70°C durante la noche para obtener el compuesto del título (3.6 g, 80%). EM (ES+) m/z: 301 $(M+H)^+$. $[\alpha]^{20}_D$ -95.6° (c 0.5, MeOH).

Los ejemplos 218-227 pueden prepararse esencialmente como se describe en el ejemplo 217 al usar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina y la amina apropiada. Los rendimientos para la etapa 1, rotación óptica o exceso enantiomérico (determinados por CLAR quiral) y Datos EM (ES+) se muestran en la tabla a continuación.



Ej.	R	Compuesto	Rendimiento (%)	$[\alpha]^{20}_D$ (c, solvente) o ee (%)	EM (ES+) m/z
218	H	Succinato de (R)-(+)-7-Cloro-6-(1-fenil-etilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	47	+100.5° (c 0.5, MeOH)	301 $(M+H)^+$
219	4-CF_3	Succinato de (+)-7-Cloro-6-[1-(4-trifluorometil-fenil)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	55	+95.7° (c 0.5, MeOH)	369 $(M+H)^+$
220	3-CF_3	Succinato de 7-Cloro-6-[1-(3-trifluorometil-fenil)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina, Isómero 1	90	95% ee	369 $(M+H)^+$
221	3,4-diF	Succinato de 7-Cloro-6-[1-(3,4-	28	94 % ee	337 $(M+H)^+$

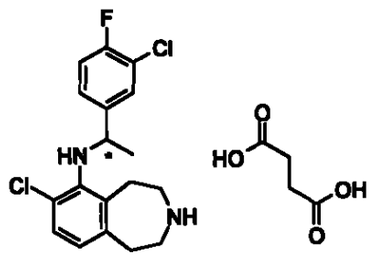
		trifluorofenil)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina, Isómero 1			
222	3,4-diF	Succinato de (+)-7-Cloro-6-[1-(3,4-trifluorofenil)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	81	+89.0° (c 0.5, MeOH)	337 $(M+H)^+$
223	3,4,5-triF	Succinato de 7-Cloro-6-[1-(3,4,5-trifluorofenil)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina, Isómero 2	40	ND	355 $(M+H)^+$
224	3-OCH_3	Clorohidrato de 7-Cloro-6-[1-(3-metoxi-fenil)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina,	53	ND	331 $(M+H)^+$

		Isómero 1			
225	4-OCH_3	Clorohidrato de 7-Cloro-6-[1-(4-metoxi-fenil)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina, Isómero 1	53	>99 % ee	331 $(M+H)^+$
226	4-OPh	Succinato de 7-Cloro-6-[1-(4-fenoxifenil)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina, Isómero 1	27	ND	393 $(M+H)^+$
227	4-OPh	Succinato de 7-Cloro-6-[1-(4-fenoxifenil)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina, Isómero 2	27	ND	393 $(M+H)^+$

ND = No se determinó

Ejemplo 228

Succinato de (-)-7-Cloro-6-[1-(3-cloro-4-fluoro-fenil)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina

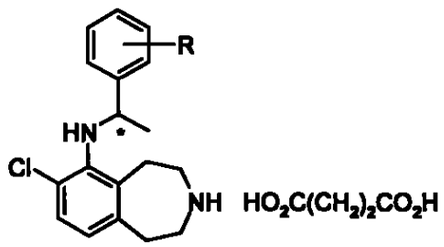


Se usa un método similar al procedimiento general 5-3 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (426 mg, 1.0 mmol) con 1-(3-cloro-4-fluoro-fenil)-etilamina Isómero 1 (226 mg, 1.3 mmol). Purificación por cromatografía en gel de sílice eluyendo con EtOAc/hexano (1:7) para dar 7-cloro-6-[1-(3-cloro-4-fluoro-fenil)-etilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite amarillo (293 mg, 65%).

Se usa un método similar al procedimiento general 1-1 para desproteger 7-cloro-6-[1-(3-cloro-4-fluoro-fenil)-etilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina Isómero 1 (293 mg, 0.65 mmol). Purificación por cromatografía en gel de sílice eluyendo con DCM/amoniaco 2M en metanol (94:6) para dar la base libre del compuesto del título como un aceite (157 mg, 68%). EM (ES+) m/z: 353

$(M+H)^+$. Se usa un método similar para la preparación E-1 para convertir la base libre al compuesto del título. $[\alpha]^{20}_D$ - 115.9° (c 0.5, MeOH).

Los ejemplos 229-235 pueden prepararse esencialmente como se describe en el ejemplo 228 al usar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina y la amina apropiada. Los rendimientos para la etapa 1 (Procedimiento general 5-3), rotación óptica y Datos EM (ES+) se muestran en la tabla a continuación.



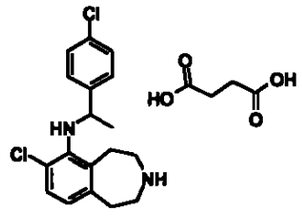
Ej.	R	Compuesto	Rendimiento (%)	$[\alpha]^{20}_D$ (c, solvente)	EM
229	3-Cl	Succinato de (+)-7-Cloro-6-[1-(3-clorofenil)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	17	+119.6° (c 0.5, CH_3OH)	335 $(M+H)^+$

230	2-Cl	Succinato de (+)-7-Cloro-6-[1-(2-clorofenil)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	30	+45.0° (c 0.5, CH_3OH)	335 $(M+H)^+$
231	4-CH_3	Succinato de (R)-(+)-7-Cloro-6-(1-p-toluiletilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	57	+107° (c 0.5, MeOH)	315 $(M+H)^+$
232	4-CH_3	Succinato de (S)-(-)-7-Cloro-6-(1-p-toluiletilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	54	-97.2° (c 0.5, MeOH)	315 $(M+H)^+$
233	3-Cl,4-F	Succinato de (+)-7-Cloro-6-[1-(3-cloro-4-fluorofenil)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	84	+115.0° (c 0.5, CH_3OH)	353 $(M+H)^+$
234	3,5-diF	Succinato de (-)-7-Cloro-6-[1-(3,5-	50	-97.6° (c 0.5,	337 (M+H)

		difluorofenil)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina		MeOH)	+
235	3,5-diF	Succinato de (+)-7-Cloro-6-[1-(3,5-difluorofenil)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	41	+91.0° (c 0.5, MeOH)	337 (M+H)+

Ejemplo 236

Succinato de (±)-7-Cloro-6-[1-(4-clorofenil)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



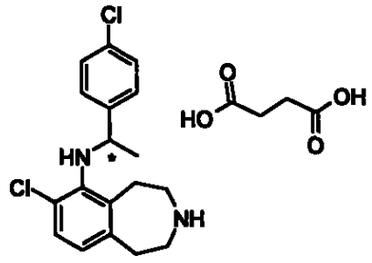
Se usa un método similar al procedimiento general 5-3 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (852 mg, 2.0 mmol) y (±)-4-cloro-(α-metil)bencilamina (622 mg, 4.0 mmol). Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (1:0 y 9:1) para obtener (±)-7-cloro-6-[1-(4-clorofenil)-

etilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (326 mg, 38%). EM (ES+) m/z: 431 $(M+H)^+$.

Se usa un método similar al procedimiento general 1-1 para desproteger (±)-7-cloro-6-[1-(4-clorofenil)-etilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina. Purificación por cromatografía en gel de sílice eluyendo con DCM/amoniaco 2M en metanol (95:5) para dar la base libre del compuesto del título (61 mg, 100%). EM (ES+) m/z: 335 $(M+H)^+$. Se usa un método similar al procedimiento general 2-1 para obtener el compuesto del título.

Ejemplos 237 y 238

Succinato de (-)-7-Cloro-6-[1-(4-clorofenil)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina y Succinato de (+)-7-Cloro-6-[1-(4-clorofenil)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se remitió (±)-7-cloro-6-[1-(4-clorofenil)-etilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (326 mg, 0.76 mmol) a cromatografía quiral (Chiralpak AD,

4.6x150 mm, eluyendo con heptano/etanol (9:1) con 0.2% DMEA, 1mL/min) para proporcionar los dos enantiómeros: 7-cloro-6-[1-(4-clorofenil)-etilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina Isómero 1 (102 mg, t_R = 5.25 min) y 7-cloro-6-[1-(4-clorofenil)-etilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina Isómero 2 (110 mg, t_R = 6.40 min).

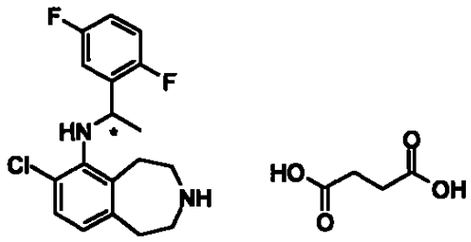
Se usa un método similar al procedimiento general 1-1 para desproteger 7-cloro-6-[1-(4-clorofenil)-etilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina Isómero 1. Purificación por cromatografía en gel de sílice eluyendo con DCM/amoniaco 2M en metanol (95:5) para dar 7-cloro-6-[1-(4-clorofenil)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina Isómero 1 (Ejemplo 237, 82 mg, 100%). EM (ES+) m/z: 335 $(M+H)^+$. Se usa un método similar al procedimiento general 2-1 para obtener el compuesto del título. $[\alpha]^{20}_D$ -127.7° (c 0.5, CH_3OH).

Se usa un método similar al procedimiento general 1-1 para desproteger 7-cloro-6-[1-(4-clorofenil)-etilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina Isómero 2. Purificación por cromatografía en gel de sílice eluyendo con DCM/amoniaco 2M en metanol (95:5) para dar 7-cloro-6-[1-(4-clorofenil)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina Isómero 2 (Ejemplo 238, 68 mg, 78%). EM (ES+) m/z: 335 $(M+H)^+$. Se usa un método similar al procedimiento

general 2-1 para obtener el compuesto del título. $[\alpha]^{20}_D$ +133.6° (c 0.5, CH_3OH).

Ejemplos 239 y 240

Succinato de 7-Cloro-6-[1-(2,5-difluorofenil)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina Isómero 1, y Succinato de 7-cloro-6-[1-(2,5-difluorofenil)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina Isómero 2



Se usa un método similar al procedimiento general 5-1 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (550 mg, 1.27 mmol) y (±)-α-metil-(2',5'-difluoro)bencilamina cruda (400 mg).

Se separaron los dos enantiómeros por cromatografía quiral (eluyente: 75:20:5 heptano/isopropanol/metanol, 4.6x250 mm Chiralpak AD, 1 mL/min, uv 260 nm) para obtener 7-cloro-6-[1-(2,5-difluorofenil)-etilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina Isómero 1 [150 mg, 29%; CLAR quiral: t_R = 4.5 min; EM (ES+) m/z: 433 $(M+H)^+$] y 7-cloro-6-[1-(2,5-difluorofenil)-

etilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina Isómero 2 [130 mg, 25%; CLAR quiral: t_R = 5.5 min; EM (ES+) m/z: 433 $(M+H)^+$], ambos como aceite opacos los cuales se solidificaron durante el reposo hasta sólidos cerosos blancos opacos.

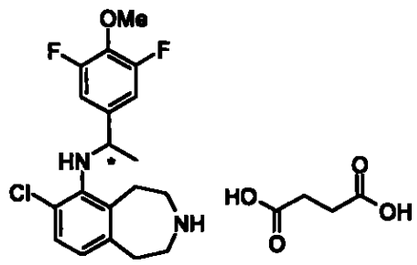
Se usa un método similar al procedimiento general 1-1 para desproteger 7-cloro-6-[1-(2,5-difluorofenil)-etilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina Isómero 1 (140 mg, 0.32 mmol). Se purifica por cromatografía SCX para dar 7-cloro-6-[1-(2,5-difluorofenil)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina Isómero 1 (102 mg, 95%) como un aceite amarillo. Se usa un método similar al procedimiento general 2-1 para obtener el Isómero 1 del compuesto del título (130 mg, 95%) como un sólido blanco opaco. EM (ES+) m/z: 337 $(M+H)^+$.

Se usa un método similar al procedimiento general 1-1 para desproteger 7-cloro-6-[1-(2,5-difluorofenil)-etilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina Isómero 2 (125 mg, 0.29 mmol). Se purifica por cromatografía SCX para dar 7-cloro-6-[1-(2,5-difluorofenil)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina Isómero 2 (87.7 mg, 90%) como un aceite amarillo. Se usa un método similar al procedimiento general 2-1 para obtener el isómero 2 del compuesto del título (117

mg, 99%) como un sólido blanco opaco. EM (ES+) m/z: 337 $(M+H)^+$.

Ejemplo 241

Succinato de (-)-7-Cloro-6-[1-(3,5-difluoro-4-metoxi-fenil)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina

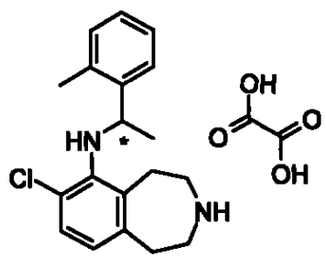


Se usa un método similar al procedimiento general 5-1 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (300 mg, 0.7 mmol) y α-metil-(3',5'-difluoro-4'-metoxi)bencilamina cruda (380 mg). Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (95:5) seguido por cromatografía quiral [heptano/isopropanol/dimetiletilamina (90:10:0.2), 4.6x250 mm Chiralpak AD, 1 mL/min, uv 250 nm] para dar 7-cloro-6-[1-(3,5-difluoro-4-metoxi-fenil)-etilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina Isómero 1 [59 mg, 18% rendimiento, 99% ee, CLAR quiral: t_R = 6.0 min; EM (ES-) m/z: 461 $(M-H)^-$] y 7-cloro-6-[1-(3,5-difluoro-4-metoxi-fenil)-etilamino]-3-(2,2,2-

trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina Isómero 2 [50 mg, 15% rendimiento, 99% ee, CLAR quiral: t_R = 7.7 min; EM (ES-) m/z: 461 $(M-H)^-$]. Se usa un método similar al procedimiento general 1-1 para desproteger 7-cloro-6-[1-(3,5-difluoro-4-metoxi-fenil)-etilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina Isómero 2 (50 mg, 0.14 mmol). Se purifica por cromatografía SCX para dar 7-cloro-6-[1-(3,5-difluoro-4-metoxi-fenil)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina Isómero 2 (35 mg, 70%) como un aceite amarillo. Se usa un método similar al procedimiento general 2-1, usando 7-cloro-6-[1-(3,5-difluoro-4-metoxi-fenil)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina Isómero 2 (35 mg, 0.10 mmol), para dar el compuesto del título (44 mg, 97%) como un polvo blanco opaco. EM (ES+) m/z: 367 $(M+H)^+$; $[\alpha]^{20}_D$ -107.0° (c 0.5, CH_3OH).

Ejemplo 242

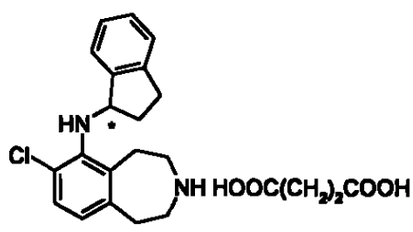
Oxalato de (+)-7-Cloro-6-[(2-metilfenil)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al procedimiento general 5-2 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (0.15 g, 0.35 mmol) con (R)-1-(2-metil)-etilamina (162 mg, 1.2 mmol) a 90°C durante 17 h. La desprotección de conformidad al procedimiento general 1-2. Se purifica por CLAR preparativa de fase inversa y se formó la sal de oxalato de conformidad al procedimiento general 2-5 para dar el compuesto del título (72 mg, 51 %). CLAR t_R = 4.0 min (Chiralpak AD 4.6x150 mm, columna de 3 micrones, 1.0 mL/min de 89.8:10:0.2 heptano/isopropanol/DMEA, isocrático; detectores a 225 nm); EMAR calculado para $C_{19}H_{23}ClN_2$ 315.1628, encontrado 315.1623. $[\alpha]^{20}_D$ +67.2° (c 0.5, CH_3OH).

Ejemplo 243

Succinato de (+)-7-Cloro-6-(indan-1-ilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

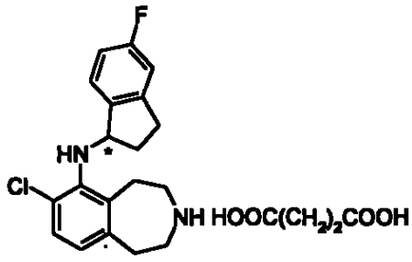


Se usa un método similar al procedimiento general 5-1 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (200 mg, 0.5 mmol) con (R)-1-aminoindan (188 mg, 1.4 mmol) en tolueno (5 mL). Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (9:1 hasta 1:1) seguido por cromatografía SCX [columna de pre-lavado con metanol seguido por DCM, cargado de material disuelto en DCM, luego eluido con DCM/amoniaco 2M en metanol (1:1) y concentrado in vacuo] para dar 7-cloro-6-(indan-1-ilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (129 mg, 67%). GC-EM m/z: 408 (M^+).

Se usa un método similar al procedimiento general 1-1 para desproteger 7-cloro-6-(indan-1-ilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (125 mg, 0.3 mmol) y purificación por cromatografía en gel de sílice eluyendo con DCM/amoniaco 2M en metanol (99:1 hasta 80:20) para dar la base libre del compuesto del título. Se usa un método similar al procedimiento general 2-1 para dar el compuesto del título (104 mg, 78 %). EM (ES+) m/z: 313 $(M+H)^+$. $[\alpha]^{20}_D$ +73.9° (c 0.5, MeOH).

Ejemplo 244

Succinato de (+)-7-Cloro-6-(5-fluoro-indan-1-ilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



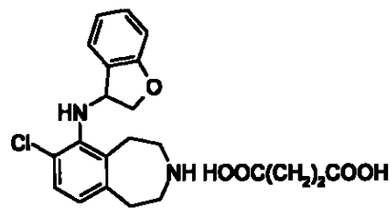
Se usa un método similar al procedimiento general 5-2 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (210 mg, 0.5 mmol) con 5-fluoro-indan-ilamina Isómero 1 (161 mg, 1.1 mmol) en tolueno (10 mL). Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (9:1 hasta 1:1) seguido por cromatografía SCX para obtener 7-cloro-6-[1-(3,5-bis-trifluorometil-fenil)-etilamino]- 3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina Isómero 1 (616 mg, 99%).

Se usa un método similar al procedimiento general 1-3 para desproteger 7-cloro-6-(5-fluoro-indan-ilamina)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina Isómero 1 (200 mg, 0.5 mmol). Purificación por cromatografía en gel de sílice eluyendo con DCM/amoniaco 2M en metanol (99/1 hasta 90/10) para dar la base libre del compuesto del título. Se usa la preparación E-1 para dar el compuesto del

título (140 mg, 66 %). EM (ES+) m/z: 331 $(M+H)^+$. $[\alpha]^{20}_D$ + 80.0° (C, 0.5, MeOH).

Ejemplo 245

Succinato de (±)-7-Cloro-6-(2,3-dihidro-benzofuran-3-ilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



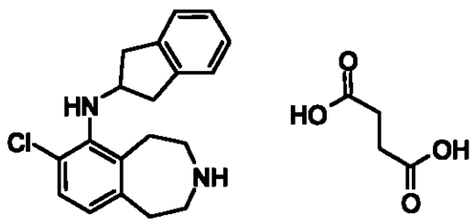
Se usa un método similar al procedimiento general 5-2 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (0.15 g, 0.35 mmol) con 2,3-dihidro-benzofuran-3-ilamina (preparado como se describe en WO 0069816) (0.14 g, 1.1 mmol) a 90°C durante 18 h.

Se usa un método similar al procedimiento general 1-2 y se purifica por CLAR preparativa de fase inversa [Zorbax SB-Fenil 4.6x150 mm, columna de 5 micrones, 1 mL/min de 0.1% TFA en agua/ACN (9:1 hasta 1:9) durante 30 min, detector a 230 y 254 nm].

Se usa un método similar al procedimiento general 2-1 para dar el compuesto del título (4.3 mg, 3%). EMAR calculado para $C_{18}H_{19}ClN_2O$ 315.1264, encontrado 315.1256.

Ejemplo 246

Succinato de 7-Cloro-6-(indan-2-il-amino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

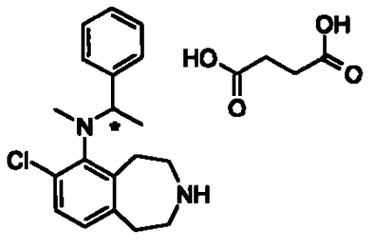


Se usa un método similar al procedimiento general 5-3, usando 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (426 mg, 1.0 mmol) y 2-aminoindano (400 mg, 3.0 mmol), para dar 7-cloro-6-(indan-2-il-amino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite ligeramente amarillo (354 mg, 86%). EM (ES+) m/z: 409 $(M+H)^+$.

Se usa un método similar al procedimiento general 1-1, desprotegiendo 7-cloro-6-(indan-2-il-amino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (354 mg, 0.87 mmol) para obtener 7-cloro-6-(indan-2-il-amino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite amarillo pálido (166 mg, 61%). EM (ES+) m/z: 313 $(M+H)^+$. Se usa un método similar al procedimiento general 2-1 para dar el compuesto del título.

Ejemplo 247

Succinato de (-)-7-Cloro-6-[(N-metil)-1-feniletilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



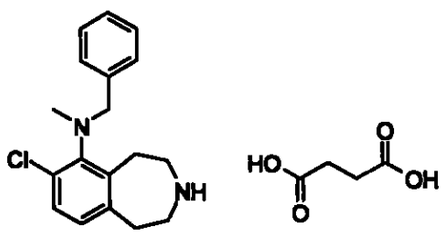
Se disuelve (-)-7-cloro-6-(1-fenil-etilamina)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (192 mg) en DCE (5 mL) y se agrega ácido acético (0.33 mL, 5.8 mmol), formaldehído (37% solución; 0.5 mL) y triacetoxiborohidruro de sodio (570 mg, 2.7 mol) y se agita la reacción a temperatura ambiente durante 16 h. La reacción se diluye con DCM y se lava con NaOH 1N acuoso. Se secan las capas orgánicas Na_2SO_4, se filtran y se concentraron. Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (20:1, 10:1 y 5:1) para dar (-)-7-cloro-6-(metil-1-feniletilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite.

Se usa un método similar al procedimiento general 1-3 para desproteger (-)-7-cloro-6-(metil-1-feniletilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina y se purifica por cromatografía SCX para dar la base libre del compuesto del título. Se usa un método similar al

procedimiento general 2-1 para dar el compuesto del título como un sólido blanco (176 mg, 85%). EM (ES+) m/z: 315 $(M+H)^+$. $[\alpha]^{20}_D$ -5.4° (c 0.5, CH_3OH).

Ejemplo 248

Succinato de 7-Cloro-6-[(N-metil)-bencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



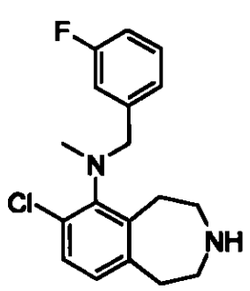
Se disuelve 6-bencilamino-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina (330 mg, 0.86 mmol) en DCM (3 mL) y se agrega trietilamina (250 □L, 1.8 mmol) seguido por di-tert-butil-bicarbonato (260 mg, 1.2 mmol). Se agita a temperatura ambiente durante 1 h. Se vació la mezcla en agua (250 mL), se extrae con DCM (3x25 mL) y se concentra in vacuo para dar, después de cromatografía en gel de sílice eluyendo con hexano/EtOAc (9:1), 6-bencilamino-3-tert-butoxicarbonil-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite incoloro (260 mg, 78%).

Se disuelve 6-bencilamino-3-tert-butoxicarbonil-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina (50 mg, 0.11 mmol) en acetonitrilo (3 mL) y se agrega una solución de formaldehído

en agua (37%, 85 µL, 0.97 mmol) seguido por cianoborohidruro de sodio (16.5 mg, 0.26 mmol). Se calienta la solución a reflujo 1 h, se enfría a temperatura ambiente, se agrega ácido acético glacial (0.25 mL) y se agita 72 h. Se vació la mezcla en agua (100 mL) que contiene metanol (1 mL), se extrae con DCM (3x20 mL), se lavaron los extractos orgánicos con salmuera, se secan sobre $MgSO_4$, se filtran y se concentraron in vacuo. Se disuelve el residuo resultante en DCM (5 mL), y se agrega ácido trifluoroacético (2 mL). Se agita durante 2 h a temperatura ambiente y se evapora el solvente. Se purifica por cromatografía SCX. Se usa un método similar al procedimiento general 2-1 para dar el compuesto del título (45 mg, 95%). EM (ES+) m/z: 301 $(M+H)^+$.

Ejemplo 249

Succinato de 7-Cloro-6-[(N-metil)-3-fluorobencilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



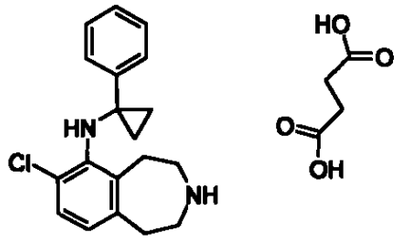
$HO_2C-(CH_2)_2-CO_2H$

El compuesto del título pueden prepararse esencialmente como se describe en el ejemplo 248 al usar 7-cloro-6-(3-

fluorobencilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (85% rendimiento y EM (ES+) m/z 319 $(M+H)^+$).

Ejemplo 250

Succinato de 7-Cloro-6-(1-fenil-ciclopropilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

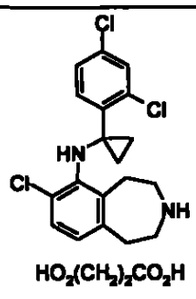


Se usa un método similar al procedimiento general 5-2 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (0.2 g, 0.47 mmol) con 1-fenil-ciclopropilamina (0.2 g, 1.41 mmol) usando tris(dibencilidenacetona)dipaladio(0) (43.0 mg, 0.05 mmol), BINAP (0.1 g, 0.15 mmol) y carbonato de cesio (0.3 g, 0.97 mmol) a 90°C durante 17 h para obtener 7-cloro-6-(1-fenil-ciclopropilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite incoloro.

Se usa un método similar al procedimiento general 1-1 para obtener la base libre del compuesto del título como un aceite amarillo. Se usa un método similar al procedimiento

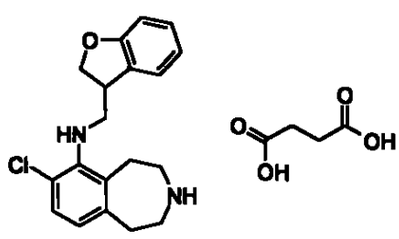
general 2-1 para obtener el compuesto del título como un sólido blanco (85 mg, 33%).

El ejemplo 251 puede prepararse esencialmente como se describe en el ejemplo 250 al usar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 1-(2,4-diclorofenil)-ciclopropilamina. El rendimiento global (3 etapas) se muestra en la tabla a continuación.

Ej.	Estructura	Compuesto	Rendimiento (%)
251		Succinato de 7-Cloro-6-[1-(2,4-diclorofenil)-ciclopropilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	19

Ejemplo 252

Succinato de (±)-7-Cloro-6-(2,3-dihidro-benzofuran-3-il-metilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

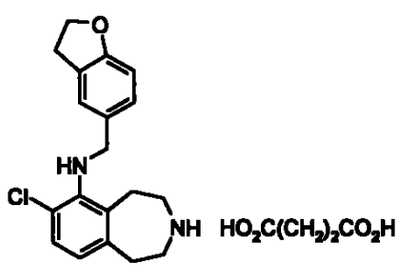


Se usa un método similar al procedimiento general 5-2 para acoplar 2,3-dihidro-benzofuran-3-il-metilamina (preparado como se describe en WO 0069816) (0.14 g, 1.1 mmol) con 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (0.15 g, 0.35 mmol) a 90°C durante 18 h.

Se usa un método similar al procedimiento general 1-2 para desproteger 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina. Se purifica por CLAR preparativa de fase inversa [columna Zorbax SB-Fenil 4.6x150 mm de 5 micrones, 1 mL/min de 1% TFA en agua/ACN (9:1 hasta 1:9) durante 30 min, detector a 230 y 254 nm]. Se usa un método similar al procedimiento general 2-1 para dar el compuesto del título (4.3 mg, 3%).

Ejemplo 253

Succinato de 7-Cloro-6-[(2,3-dihidrobenzo[b]furan-5-il)-metilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



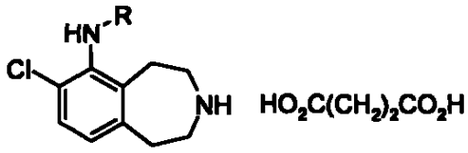
Se suspendió el clorohidrato de 2,3-dihidrobenzo[b]furan-5-il-metilamina comercialmente disponible (1.0 g, 5.4 mmol) en DCM (100 mL). Se agrega NaOH 1N acuoso (15 mL) y se agita hasta que todos los sólidos se disolvieron. Se agregaron dos espátulas de NaCl. Se agita la mezcla y se extrae dos veces con DCM. Las capas orgánicas combinadas, se secan sobre Na_2SO_4, y se concentraron in vacuo para obtener 2,3-dihidrobenzo[b]furan-5-il-metilamina (650 mg, 81%). EM (ES+) m/z: 133 $(M+H-NH_3)^+$.

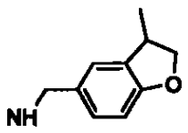
Se usa un método similar al procedimiento general 5-3 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (426 mg, 1.0 mmol) con 5-aminometil-2,3-dihidrobenzo[b]furano (223 mg, 1.5 mmol). Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (1:0 y 9:1) para obtener 7-cloro-6-[(2,3-dihidrobenzo[b]furan-5-il)-metilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (244 mg, 58%). EM (ES+) m/z: 425 $(M+H)^+$.

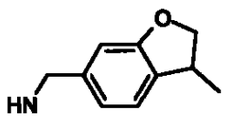
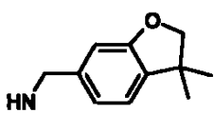
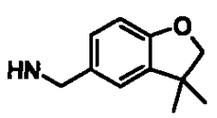
Se usa un método similar al procedimiento general 1-1 para desproteger 7-cloro-6-[(2,3-dihidrobenzo[b]furan-5-il)-metilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina. Purificación por cromatografía en gel de sílice eluyendo con DCM/amoniaco 2M en metanol (95:5) para dar la base libre del compuesto del título (105 mg, 32%). EM (ES+) m/z: 329 $(M+H)^+$. Se usa un método similar al

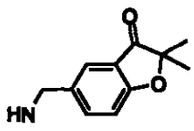
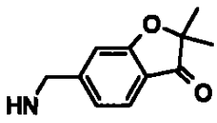
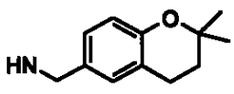
procedimiento general 2-1 para obtener el compuesto del título.

Los ejemplos 254-260 pueden prepararse esencialmente como se describe en el ejemplo 253 al usar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina y la amina apropiada. Los rendimientos para la etapa 1 (Procedimiento general 5-3) y Datos EM (ES+) se muestran en la tabla a continuación.



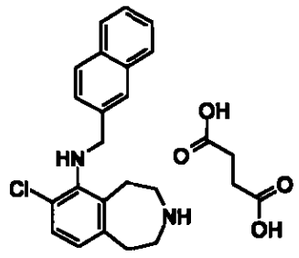
Ej.	NH-R	Compuesto	Rendimiento (%)	EM (ES+) m/z
254		Succinato de (±)-7-Cloro-6-[C-(3-metil-2,3-dihidro-benzofuran-5-il)-metilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	50	343 $(M+H)^+$

255		Succinato de (±)-7-Cloro-6-[C-(3-metil-2,3-dihidro-benzofuran-6-il)-metilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	66	343 (M+H)$^+$
256		Succinato de 7-Cloro-6-[C-(3,3-dimetil-2,3-dihidro-benzofuran-6-il)-metilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	57	357 (M+H)$^+$
257		Succinato de 7-Cloro-6-[C-(3,3-dimetil-2,3-dihidro-benzofuran-5-il)-metilamino]-2,3,4,5-tetrahidro-1H-	64	357 (M+H)$^+$

		benzo[d]azepina		
258		Succinato de 7-Cloro-6-[C-(2,2-dimetil-3-oxo-2,3-dihidro-benzofuran-5-il)-metilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	47	371 (M+H)$^+$
259		Succinato de 7-Cloro-6-[C-(2,2-dimetil-3-oxo-2,3-dihidro-benzofuran-6-il)-metilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	67	371 (M+H)$^+$
260		Succinato de 7-Cloro-6-[(2,2-dimetil-croman-6-il)-metilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	24	371 (M+H)$^+$

Ejemplo 261

Succinato de 7-Cloro-6-(naftalen-2-il-metilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



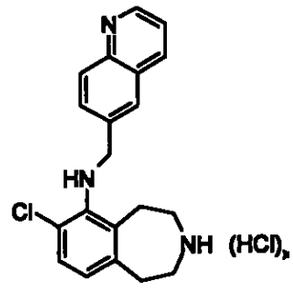
Se usa un método similar al procedimiento general 5-2 para acoplar 2-aminometilnaftaleno (preparado como se describe en WO 9509159) (0.17 g, 1.1 mmol) con 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (0.15 g, 0.35 mmol) a 90°C durante 18 h.

Se usa un método similar al procedimiento general 1-2 para dar la base libre del compuesto del título. EMAR calculado para $C_{21}H_{21}ClN_2$ 337.1471, encontrado 337.1461. Se usa un método similar al procedimiento general 2-1 para dar el compuesto del título (104 mg, 66 % general).

Ejemplo 262

1010

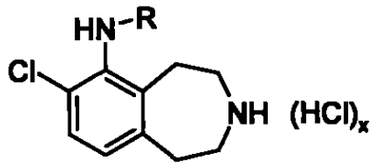
Clorohidrato de 7-Cloro-6-[(quinolin-6-il-metil)-amino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina

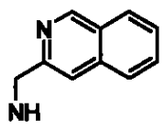
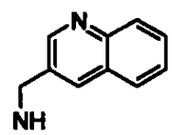


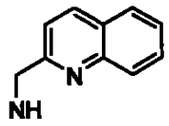
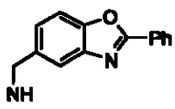
Se usa un método similar al procedimiento general 5-2, usando 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (0.2 g, 0.35 mmol) y 6-aminometil-quinolina (0.2 g, 1.06 mmol) con tris(dibencilidenacetona)dipaladio(0) (32.0 mg, 0.04 mmol), BINAP (44.0 mg, 0.07 mmol) y carbonato de cesio (0.2 g, 0.71 mmol) a 90°C durante 17 h, para obtener 7-cloro-6-[(quinolin-6-il-metil)-amino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite incoloro.

Se usa un método similar al procedimiento general 1-1 para obtener la base libre del compuesto del título como un aceite amarillo. Se usa un método similar al procedimiento general 2-2 para formar la sal de clorohidrato y se purifica por CLAR preparativa de fase inversa [Zorbax SB-Fenil 21.2x250 mm, columna de 5 micrones, 22 mL/min de 0.1% HCl en agua/acetonitrilo (9:1 hasta 1:1) durante 30 min, detector a 230 nm) para obtener el compuesto del título como un sólido blanco (50 mg, 56% general). EM (ES+) m/z: 338 $(M+H)^+$.

Los ejemplos 263-266 pueden prepararse esencialmente como se describe en el ejemplo 262 al usar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina y la amina apropiada. Los rendimientos generales y Datos EM (ES+) se muestran en la tabla a continuación.

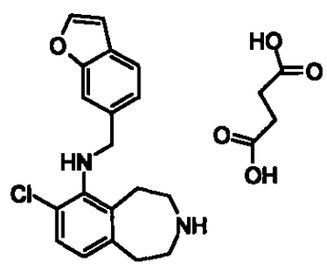


Ej.	NH-R	Compuesto	Rendimiento (%)	EM (ES+) m/z
263		Clorohidrato de 7-Cloro-6-[(isoquinolin-3-il-metil)-amino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	63	338 $(M+H)^+$
264		Clorohidrato de 7-Cloro-6-[(quinolin-3-il-metil)-amino]-2,3,4,5-	35	338 $(M+H)^+$

		tetrahidro-1H-benzo[d]azepina		
265		Clorohidrato de 7-Cloro-6-[(quinolin-2-il-metil)-amino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	20	338 $(M+H)^+$
266		Clorohidrato de 7-Cloro-6-[(2-fenil-benzoxazol-6-il-metil)-amino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	15	404 $(M+H)^+$

Ejemplo 267

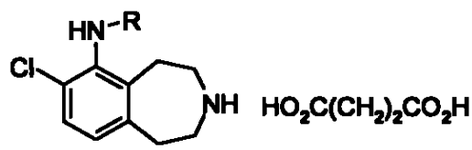
Succinato de 6-[(Benzofuran-6-ilmetil)-amino]-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina

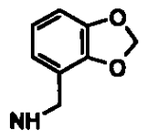
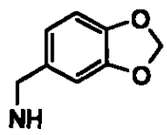
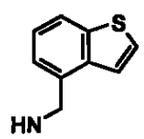


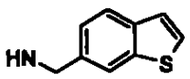
Se usa un método similar al procedimiento general 5-2, usando 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (0.2 g, 0.35 mmol) y 6-aminometil-benzofuran (0.2 g, 1.06 mmol) con tris(dibencilidenacetona)dipaladio (0) (32.0 mg, 0.04 mmol), BINAP (88.0 mg, 0.11 mmol) y carbonato de cesio (0.2 g, 0.71 mmol) a 90°C durante 17 h, para obtener 6-[(benzofuran-6-il-metil)-amino]-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite incoloro.

Se usa un método similar al procedimiento general 1-1 para obtener la base libre del compuesto del título como un aceite amarillo. Se usa un método similar al procedimiento general 2-1 para obtener el compuesto del título como un sólido blanco (72 mg, 46% general). EM (ES+) m/z: 327 $(M+H)^+$.

Los ejemplos 268-271 pueden prepararse esencialmente como se describe en el ejemplo 267 al usar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina y la amina apropiada. Los rendimientos generales y datos EM (ES+) se muestran en la tabla a continuación.

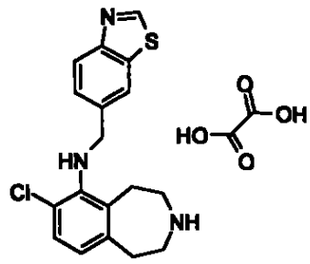


Ej.	NH-R	Compuesto	Rendimiento (%)	EM (ES+) m/z
268		Succinato de 6-[(Benzo[1,3]dioxol-4-il-metil)-amino]-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina	54	331 $(M+H)^+$
269		Succinato de 6-[(Benzo[1,3]dioxol-5-il-metil)-amino]-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina	55	331 $(M+H)^+$
270		Succinato de 6-(Benzo[b]tiofen-4-il-metilamino)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina	73	343 $(M+H)^+$

271		Succinato de 6-(Benzo[b]tiofen-6-il-metilamino)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina	48	343 $(M+H)^+$

Ejemplo 272

Oxalato de 6-[(Benzotiazol-6-il-metil)-amino]-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina

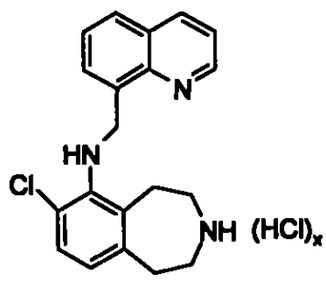


Se usa un método similar al Procedimiento general 5-4, que combina 6-amino-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (0.1 g, 0.35 mmol), 6-bromometil-Benzotiazol (80 mg, 0.35 mmol), y carbonato de potasio (47.0 mg, 0.35 mmol) en DMF anhidro (1 mL) en un tubo sellado. Se calienta a 150°C durante 3 h para obtener 6-[(Benzotiazol-6-il-metil)-amino]-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite incoloro.

Se usa un método similar al procedimiento general 1-1 para obtener la base libre del compuesto del título como un aceite amarillo. Se usa un método similar al procedimiento general 2-5 para obtener el compuesto del título como un sólido blanco (25 mg, 16% general). EM (ES+) m/z: 344 $(M+H)^+$.

Ejemplo 273

Clorohidrato de 7-Cloro-6-[(quinolin-8-il-metil)-amino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina

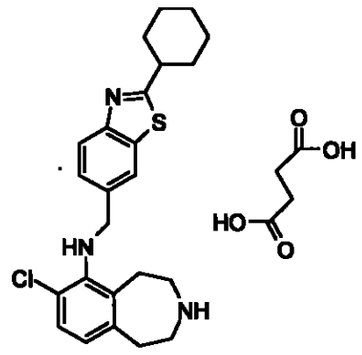


Se usa un método similar al Procedimiento general 5-4, que combina 6-amino-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d] azepina (0.1 g, 0.35 mmol), 8-bromometil-quinolina (83.6 mg, 0.038 mmol), carbonato de cesio (0.2 g, 0.68 mmol) y acetonitrilo anhidro (1 mL) en un tubo sellado y se calienta a 50°C durante 12 h para obtener 7-cloro-6-[(quinolin-8-il-metil)-amino)-amino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite incoloro.

Se usa un método similar al procedimiento general 1-1 para obtener la base libre del compuesto del título como un aceite amarillo. Se usa un método similar al procedimiento general 2-2 para formar la sal de clorohidrato y se purifica por CLAR preparativa de fase inversa [Zorbax SB-Fenil 21.2x250 mm, columna de 5 micrones, 22 mL/min de 0.1% HCl en agua/acetonitrilo (9:1 hasta 1:1) durante 30 min, detector a 230 nm) para obtener el compuesto del título como un sólido blanco (13 mg, 8% general). EM (ES+) m/z: 338 $(M+H)^+$.

Ejemplo 274

Succinato de 7-Cloro-6-[(2-ciclohexil-Benzotiazol-6-il-metil)-amino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina

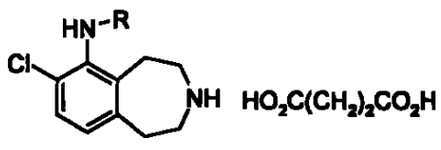


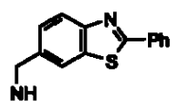
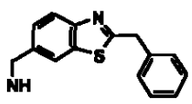
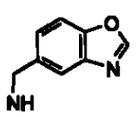
Se usa un método similar al Procedimiento general 5-4, que combina 6-amino-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d] azepina (60 mg, 0.21

mmol), 6-bromometil-2-ciclohexil-Benzotiazol (0.1 g, 0.31 mmol), carbonato de potasio (58 mg, 0.42 mmol) y tolueno anhidro (2 mL) en un tubo sellado y se calienta a 100°C durante 72 h para obtener 7-cloro-6-[(2-ciclohexil-Benzotiazol-6-il-metil)-amino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite incoloro.

Se usa un método similar al procedimiento general 1-1 para obtener la base libre del compuesto del título como un aceite amarillo. Se usa un método similar al procedimiento general 2-1 para obtener el compuesto del título como un sólido blanco (40 mg, 35% general). EM (ES+) m/z: 427 $(M+H)^+$.

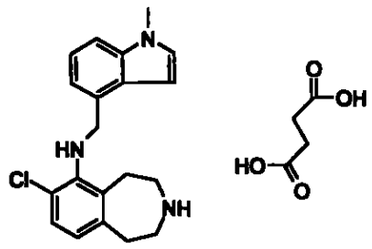
Los ejemplos 275-277 pueden prepararse esencialmente como se describe en el ejemplo 274 al usar 6-amino-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d] azepina y el bromuro apropiado. Los rendimientos generales y Datos EM (ES+) se muestran en la tabla a continuación.



Ej.	NH-R	Compuesto	Rendimiento (%)	EM (ES+) m/z
275		Succinato de 7-Cloro-6-[(2-fenil-Benzotiazol-6-il-metil)-amino]-2,3,4,5-tetrahidro-1H-benzo [d]azepina	39	420 $(M+H)^+$
276		Succinato de 6-[(2-Bencil-Benzotiazol-6-il-metil)-amino]-7-cloro-2,3,4,5-tetrahidro-1H-benzo [d]azepina	36	453 $(M+H)^+$
277		Succinato de 6-[(Benzoxazol-6-il-metil)-amino]-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina	7	328 $(M+H)^+$

Ejemplo 278

Succinato de 7-Cloro-6-[(1-metil-indol-4-il-metil)-amino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina

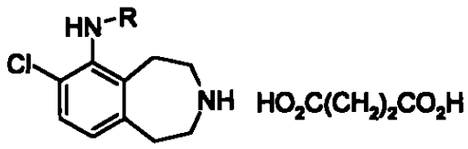


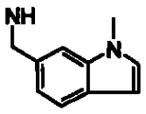
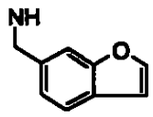
Se usa un método similar al Procedimiento general 5-1, que acopla 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetra-hidro-1H-benzo[d]azepina (0.1 g, 0.24 mmol) con 4-aminometil-1-metilindol (0.1 g, 0.71 mmol) para obtener 7-cloro-6-[(1-metil-indol-4-il-metil)-amino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite incoloro.

Se usa un método similar al procedimiento general 1-1 para obtener la base libre del compuesto del título como un aceite amarillo. Se usa un método similar al procedimiento general 2-1 para obtener el compuesto del título como un sólido blanco (0.1 g, 91% general). EM (ES+) m/z: 340 $(M+H)^+$.

Los ejemplos 279-280 pueden prepararse esencialmente como se describe en el ejemplo 278 al usar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-

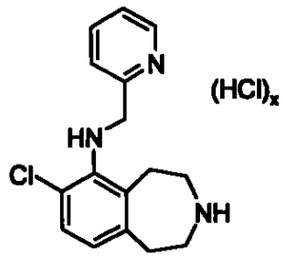
tetrahidro-1H-benzo[d]azepina con la amina apropiada. Los rendimientos generales y datos EM (ES+) se muestran en la tabla a continuación.



Ej.	NH-R	Compuesto	Rendimiento (%)	EM (ES+) m/z
279		Succinato de 7-Cloro-6-[(1-metil-indol-6-il-metil)-amino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	42	340 $(M+H)^+$
280		Succinato de 6-[(Benzofuran-6-ilmetil)-amino]-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina	46	327 $(M+H)^+$

Ejemplo 281

Clorohidrato de 7-Cloro-6-(piridin-2-ilmetilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



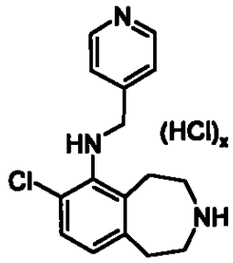
Se usa un método similar al procedimiento general 5-1 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (500 mg, 1.17 mmol) con piridin-2-ilmetilamina (254 mg, 2 equiv.) usando acetato de paladio (0.1 equiv.), BINAP (0.3 equiv.) y carbonato de cesio (1.4 equiv.) en tolueno (5 mL). Se purifica el residuo por cromatografía en gel de sílice eluyendo con hexano/EtOAc (10:1, 5:1, 3:1, y 1:1) para dar 7-cloro-6-(piridin-2-ilmetilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite.

Se usa un método similar al procedimiento general 1-3 para desproteger 7-cloro-6-(piridin-2-ilmetilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina. Se purifica por cromatografía SCX seguido por cromatografía de gel de sílice eluyendo con DCM/amoniaco 2M en metanol (1:0, 40:1, 20:1 y 10:1) para dar la base libre del compuesto del

título. Se usa un método similar al procedimiento general 2-2 para dar el compuesto del título como un sólido blanco opaco (207 mg, 55% general). EM (ES+) m/z: 288 $(M+H)^+$.

Ejemplo 282

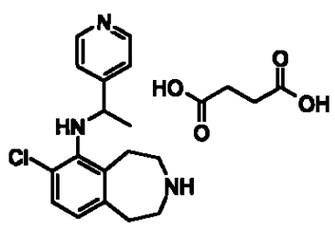
Clorohidrato de 7-Cloro-6-(piridin-4-ilmetilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Puede prepararse esencialmente como se describe en el ejemplo 281 al usar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina y piridin-4-ilmetilamina (28% rendimiento, y EM (ES+) 288 $(M+H)^+$).

Ejemplo 283

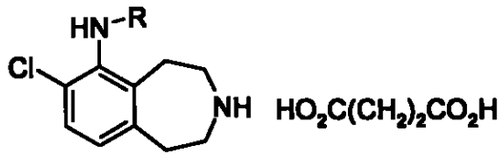
Succinato de (±)-7-Cloro-6-[(1-piridin-4-il-etil)-amino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina

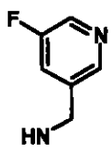
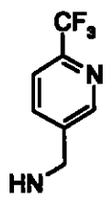
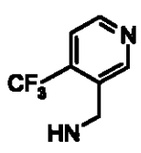


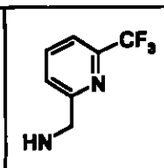
Se usa un método similar al procedimiento general 5-3 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (400 mg, 0.94 mmol) y (±)-1-piridin-4-il-etilamina (preparado como se describe en Bull. Kor. Chem. Soc. 1998, 19 (8), 891-893) (172 mg, 1.41 mmol). Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (1:0, 4:1 y 1:1) para dar (±)-7-cloro-6-[(1-piridin-4-il-etil)-amino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina.

Se usa un método similar al procedimiento general 1-1 para dar la base libre del compuesto del título (73 mg, 26%). Se usa un método similar al procedimiento general 2-1, usando (±)-7-cloro-6-[(1-piridin-4-il-etil)-amino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina (73 mg, 0.243 mmol), para dar el compuesto del título (31 mg, 31%). EM (ES+) m/z: 302 $(M+H)^+$.

Los ejemplos 284-287 pueden prepararse esencialmente como se describe en el ejemplo 283 al usar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina y la amina apropiada. Los rendimientos para la etapa 1 (Procedimiento general 5-3) y Datos EM (ES+) se muestran en la tabla a continuación.

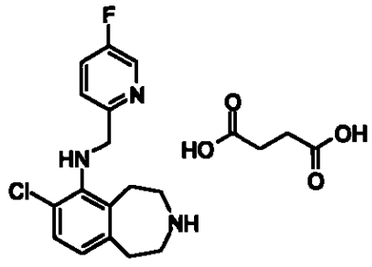


Ej.	NH-R	Compuesto	Rendimiento (%)	EM (ES+) m/z
284		Succinato de 7-Cloro-6-(5-fluoro-piridin-3-ilmetilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	88	306 $(M+H)^+$
285		Succinato de 7-Cloro-6-(6-trifluorometil-piridin-3-il-metilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	83	356 $(M+H)^+$
286		Succinato de 7-Cloro-6-(4-trifluorometil-piridin-3-il-metilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	60	356 $(M+H)^+$

287		Succinato de 7-Cloro-6-[(6-trifluorometil-piridin-2-ilmetil)-amino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	84	356 $(M+H)^+$

Ejemplo 288

Succinato de 7-Cloro-6-[(5-fluoro-piridin-2-ilmetil)-amino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



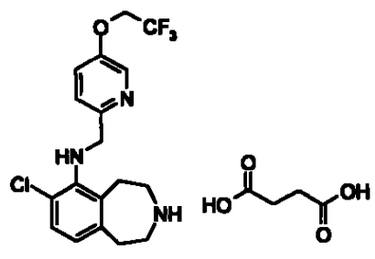
Se usa un método similar al procedimiento general 5-1 para acoplar 2-aminometil-5-fluoro-piridina (230 mg, 1.8 mmol) y una solución de 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (500 mg, 1.2 mmol) en tolueno (4 mL). Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (9:1 hasta 1:1) seguido por cromatografía SCX para dar 7-cloro-6-[(5-fluoro-piridin-2-ilmetil)-amino]-3-

(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (302 mg, 64%). GC-EM m/z: 402 (M^+).

Se disuelve 7-cloro-6-[(5-fluoro-piridin-2-ilmetil)-amino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (297 mg, 0.74 mmol) en etanol (5 mL). Se agrega NaOH acuoso 5N (10 equiv.) y se agita durante 1 h a temperatura ambiente. Se concentra in vacuo y se purifica por cromatografía SCX seguido por cromatografía en gel de sílice eluyendo con DCM/amoniaco 2M en metanol (99:1 hasta 9:1) para obtener la base libre del compuesto del título. Se usa un método similar al procedimiento general 2-1 y se cristaliza el sólido a partir de metanol y éter dietílico. Se secó el sólido en horno al vacio a 60°C durante la noche para obtener el compuesto del título (181 mg, 58%). EM (ES+) m/z: 306 $(M+H)^+$.

Ejemplo 289

Succinato de 7-Cloro-6-{[5-(2,2,2-trifluoro-etoxi)-piridin-2-ilmetil]-amino}-2,3,4,5-tetrahidro-1H-benzo[d]azepina

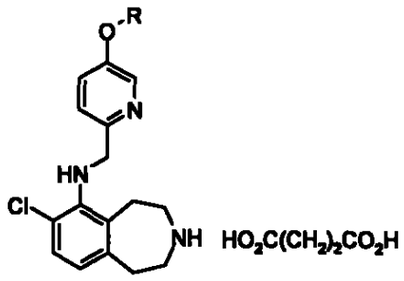


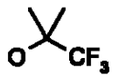
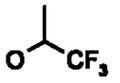
Se usa un método similar al procedimiento general 5-2 para acoplar 7-cloro-6-trifluorometansulfoniloxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (370 mg, 0.9 mmol) con 2-aminometil-5-(2,2,2-trifluoroetoxi)-piridina (180 mg, 0.9 mmol) en tolueno (8 mL). Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (10:1, 5:1 y 3:1) seguido por cromatografía SCX [columna de pre-lavado con metanol seguido por DCM, cargado de material disuelto en DCM, luego eluido con DCM/amoniaco 2M en metanol (1:1) y concentrado in vacuo] para obtener 7-cloro-6-{[5-(2,2,2-trifluoro-etoxi)-piridin-2-ilmetil]-amino}-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina.

Se usa un método similar al procedimiento general 1-3 para desproteger 7-cloro-6-{[5-(2,2,2-trifluoro-etoxi)-piridin-2-ilmetil]-amino}-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina. La purificación por cromatografía en gel de sílice eluyendo con DCM/amoniaco 2M en metanol (99/1 hasta 90/10) para obtener la base libre del compuesto del título. Se usa un método similar al procedimiento general 2-1 para dar el compuesto del título (184 mg, 42 %). EM (ES+) m/z: 386 $(M+H)^+$.

Los ejemplos 290-291 pueden prepararse esencialmente como se describe en el ejemplo 289 al usar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-

tetrahidro-1H-benzo[d]azepina y la amina apropiada. Los rendimientos generales y Datos EM (ES+) se muestran en la tabla a continuación.

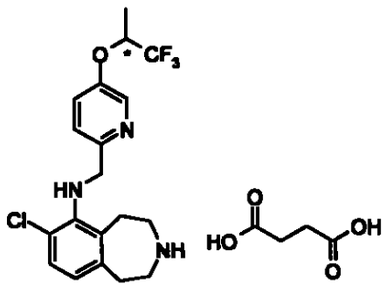


Ej.	O-R	Compuesto	Rendimiento (%)	EM (ES+) m/z
290		Succinato de 7-Cloro-6-{[5-(2,2,2-trifluoro-1,1-dimetil-etoxi)-piridin-2-ilmetil]-amino}-2,3,4,5-tetrahidro-1H-benzo[d]azepina	48	414 $(M+H)^+$
291		Succinato de (±)-7-Cloro-6-{[5-(2,2,2-trifluoro-1-metil-etoxi)-	49	400 $(M+H)^+$

		piridin-2-ilmetil]-amino}-2,3,4,5-tetrahidro-1H-benzo[d]azepin		

Ejemplos 292 y 293

Succinato de (-)-7-Cloro-6-{[5-(2,2,2-trifluoro-1-metil-etoxi)-piridin-2-ilmetil]-amino}-2,3,4,5-tetrahidro-1H-benzo[d]azepina y Succinato de (+)-7-Cloro-6-{[5-(2,2,2-trifluoro-1-metil-etoxi)-piridin-2-ilmetil]-amino}-2,3,4,5-tetrahidro-1H-benzo[d]azepina

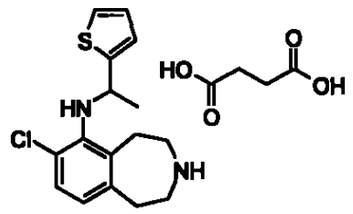


Se separaron los dos enantiómeros de succinato de (±)-7-cloro-6-{[5-(2,2,2-trifluoro-1-metil-etoxi)-piridin-2-ilmetil]-amino}-2,3,4,5-tetrahidro-1H-benzo[d]azepina por CLAR quiral de fase normal (Chiralcel OD 8x35 cm, eluido con 4:1 heptano/3A-etanol con 0.2 % DMEA). Se purifica cada enantiómero por cromatografía en gel de sílice eluyendo con DCM/amoniaco 2M en metanol (20:1). Se usa un método similar

al procedimiento general 2-1 para obtener los compuestos del título: succinato de (-)-7-Cloro-6-{[5-(2,2,2-trifluoro-1-metil-etoxi)-piridin-2-ilmetil]-amino}-2,3,4,5-tetrahidro-1H-benzo[d]azepina (Ejemplo 292, 75 mg, 38%), 95% ee [Chiralpak AD, 4.6x150 mm, eluyente: 85/15 heptano/3A etanol con 0.2% DMEA, 0.6 mL/min)]; EM (ES+) m/z: 400 $(M+H)^+$. $[\alpha]^{20}_D$ -12.1° (c 0.5, MeOH). Succinato de (+)-7-Cloro-6-{[5-(2,2,2-trifluoro-1-metil-etoxi)-piridin-2-ilmetil]-amino}-2,3,4,5-tetrahidro-1H-benzo[d]azepina (Ejemplo 293, 72 mg, 37%), 93% ee [Chiralpak AD, 4.6x150 mm, eluyente: 85/15 heptano/3A etanol con 0.2% DMEA, 0.6 mL/min)]. EM (ES+) m/z: 400 $(M+H)^+$. $[\alpha]^{20}_D$ +7.4° (c 0.5, MeOH).

Ejemplo 294

Succinato de (±)-7-Cloro-6-[(1-tiofen-2-il-etil)-amino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



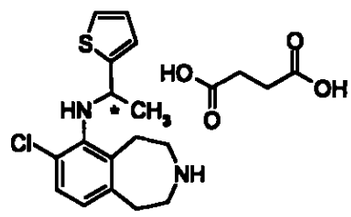
Se usa un método similar al procedimiento general 5-3 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (200 mg, 0.47 mmol) con (±)-1-tiofen-2-

il-etilamina (preparado como se describe en J. Amer. Chem. Soc. 1942, 64, 477-479) (200 mg, 1.57 mmol). Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (1:0, 9:1 y 4:1) para dar (±)-7-cloro-6-[(1-tiofen-2-il-etil)-amino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (126 mg, 67%).

Se usa un método similar al procedimiento general 1-1, usando (±)-7-cloro-6-[(1-tiofen-2-il-etil)-amino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (126 mg, 0.313 mmol), para dar la base libre del compuesto del título (73 mg, 77%). Se usa un método similar al procedimiento general 2-1, usando (±)-7-cloro-6-[(1-tiofen-2-il-etil)-amino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina (73 mg, 0.241 mmol) para dar el compuesto del título (100 mg, 50% general). EM (ES+) m/z: 307 $(M+H)^+$.

Ejemplo 295

Succinato de (+)-7-Cloro-6-[(1-tiofen-2-il-etil)-amino]-2,3,4,5-tetrahidro-1H-benzo[d]azepin, Isómero 1

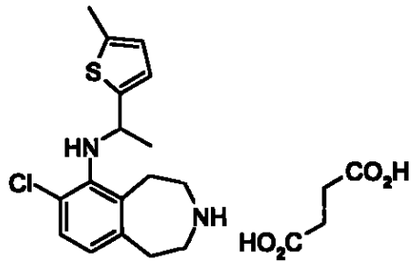


Se separaron los dos enantiómeros de (±)-7-cloro-6-[(1-tiofen-2-il-etil)-amino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina por CLAR preparativa quiral (Chiralpak AD, 8x30 cm; eluyente: 9:1 heptano/isopropanol con 0.2% DMEA; flujo: 350 mL/min a 240 nm (UV), ~650 mg carga] para obtener 7-cloro-6-[(1-tiofen-2-il-etil)-amino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina Isómero 1, ee=100% [Columna analítica: Chiralpak AD, 4.6x250mm; eluyente: 9:1 heptano/isopropanol con 0.2% DMEA; flujo: 1 mL/min a 250nm (UV).

Se usa un método similar al procedimiento general 1-1, usando 7-cloro-6-[(1-tiofen-2-il-etil)-amino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina Isómero 1, para dar 7-cloro-6-[(1-tiofen-2-il-etil)-amino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina Isómero 1. Se usa un método similar al procedimiento general 2-1, usando 7-cloro-6-[(1-tiofen-2-il-etil)-amino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina Isómero 1 (73 mg, 0.241 mmol) para dar el compuesto del título (100 mg, 98%). EM (ES+) m/z: 307 $(M+H)^+$. $[\alpha]^{20}_D$ +115.0° (c 0.5, MeOH).

Ejemplo 296

Succinato de (±)-7-Cloro-6-[1-(5-metiltiofen-2-il)etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



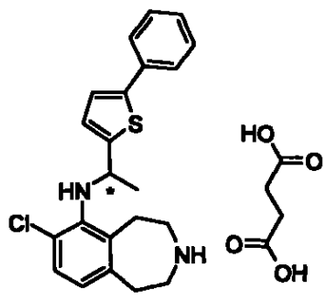
Se usa un método similar al procedimiento general 5-1 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (96 mg, 0.227 mmol) con (±)-2-(1-aminoetil)-5-metiltiofeno (48 mg, 0.34 mmol) usando acetato de paladio (II) (10 mg, 0.0454 mmol), BINAP (60 mg, 0.0908 mmol) y carbonato de cesio (148 mg, 0.454 mmol) en tolueno (10 mL). Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (1:0, 19:1) para dar (±)-7-cloro-6-[1-(5-metiltiofen-2-il)etilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite (47 mg, 50%). GC-EM m/z 416 (M^+).

Se usa un método similar al procedimiento general 1-2, usando (±)-7-cloro-6-[1-(5-metiltiofen-2-il)etilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (47 mg, 0.113 mmol) para dar (±)-7-cloro-6-[1-(5-metiltiofen-2-il)etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un

aceite (30 mg, 83%) que se usa sin purificación adicional. Se usa un método similar al procedimiento general 2-1 para dar el compuesto del título como un sólido blanco (36 mg, 88%). EM (ES+) m/z: 321 $(M+H)^+$.

Ejemplo 297

Succinato de (+)-7-Cloro-6-[1-(5-fenil-tiofen-2-il)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



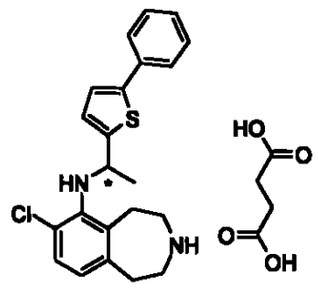
Se usa un método similar al procedimiento general 5-3 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (0.328 g, 0.773 mmol) con 1-(5-fenil-tiofen-2-il)etilamina Isómero 1 (0.236 g, 1.16 mmol) usando acetato de paladio (II) (69 mg, 0.309 mmol), tris(dibencilidenacetona)-dipaladio (0) (142 mg, 0.155 mmol), BINAP (578 mg, 0.928 mmol) y carbonato de cesio (504 mg, 1.546 mmol) en tolueno (10 mL). Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (1:0 y 19:1) para dar 7-cloro-6-[1-(5-

fenil-tiofen-2-il)-etilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina Isómero 1 (89 mg, 34%).

Se usa un método similar al procedimiento general 1-2, usando 7-cloro-6-[1-(5-fenil-tiofen-2-il)-etilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina Isómero 1 (89 mg, 0.186 mmol) para dar 7-cloro-6-[1-(5-fenil-tiofen-2-il)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina Isómero 1 (65 mg, 92%) como un aceite que se usa sin purificación adicional. Se usa un método similar al procedimiento general 2-1, usando 7-cloro-6-[1-(5-fenil-tiofen-2-il)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina Isómero 1 (65 mg, 0.17 mmol), para dar el compuesto del título como un sólido blanco (58 mg, 68%). EM (ES+) m/z: 383 $(M+H)^+$; $[\alpha]^{20}_D$ +159.0° (c 0.5, MeOH).

Ejemplo 298

Succinato de (-)-7-Cloro-6-[1-(5-fenil-tiofen-2-il)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



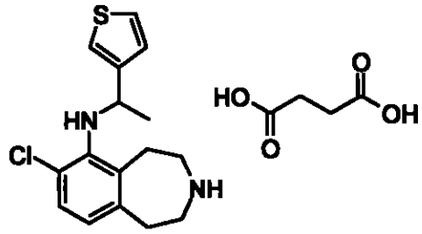
Se usa un método similar al procedimiento general 5-3 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (0.484 g, 1.138 mmol) con 1-(5-fenil-tiofen-2-il)etilamina Isómero 2 (0.347 g, 1.71 mmol) usando acetato de paladio (II) (102 mg, 0.45 mmol), tris(dibencilidenacetona)-dipaladio (O) (209 mg, 0.228 mmol), BINAP (851 mg, 1.366 mmol) y carbonato de cesio (741 mg, 2.276 mmol) en tolueno (12 mL). Purificación por cromatografía en gel de sílice eluyendo con hexano:EtOAc (1:0 y 19:1) para dar 7-cloro-6-[1-(5-fenil-tiofen-2-il)-etilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina Isómero 2 (247 mg, 63 %).

Se usa un método similar al procedimiento general 1-2, usando 7-cloro-6-[1-(5-fenil-tiofen-2-il)-etilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina Isómero 2 (247 mg, 0.516 mmol) para dar 7-cloro-6-[1-(5-fenil-tiofen-2-il)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina Isómero 2 (184 mg, 93%) como un aceite que se usa sin purificación adicional. Se usa un método similar al procedimiento general 2-1, usando 7-cloro-6-[1-(5-fenil-tiofen-2-il)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina

Isómero 2 (184 mg, 0.48 mmol) para dar el compuesto del título como un sólido blanco (200 mg, 83%). EM (ES+) m/z: 383 $(M+H)^+$; $[\alpha]^{20}_D$ -196.5° (c 0.5, MeOH).

Ejemplo 299

Succinato de (±)-7-Cloro-6-[(1-tiofen-3-il-etil)-amino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



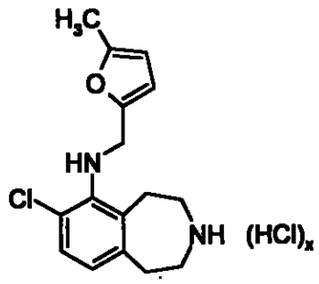
Se usa un método similar al procedimiento general 5-3 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (200 mg, 0.47 mmol) con (±)-1-tiofen-3-il-etilamina (preparado como se describe en J. Heterocycl. Chem. 1988, 25, 1571-1581) (90 mg, 0.70 mmol). Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (1:0, 9:1 y 4:1) para dar (±)-7-cloro-6-(1-tiofen-3-il-etilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (100 mg, 53%).

Se usa un método similar al procedimiento general 1-1, usando (±)-7-cloro-6-(1-tiofen-3-il-etilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (100

mg, 0.248 mmol), para dar la base libre del compuesto del título (74 mg, 98%). Se usa un método similar al procedimiento general 2-1, usando (±)-7-cloro-6-(1-tiofen-3-il-etilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (74 mg, 0.242 mmol) para dar el compuesto del título (108 mg, 54% general). EM (ES+) m/z: 307 $(M+H)^+$.

Ejemplo 300

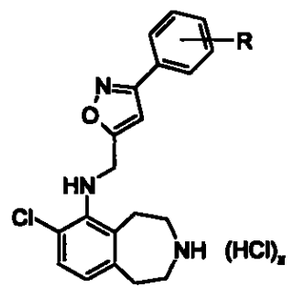
Clorohidrato de 7-Cloro-6-[(5-metilfuran-2-ilmetil)-amino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se combinó 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (100 mg, 0.24 mmol), 2-(di-tert-butilfosfino)-bifenil (6.8 mg, 0.023 mmol), tris(dibencilidenacetona)dipaladio (11 mg, 0.012 mmol) y fosfato de potasio (70 mg, 0.33 mmol) en un tubo a presión y desgasificado. Se disuelve la mezcla en tolueno seco (2 mL) y se desgasifica. Se agrega una solución de 5-metilfurfurilamina (30 mg, 0.27 mmol) en tolueno (1 mL) y se desgasifica. Se agita a 90°C durante 24 h. Se enfría a

temperatura ambiente, se diluye con éter etílico y se filtra a través de Celite®. Se concentra y se purifica por cromatografía en gel de sílice eluyendo con hexano/EtOAc (20:1). Se removió el solvente y se agrega amoniaco 7M en metanol (4 mL). Se agita a temperatura ambiente durante 24 h. Se concentra y se purifica por cromatografía SCX para dar la base libre del compuesto del título. Se usa un método similar al procedimiento general 2-2 para obtener el compuesto del título como un sólido (56 mg, 66%). EM (ES+) m/z: 291 $(M+H)^+$.

Los ejemplos 301-302 pueden prepararse esencialmente como se describe en el ejemplo 300 al usar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina y la amina apropiada. Los rendimientos generales y datos EM (ES+) se muestran en la tabla a continuación.

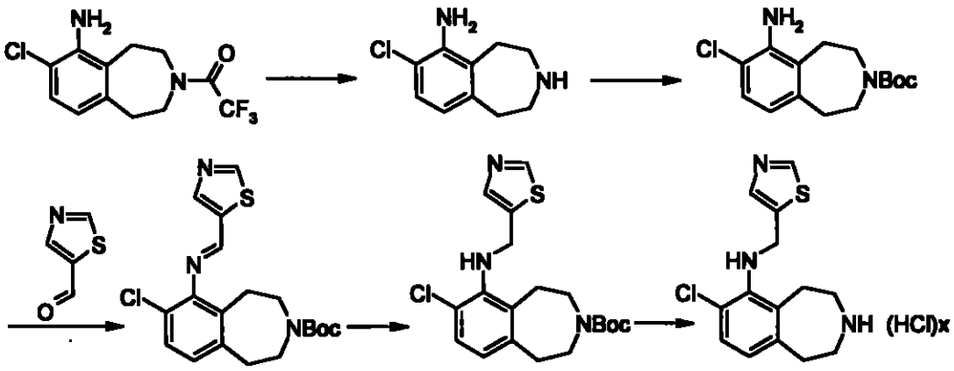


Ej.	R	Compuesto	Rendimiento (%)	EM (ES+) m/z
301	4-Cl	Clorohidrato de 7-	30	389

		Cloro-6-{[3-(4-clorofenil)-isoxazol-5-ilmetil]-amino}-2,3,4,5-tetrahidro-1H-benzo[d]azepina		$(M+H)^+$
302	4-OMe	Clorohidrato de 7-Cloro-6-{[3-(4-metoxifenil)-isoxazol-5-ilmetil]-amino}-2,3,4,5-tetrahidro-1H-benzo[d]azepina	54	384 $(M+H)^+$

Ejemplo 303

Clorohidrato de 7-Cloro-6-(tiazol-5-ilmetil-amino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Tiazol-5-carbaldehído: Se agrega DEMO lentamente a una solución de cloruro de oxalilo (1.6 g, 13 mmol) en DCM anhidro (30 mL) bajo nitrógeno a -78°C y se agita durante 10 min. Se agrega gota a gota una solución de 5-

hidroximetiltiazol (1.15 g, 10 mmol) en DCM (10 mL) y se agita la mezcla durante 40 min. Se agrega trietilamina y se agita durante 5 min y luego se apagó la reacción con agua. Se extrae la mezcla tres veces con éter, se combinaron los extractos orgánicos, se lavaron con salmuera, se secan sobre Na_2SO_4, se filtran y concentraron in vacuo. Purificación por cromatografía en gel de sílice eluyendo con EtOAc/hexano (2:5) para dar tiazol-5-carbaldehído (337 mg, 29%).

3-(tert-Butoxicarbonil)-7-cloro-6-(tiazol-5-ilmetilenamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Se disuelve 6-amino-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (285 mg, 0.97 mmol) en metanol (10 mL). Se agrega amoniaco 7N en metanol (10 mL) y se agita durante la noche a temperatura ambiente. Se concentra in vacuo y se disuelve el residuo en THF (10 mL). Se agrega $NaHCO_3$ acuoso saturado (5 mL) y di-tert-butil-bicarbonato (254 mg, 1.16 mmol). Se agita la mezcla de reacción a temperatura ambiente durante 4 h. Se diluye la mezcla con agua, se extrae tres veces con EtOAc, se combinaron los extractos orgánicos, se secan sobre Na_2SO_4, se filtran y se concentraron in vacuo para dar el material crudo. Se mezcla tiazol-5-carbaldehído (165 mg, 1.45 mmol) con el residuo crudo de arriba (0.97 mmol, suponiendo 100% conversión), ácido acético (87 mg, 1.45 mmol) y 1,2-dicloroetano (10 mL). Se agita a temperatura ambiente durante 20 min. Se agrega

triacetoxiborohidruro de sodio y se agita bajo nitrógeno durante la noche. Se apaga la reacción con $NaHCO_3$ acuoso saturado, se separa la capa orgánica y se extrae la capa acuosa tres veces con DCM. Se combinan los extractos orgánicos, se secan sobre Na_2SO_4, se filtran y se concentraron in vacuo. Purificación por cromatografía en gel de sílice eluyendo con EtOAc/hexano (1:3) para proporcionar el intermediario deseado como un aceite amarillo (228 mg, 60% tres etapas). EM (ES+) m/z: 392 $(M+H)^+$.

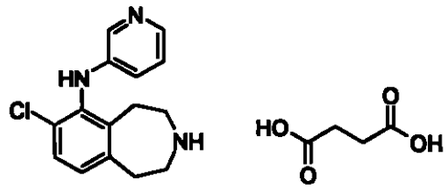
3-(t-Butoxicarbonil)-7-cloro-6-(tiazol-5-ilmetil-amino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Se disuelve 3-(t-butoxicarbonil)-7-cloro-6-(tiazol-5-ilmetilenamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (228 mg, 0.58 mmol) en metanol (10 mL), se agrega borohidruro de sodio (263 mg, 7 mmol) y se pone a reflujo durante 28 h. Se enfría a temperatura ambiente, se diluye con EtOAc y se agrega lentamente agua. Se separa la capa orgánica, se extrae la capa acuosa tres veces con EtOAc. Se combinan los extractos orgánicos, se secan sobre Na_2SO_4, se filtran y se concentran in vacuo. Purificación por cromatografía en gel de sílice eluyendo con EtOAc/hexano (1:3) para dar el intermediario deseado como un aceite incoloro (134 mg, 58%). EM (ES+) m/z: 394 $(M+H)^+$.

Clorohidrato de 7-Cloro-6-(tiazol-5-ilmetil-amino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Se usa un método similar al procedimiento general 1-6 para desproteger 3-

(tert-butoxicarbonil)-7-cloro-6-(tiazol-5-ilmetil-amino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (134 mg, 0.34 mmol). Purificación por cromatografía en gel de sílice eluyendo con DCM/amoniaco 2M en metanol (94:6) para dar 7-cloro-6-(tiazol-5-ilmetil-amino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite (90 mg, 90%). EM (ES+) m/z: 294 $(M+H)^+$. Se usa un método similar al procedimiento general 2-2 para obtener el compuesto del título.

Ejemplo 304

Succinato de 7-Cloro-6-[(3-piridil)amino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina

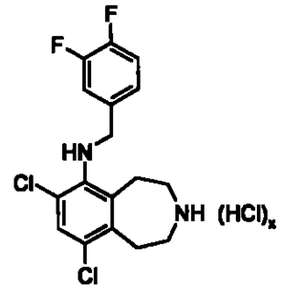


Se usa un método similar al procedimiento general 5-1 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (300 mg, 0.7 mmol) con 3-aminopiridina (75 mg, 0.85 mmol). Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (4:1) para dar 7-cloro-6-[(3-piridil)amino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un sólido blanco opaco (20 mg, 8%). EM (ES+) m/z: 370 $(M+H)^+$.

Se usa un método similar al procedimiento general 1-1 para desproteger 7-cloro-6-[(3-piridil)amino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (20 mg, 0.05 mmol). Se purifica por cromatografía SCX para dar 7-cloro-6-[(3-piridil)amino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite amarillo (15 mg, 99%). Se usa un método similar al procedimiento general 2-1, usando 7-cloro-6-[(3-piridil)amino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina (15.1 mg, 0.05 mmol), para dar el compuesto del título como un sólido amarillo ligero (20 mg, 97%). EM (ES+) m/z: 319 $(M+H)^+$.

Ejemplo 305

Clorohidrato de 7,9-Dicloro-6-(3,4-difluorobencilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



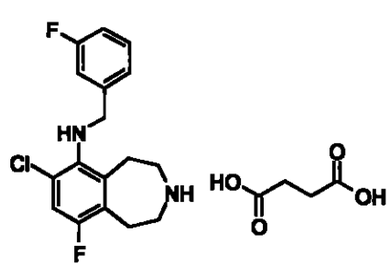
Se disuelve 7-dicloro-6-(3,4-difluorobencilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (150 mg, 0.36 mmol) en tolueno anhidro (20 mL). Se agrega N-clorosuccinimida (140 mg, 1 mmol) y se calienta a 60°C durante 4 h. Se enfría a temperatura ambiente, se vacía la

mezcla de reacción en agua (250 mL) y se extrae con EtOAc (3x50 mL). Se lavan los extractos orgánicos con agua, salmuera, se secan sobre Na_2SO_4, se filtran, y se concentran in vacuo. Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (4:1) para dar 7,9-dicloro-6-(3,4-difluorobencilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (110 mg, 67%). EM (ES+) m/z: 453 $(M+H)^+$.

Se usa un método similar al procedimiento general 1-1 para desproteger 7,9-dicloro-6-(3,4-difluorobencilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (120 mg, 0.26 mmol). Se purifica por cromatografía SCX para dar 7,9-dicloro-6-(3,4-difluorobencilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite amarillo (81 mg, 88%). Se usa un método similar al procedimiento general 2-2, usando 7,9-dicloro-6-(3,4-difluorobencilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (75 mg, 0.21 mmol), para dar el compuesto del título como una goma amarilla (80 mg, 96%). EM (ES+) m/z: 357 $(M+H)^+$.

Ejemplo 306

Succinato de 7-Cloro-9-fluoro-6-(3-fluorobencilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

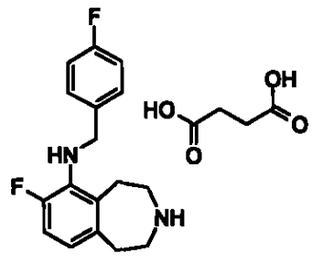


Se usa un método similar al procedimiento general 5-1 para acoplar 7-cloro-9-fluoro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (130 mg, 0.3 mmol) con 3-fluorobencilamina (100 □L, 0.89 mmol). Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (9:1 and 4:1) seguido por cromatografía SCX para dar 7-cloro-9-fluoro-6-(3-fluorobencilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite amarillo (35 mg, 28%). EM (ES+) m/z: 401 $(M+H)^+$.

Se usa un método similar al procedimiento general 1-1 para desproteger 7-cloro-9-fluoro-6-(3-fluorobencilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (32 mg, 0.08 mmol). Se purifica por cromatografía SCX para dar 7-cloro-9-fluoro-6-(3-fluorobencilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite amarillo (10 mg, 45%). Se usa un método similar al procedimiento general 2-1, usando 7-cloro-9-fluoro-6-(3-fluorobencilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (10 mg, 0.033 mmol), para dar el compuesto del título como un sólido amarillo ligero (14 mg, 97%). EM (ES+) m/z: 323 $(M+H)^+$.

Ejemplo 307

Succinato de 7-Fluoro-6-(4-fluorobencilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



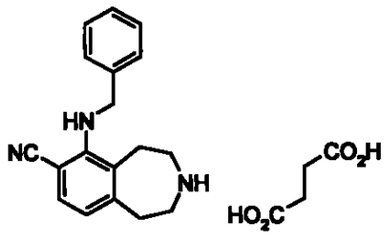
Se usa un método similar al procedimiento general 5-1 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (250 mg, 0.61 mmol) con 4-fluorobencilamina (92 mg, 1.2 equiv.) usando acetato de paladio (II) (0.1 equiv.), BINAP (0.3 equiv.) y carbonato de cesio (1.4 equiv.) en tolueno (5 mL). Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (10:1, 5:1, 3:1 y 1:1) para dar 7-fluoro-6-(4-fluorobencilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite.

Se usa un método similar al procedimiento general 1-3 para desproteger 7-fluoro-6-(4-fluorobencilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina. Se purifica por cromatografía SCX para dar la base libre del compuesto del título. Se usa un método similar al procedimiento general 2-1 para dar el compuesto del título

como un sólido blanco opaco (14 mg, 6%). EM (ES+) m/z: 289 $(M+H)^+$.

Ejemplo 308

Succinato de 6-Bencilamino-7-ciano-2,3,4,5-tetrahidro-1H-benzo[d]azepina

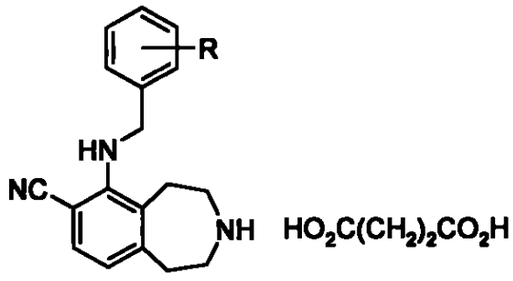


Se usa un método similar al procedimiento general 5-1 para acoplar 7-ciano-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (125 mg, 0.3 mmol) con bencilamina (0.1 mL, 0.9 mmol) usando acetato de paladio (II) (7 mg, 0.03 mmol), BINAP (37 mg, 0.06 mmol) y carbonato de cesio (137 mg, 0.4 mmol) en tolueno (3 mL). Purificación por cromatografía en gel de sílice eluyendo con heptano/EtOAc (4:1 to 1:1) para dar 6-bencilamino-7-ciano-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite claro (60 mg, 54%). EM (ES+) m/z: 374 $(M+H)^+$.

Se usa un método similar al procedimiento general 1-2, usando 6-bencilamino-7-ciano-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (56 mg, 0.15 mmol),

para dar 6-bencilamino-7-ciano-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite claro (38 mg, 93%). EM (ES+) m/z: 278 $(M+H)^+$. Se usa un método similar al procedimiento general 2-1 para dar el compuesto del título como un polvo blanco (39 mg, 71%). EM (ES+) m/z: 278 $(M+H)^+$.

Los ejemplos 309-310 pueden prepararse esencialmente como se describe en el ejemplo 308 al usar 7-ciano-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina y la amina apropiada. Los rendimientos generales y Datos EM (ES+) se muestran en la tabla a continuación.

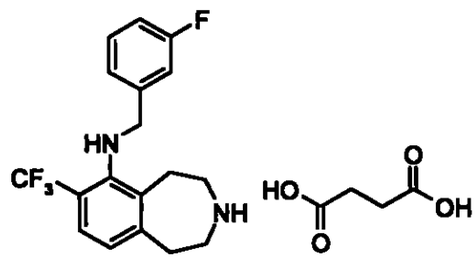


Ej.	R	Compuesto	Rendimiento (%)	EM (ES+) m/z
309	4-F	Succinato de 7-	46	296

		Ciano-6-(4-fluorobencil amino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina		$(M+H)^+$
310	2-F	Succinato de 7-Ciano-6-(2-fluorobencilamino)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	43	296 $(M+H)^+$

Ejemplo 311

Succinato de 6-(3-Fluorobencilamino)-7-trifluorometil-2,3,4,5-tetrahidro-1H-benzo[d]azepina



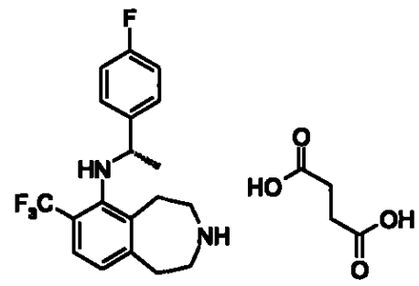
Se usa un método similar al procedimiento general 5-1 para acoplar 3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-7-trifluorometil-2,3,4,5-tetrahidro-1H-benzo[d]azepina (110 mg, 0.24 mmol) y 3-fluorobencil amina (90 µL, 0.7 mmol). Purificación por

cromatografía en gel de sílice eluyendo con hexano/EtOAc (95:5) seguido por cromatografía SCX para dar 6-(3-fluorobencilamino)-3-(2,2,2-trifluoroacetil)-7-trifluorometil-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite amarillo (55 mg, 53%). EM (ES+) m/z: 435 $(M+H)^+$.

Se usa un método similar al procedimiento general 1-1 para desproteger 6-(3-fluorobencilamino)-3-(2,2,2-trifluoroacetil)-7-trifluorometil-2,3,4,5-tetrahidro-1H-benzo[d]azepina (55 mg, 0.13 mmol). Se purifica por cromatografía SCX para dar 6-(3-fluorobencilamino)-7-trifluorometil-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite amarillo (34 mg, 81%). Se usa un método similar al procedimiento general 2-1 para dar el compuesto del título como un sólido blanco opaco (33 mg, 72%). EM (ES+) m/z: 339 $(M+H)^+$.

Ejemplo 312

Succinato de (S)-(-)-6-[1-(4-Fluorofenil)-etilamino]-7-trifluorometil-2,3,4,5-tetrahidro-1H-benzo[d]azepina

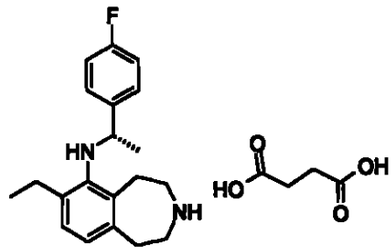


Se usa un método similar al procedimiento general 5-3 para acoplar 3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-7-trifluorometil-2,3,4,5-tetrahidro-1H-benzo[d]azepina (430 mg, 0.94 mmol) con (S)-1-(4-fluorofenil)etilamina (195 mg, 1.40 mmol). Purificación por cromatografía en gel de sílice eluyendo con EtOAc/hexano (1:8) para dar (S)-6-[1-(4-fluorofenil)-etilamino]-3-(2,2,2-trifluoroacetil)-7-trifluorometil-2,3,4,5-tetrahidro-1H-benzo[d]azepina (279 mg, 66%). EM (ES+) m/z: 449 $(M+H)^+$.

Se usa un método similar al procedimiento general 1-1 para desproteger (S)-6-[1-(4-fluorofenil)-etilamino]-3-(2,2,2-trifluoroacetil)-7-trifluorometil-2,3,4,5-tetrahidro-1H-benzo[d]azepina (279 mg, 0.62 mmol). Purificación por cromatografía en gel de sílice eluyendo con DCM/amoniaco 2M en metanol (94:6) para obtener (S)-6-[1-(4-fluorofenil)-etilamino]-7-trifluorometil-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite incoloro (190 mg, 87%). EM (ES+) m/z: 353 $(M+H)^+$. Se usa un método similar al procedimiento general 2-1 para dar el compuesto del título. $[\alpha]^{20}_D$ -96.7° (c 0.5, MeOH).

Ejemplo 313

Succinato de (S)-7-Etil-6-[1-(4-fluorofenil)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



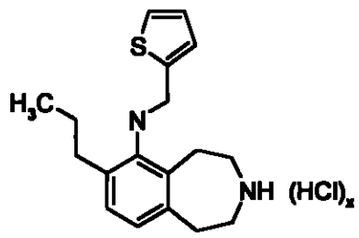
Se usa un método similar al procedimiento general 5-3 para acoplar 7-etil-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina (335 mg, 0.8 mmol) y (S)-1-(4-fluorophenol)etil amina (557 mg, 4.0 mmol). Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (1:0, 9:1 y 17:3) para dar (S)-7-etil-6-[1-(4-fluorofenil)-etilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (127 mg, 39%). EM (ES+) m/z: 409 $(M+H)^+$.

Se usa un método similar al procedimiento general 1-1 para desproteger (S)-7-etil-6-[1-(4-fluorofenil)-etilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina. Purificación por cromatografía en gel de sílice eluyendo con DCM/amoniaco 2M en metanol (93:7) para dar (S)-7-etil-6-[1-(4-fluorofenil)-etilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina (70 mg, 72%). EM (ES+) m/z: 313 $(M+H)^+$. Se usa un método similar al

procedimiento general 2-1 para obtener el compuesto del título.

Ejemplo 314

Clorohidrato de 7-Propil-6-[(2-tienil)metilamino]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al procedimiento general 5-1 para acoplar 7-propil-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 2-(aminometil)-tiofeno. Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (9:1 and 4:1) para dar 7-propil-6-[(2-tienil)metilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un sólido amarillo. EM (ES+) m/z: 397 $(M+H)^+$.

Se usa un método similar al procedimiento general 1-1 para desproteger 7-propil-6-[(2-tienil)metilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina. Se purifica por cromatografía SCX para dar la base libre del compuesto del título como un aceite amarillo. Se usa un

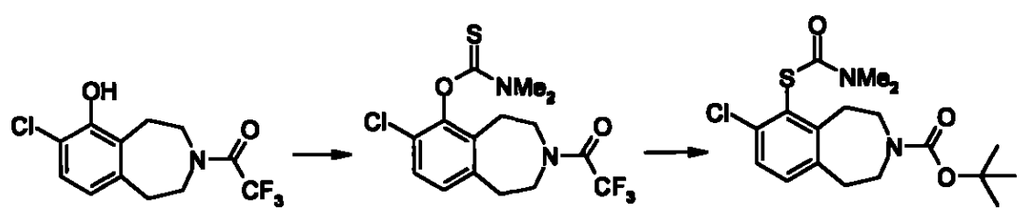
método similar al procedimiento general 2-2 para dar el compuesto del título como un sólido amarillo ligero. EM (ES+) m/z: 301 $(M+H)^+$.

Procedimiento general 7

Se disuelve la 3-tert-butoxicarbonil-6-dimetilcarbamoil-tio-2,3,4,5-tetrahidro-1H-benzo[d]azepina substituida apropiada (1.0 equiv) en metanol (0.1-0.2 M solución). Se agrega hidróxido de potasio (32 equiv.) y se calienta la mezcla a 50°C durante 2-8 h. Se enfría la reacción a temperatura ambiente y se agrega el haluro apropiado (1.0-5.0 equiv.). Se agita la mezcla a temperatura ambiente durante 0.5-16 h. Se removió el solvente in vacuo y se divide el residuo entre DCM y agua. Se extrae la fase acuosa con DCM, se combinan los extractos orgánicos, se secan sobre Na_2SO_4, se filtran y se concentran. Se purifica por cromatografía en gel de sílice eluyendo con mezclaz de hexano/EtOAc para obtener el compuesto deseado.

Preparación 172

3-tert-Butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina



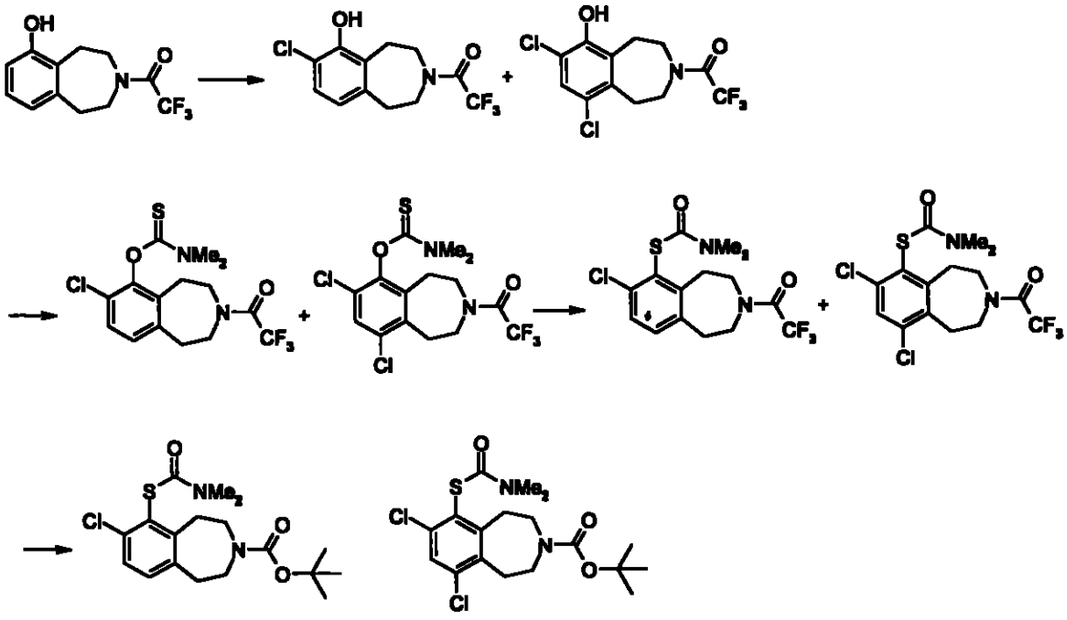
7-Cloro-6-dimetiltiocarbamoiloxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Se coloca 7-cloro-6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (64.3 g, 219 mmol) en acetona (450 mL) y agua (200 mL) con K_2CO_3 (91.8 g, 664 mmol) y cloruro de dimetiltiocarbamoil (31.5 g, 255 mmol). Se agita a temperatura ambiente durante 1.25 h. Se agrega cloruro de dimetiltiocarbamoilo adicional (3 g, 24 mmol) y se agita durante 1.75 horas adicionales a temperatura ambiente. Se agrega más cloruro de dimetiltiocarbamoilo (0.7 g, 5.7 mmol) y agua (150 mL) a la mezcla y se agita durante 0.5 h a temperatura ambiente. Se agrega lentamente agua (500 mL) a la reacción durante 2 h para promover la cristalización y se agita la mezcla espesa resultante a temperatura ambiente durante 1.5 h. Se colecta el sólido por filtración para dar el intermediario deseado (76 g, 91%).

3-tert-Butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Se disuelve 7-cloro-6-dimetiltiocarbamoiloxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (155 g, 407 mmol) en difenil éter (1500 mL) y se calienta a 250°C durante 2.5 h. Se enfría la reacción y se diluye con metanol (308 mL). Se

agrega NaOH 1N acuoso (616 mL) y se agita a 60°C durante 4 h. Se enfría la reacción a temperatura ambiente y se extrae entre DCM (3 x 500 mL) y agua (500 mL). Se combinan los extractos orgánicos y se agregan a HCl 1N acuoso (1 L). Se agita la reacción a temperatura ambiente durante 0.25 h luego se lava con hexano (5 x 400 mL). Se ajusta el pH de la capa acuosa a 7.0 con NaOH 5N acuoso y se mezcla la solución acuosa con DCM (2.5 L). La mezcla se enfría en un baño de hielo y se agrega K_2CO_3 (169 g, 1221 mmol) y bicarbonato de di-t-butilo (67.5 g, 390 mmol) y se agita la reacción a temperatura ambiente durante 0.5 h. Se agrega bicarbonato de di-t-butilo (16.35 g, 75 mmol) y se agita durante 0.3 h a temperatura ambiente. Se agrega bicarbonato de di-t-butilo (0.1 g, 0.46 mmol) y se agita durante 0.25 h a temperatura ambiente. Se concentra la mezcla in vacuo para remover los volátiles y se calienta a 45°C. Se sembró la mezcla con una pequeña cantidad del compuesto del título y se agita durante 1 h a 45°C. Se enfría la reacción en un baño de hielo y se agita durante 2 horas adicionales. Se colecta el sólido resultante por filtración y se enjuaga con hexano frío (100 mL). Se concentra el filtrado in vacuo, se recristaliza a partir de DCM/heptano, y se aislan los sólidos por filtración. Se combinan los sólidos y se secan in vacuo para dar el compuesto del título como un sólido cristalino blanco (142 g, 91%). EM (ES+) m/z 385 $(M+H)^+$.

Preparación 173

3-tert-Butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 3-tert-butoxicarbonil-7,9-dicloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina



7-Cloro-6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 7,9-dicloro-6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina: A una solución de 6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (0.961 g, 3.71 mmol) en tolueno (30 mL) a 70°C, Se agrega

diisobutilamina (52 µL, 0.30 mmol) seguido por adición lenta de cloruro de sulfurilo puro (343 µL, 4.27 mmol). Se agita durante 1 h a 70°C y se concentra in vacuo. Se diluye el residuo con agua, se extrae tres veces con EtOAc, se seca sobre Na_2SO_4 anhidro y se concentra in vacuo para proporcionar una mezcla 4:1 de 7-cloro-6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 7,9-dicloro-6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un sólido blanco (1.07 g, 98%).

7-Cloro-6-dimetiltiocarbamoiloxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 7,9-dicloro-6-dimetiltiocarbamoiloxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina: A una mezcla de 4:1 7-cloro-6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 7,9-dicloro-6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (0.513 g, 1.75 mmol) en dioxano anhidro (10 mL) bajo nitrógeno, se agrega cloruro de dimetil tiocarbamoilo (0.432 g, 3.50 mmol), 4-dimetilaminopiridina (21 mg, 0.18 mmol) y trietilamina (731 µL, 5.24 mmol) y se calienta bajo reflujo durante la noche. Se enfría la mezcla de reacción a temperatura ambiente y se diluye con agua, se extrae tres veces con EtOAc, se seca

sobre Na_2SO_4 anhidro y se concentra in vacuo. Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (17:1) para proporcionar una mezcla de 4:1 7-cloro-6-dimetiltiocarbamoiloxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 7,9-dicloro-6-dimetiltiocarbamoiloxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite amarillo (0.64 g, 95%)

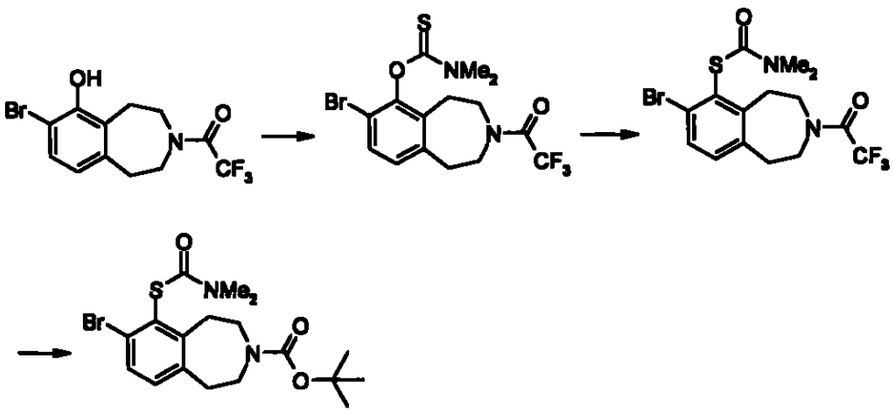
7-Cloro-6-dimetilcarbamoiltio-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 7,9-dicloro-6-dimetilcarbamoiltio-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Se calienta la mezcla de 4:1 7-cloro-6-dimetiltiocarbamoiloxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 7,9-dicloro-6-dimetiltiocarbamoiloxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (0.630 g, 1.66 mmol) en difenil éter (4.5 mL) a 250°C durante 4 h bajo nitrógeno. Se enfría a temperatura ambiente. Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (7:3) para dar una mezcla de 4:1 7-cloro-6-dimetilcarbamoiltio-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 7,9-dicloro-6-dimetilcarbamoiltio-3-(2,2,2-trifluoroacetil)-2,3,4,5-

tetrahidro-1H-benzo[d]azepina como un aceite amarillo (0.54 g, 85%).

3-tert-Butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 3-tert-butoxicarbonil-7,9-dicloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina: A la mezcla 4:1 de 7-cloro-6-dimetilcarbamoiltio-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 7,9-dicloro-6-dimetilcarbamoiltio-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (0.536 g, 1.47 mmol) en metanol (7 mL), se agrega carbonato de potasio acuoso (0.812 g, 5.88 mmol en 1.5 mL de agua). Se agita durante 5 h a temperatura ambiente, se agrega bicarbonato de di-tert-butilo (418 mg, 1.91 mmol) y se agita durante 30 minutos adicionales. Se diluye con EtOAc y agua. Se separaron las capas y se extrae la capa acuosa tres veces con EtOAc. Se secan sobre Na_2SO_4 anhidro, y se concentran in vacuo. Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (7:3) para dar una mezcla de 4:1 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 3-tert-butoxicarbonil-7,9-dicloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un sólido blanco (0.52 g, 96%).

Preparación 174

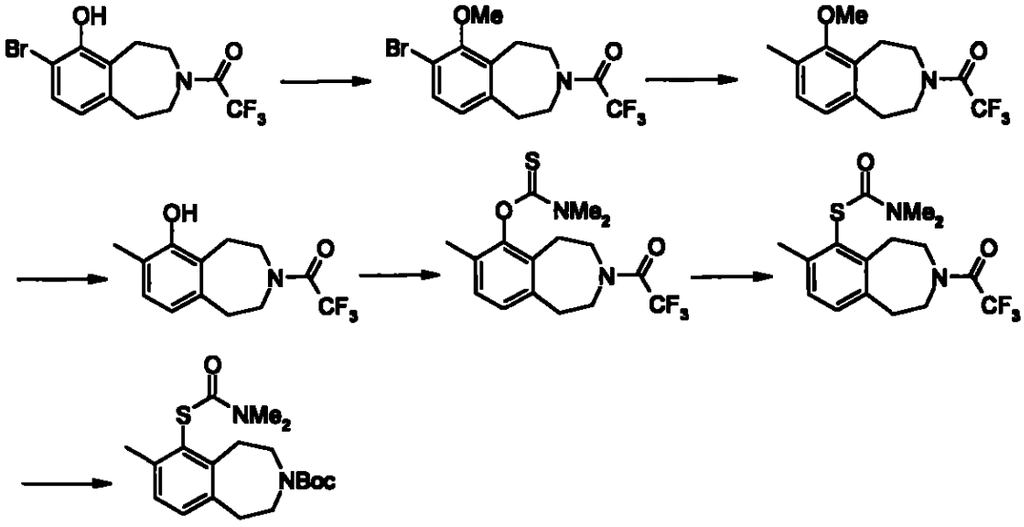
7-Bromo-3-tert-butoxicarbonil-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar para la preparación 172, usando 7-bromo-6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina para dar el compuesto del título.

Preparación 175

3-tert-Butoxicarbonil-6-dimetilcarbamoiltio-7-metil-2,3,4,5-tetrahidro-1H-benzo[d]azepina



7-Bromo-6-metoxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Se agrega carbonato de potasio (10.214 g, 73.9 mmol) a una solución de 7-bromo-6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (5.0 g, 14.8 mmol) en acetona (50 mL) y se agita durante 10 min. Se agrega yoduro de metilo (4.2 g, 1.5 mL, 29.6 mmol) y se agita la mezcla durante la noche a temperatura ambiente. Se removió el solvente in vacuo y se divide el residuo entre agua y DCM. Se extrae la fase acuosa dos veces con DCM. Se combinan los extractos orgánicos, se secan sobre Na_2SO_4, se filtran y se concentran in vacuo para obtener el intermediario deseado como un sólido (5.15 g, 99%). EM (ES+) m/z: 352 $(M+H)^+$.

6-Metoxi-7-metil-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Se agrega carbonato de potasio (5.65 g, 40.91 mmol), tetraquis(trifenilfosfina)paladio (1.576 g, 1.363 mmol) y trimetilboroxina (2.053 g, 2.3 mL, 16.35 mmol) a una solución de 7-bromo-6-metoxi-3-(2,2,2-

trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (4.8 g, 13.63 mmol) en dimetilformamida (40 mL) bajo nitrógeno. Se calienta la mezcla a 115°C durante 6 h. Se agrega agua y se extrae la fase acuosa dos veces con EtOAc. Se combinan los extractos orgánicos, se secan sobre Na_2SO_4, se filtran y se concentran in vacuo. Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (1:0 and 19:1) para obtener el intermediario deseado como un sólido (3.23 g, 83%). GC-EM m/z 287 (M^+).

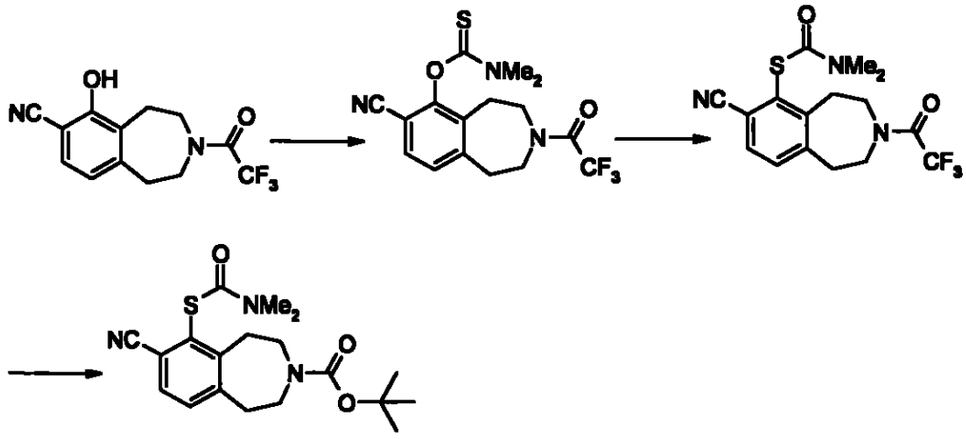
6-Hidroxi-7-metil-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Se agrega tribromuro de boro (21.6 mL, 1.0 M solución en DCM) a una solución de 6-metoxi-7-metil-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (3.1 g, 10.8 mmol) en DCM (200 mL) a 0°C bajo nitrógeno. Se calienta a temperatura ambiente y se agita durante la noche. Se diluye con DCM y se lava con agua. La capa orgánica se seca sobre Na_2SO_4, se filtra y se concentra in vacuo. Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (1:0 y 9:1) para obtener el intermediario deseado como un sólido (2.74 g, 93%). EM (ES+) m/z: 274 $(M+H)^+$.

6-Dimetiltiocarbamoiloxi-7-metil-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Se disuelve 6-hidroxi-

dimetilcarbamoiltio-7-metil-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (1.048 g, 2.9 mmol) en metanol (40 mL). Se agrega una solución de carbonato de potasio (1.6 g, 11.6 mmol) en agua (10 mL). Se agita a temperatura ambiente durante la noche. Se removió el solvente y se divide el residuo entre agua y DCM. Se extrae la fase acuosa dos veces con DCM. Se combinan los extractos orgánicos, se secan sobre Na_2SO_4, se filtran y se concentran. Se disuelve el residuo (0.756 g, 2.86 mmol) en DCM (50 mL). Se agrega trietilamina (0.579 g, 0.8 mL, 2.0 equiv) y bicarbonato de di-tert-butilo (0.624 g, 2.86 mmol) y se agita a temperatura ambiente durante la noche. Se diluye con DCM y se lava con agua. La fase orgánica se seca sobre Na_2SO_4, se filtra y se concentra para obtener el compuesto del título como espuma (1.038 g, 99%). EM (ES+) m/z: 264 $(M+H-Boc)^+$.

Preparación 176

3-tert-Butoxicarbonil-7-ciano-6-dimetilcarbamoilsulfanil-2,3,4,5-tetrahidro-1H-benzo[d]azepina



7-Ciano-6-dimetiltiocarbamoiloxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Se agrega cloruro de dimetiltiocarbamoilo (197 mg, 1.58 mmol) a una solución agitada de 7-ciano-6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (150 mg, 0.53 mmol), DMAP (6 mg, 0.05 mmol) y trietilamina seco (300 µL) en 1,4-dioxano seco (5 mL) bajo una atmósfera de nitrógeno y se calienta a 120°C durante 6 h. Se enfría y se continua agitando durante 2 días a temperatura ambiente. Se diluye con EtOAc, se lava con HCl 1N acuoso, agua, Na_2CO_3 acuoso saturado y salmuera. Se secan sobre $MgSO_4$ luego se concentra in vacuo. Purificación por cromatografía en gel de sílice eluyendo con EtOAc:heptano (0:1 hasta 3:10) para dar el intermediario deseado como un sólido blanco (158 mg, 81%).

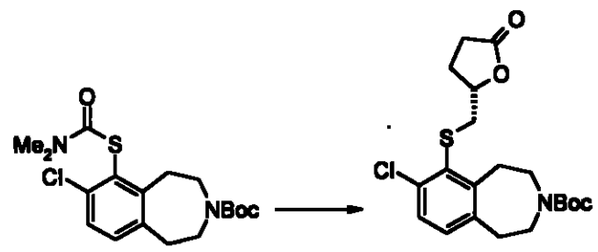
7-Ciano-6-dimetilcarbamoilsulfanil-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Se calienta un matraz de fondo redondo que contiene una solución de 7-ciano-6-dimetiltiocarbamoiloxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (786 mg, 2.12 mmol) en difenil éter (21 mL) en un baño de aceite precalentado a 230°C durante 2 h. Se enfría y se purifica por cromatografía en gel

de sílice eluyendo con EtOAc:heptano (0:1 hasta 1:1) para dar el intermediario deseado como una espuma amarilla (740 mg, 94%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60-7.56 (d, 1H), 7.36-7.30 (d, 1H), 3.88-3.68 (m, 4H), 3.34-3.03 (m, 10H).

3-tert-Butoxicarbonil-7-ciano-6-dimetilcarbamoilsulfanil-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Se agrega carbonato de potasio (4.13 g, 30 mmol) a una solución agitada de 7-ciano-6-dimetilcarbamoilsulfanil-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (740 mg, 2.0 mmol) en metanol (40 mL)/agua (15 mL) y se agita durante 1.5 h. Se agrega DCM (10 mL), bicarbonato de di-tert-butilo (480 mg, 2.2 mmol) y se agita a temperatura ambiente durante 3 días. Se concentra in vacuo y se diluye con DCM, se lava con agua y se extrae con DCM. Las capas orgánicas combinadas, se lava con salmuera, se secan sobre $MgSO_4$ y se concentran in vacuo. Purificación por cromatografía en gel de sílice eluyendo con EtOAc:heptano (0:1 hasta 1:1) para dar el compuesto del título como una espuma incoloro (370 mg, 50%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, J 8 Hz, 1H), 7.29 (d, J 8 Hz, 1H), 3.69-3.48 (m, 4H), 3.26-3.02 (m, 10H), 1.45 (s, 9H).

Preparación 177

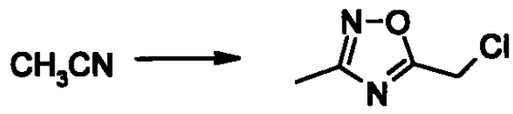
(S)-3-tert-Butoxicarbonil-7-cloro-6-(5-oxo-tetrahidro-furan-2-ilmetiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



A una solución de 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-benzo[d]azepina (137 mg, 0.356 mmol) en metanol (2 mL) se agrega hidróxido de potasio peletizado (640 mg, 11.4 mmol) y se calienta durante 3 h a 50°C. Se enfría a temperatura ambiente, se agrega NH_4Cl acuoso saturado, se extrae tres veces con EtOAc, se secan sobre Na_2SO_4 anhidro, y se concentra in vacuo. Se disuelve el tiofenol crudo así obtenido en DMF seco (2 mL), y se agrega con hidruro de sodio agitado (18 mg, 0.713 mmol, 95% dispersión), seguido por (S)-(+)-dihidro-5-(p-toluilsulfoniloximetil)-2-(3H)-furanona (144 mg, 0.533 mmol). Se continua agitando durante la noche a temperatura ambiente, luego se diluye cuidadosamente con EtOAc y se enfria con NH_4Cl acuoso saturado. Se extrae tres veces con EtOAc, se seca sobre Na_2SO_4 anhidro, y se concentra in vacuo. Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (7:3) para dar el compuesto del título como un aceite incoloro.

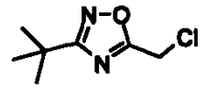
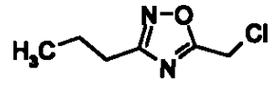
Preparación 178

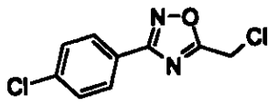
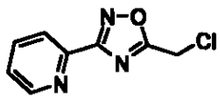
5-Clorometil-3-metil-[1,2,4]oxadiazol



Se agrega con agitación hidroxilamina (50% en agua, 25.0 mL, 0.380 mol) a una solución de acetonitrilo (5.0 mL, 95.0 mmol) y etanol (500 mL). Se calienta a 70°C durante 18 h. se concentra in vacuo para proporcionar N-hidroxiacetamidina cruda (7.0 g, 100 %). Se agrega lentamente con cloroacetato de vinilo agitado (2.1 mL) a N-hidroxiacetamidina (J. Org. Chem. 1971, 36, 1306-1307) (1.00 g, 13.5 mmol) y se calienta a 90°C durante 5 h. Se enfría a temperatura ambiente, se diluye con DCM, se lava con NaOH 1N acuoso saturado, se seca sobre Na_2SO_4 anhidro y se concentra in vacuo para dar el compuesto del título (904 mg, 50%).

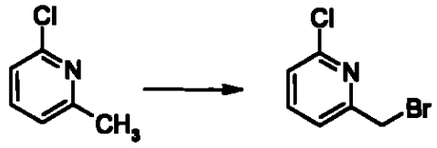
Los compuestos de la preparación 179-182 se prepararon esencialmente como se describe en la preparación 178.

Prep.	Estructura	Compuesto
179		3-tert-Butil-5-clorometil-[1,2,4]oxadiazol
180		5-Clorometil-3-propil-[1,2,4]oxadiazol

181		5-Clorometil-3-(4-cloro-fenil)-[1,2,4]oxadiazol
182		2-(5-Clorometil-[1,2,4]oxadiazol-3-il)-piridina

Preparación 183

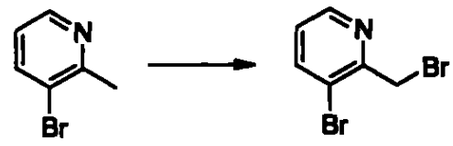
2-Bromometil-6-cloropiridina



Se calienta una mezcla de 2-cloro-6-metilpiridina (5.46 g, 42.8 mmol), NBS (8.38 g, 47.08 mmol), y peróxido de benzoilo (500 mg, 2.06 mmol) en tetracloruro de carbono (80 mL) durante 20 h a 85°C. Se enfría a temperatura ambiente, se filtra, y se concentra in vacuo. Purificación por cromatografía en gel de sílice eluyendo con hexano/tolueno (4:3) para proporcionar el compuesto del título como un sólido blanco (3.64 g, 41%).

Preparación 184

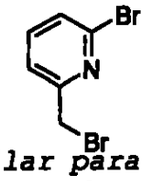
3-Bromo-2-bromometil-piridina



Se calienta una mezcla de 3-bromo-2-metilpiridina (J. Med. Chem. 1987, 30, 871-880) (2.7 g, 15.8 mmol), NBS (3.10 g, 17.42 mmol), y peróxido de benzoilo (190 mg, 0.78 mmol) en tetracloruro de carbono (50 mL) durante la noche a 85°C. Se enfría a temperatura ambiente, se filtra, y se concentra in vacuo. Purificación por cromatografía en gel de sílice eluyendo con tolueno para proporcionar el compuesto del título como un sólido blanco (1.81 g, 45%).

Preparación 185

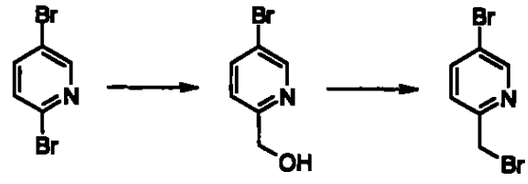
2-Bromo-6-bromometil-piridina



Se usa un método similar para la preparación 184, usando 2-bromo-6-metilpiridina, para dar el compuesto del título.

Preparación 186

5-Bromo-2-bromometilpiridina

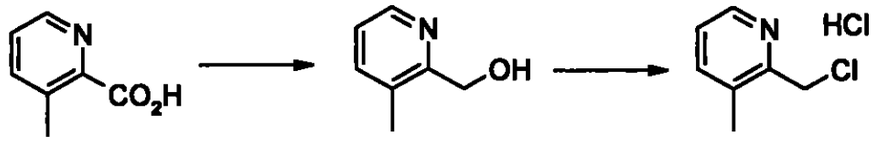


2-Hidroximetil-5-bromopiridina: Se disuelve 2,5-dibromopiridina (10 g, 42 mmol) en tolueno (500 mL) y se enfría a -78°C. Se agrega 2.5M n-butilitio en hexano (20.3 mL, 50.6 mmol) y se agita la mezcla durante 7 h a la misma temperatura. Se agrega DMF (4.2 mL, 54.87 mmol) y se agita durante 1 h. Se calienta la solución a 0°C y se agrega borohidruro de sodio (3.2 g, 84.42 mmol). Se agita la mezcla a temperatura ambiente durante 3 h. Se diluye con EtOAc y NH_4Cl acuoso saturado. Se separaron las capas y se extrae la capa acuosa tres veces con EtOAc. Se secan sobre Na_2SO_4 anhidro, se filtran y se concentran in vacuo. La recristalización del hexano/EtOAc (9:1) da el intermediario deseado como un sólido blanco (5.3 g, 66%).

5-Bromo-2-bromometil-piridina: Se disuelve 2-hidroximetil-5-bromopiridina (5.21 g, 27.7 mmol) en 48% ácido bromhídrico acuoso (20 mL). Se calienta la mezcla a 150°C durante 2 h. Se enfría a temperatura ambiente y se remueve el exceso de ácido bromhídrico bajo vacío. Se diluye con agua, se agrega cuidadosamente $NaHCO_3$ y se extrae tres veces con EtOAc. Se seca sobre Na_2SO_4 anhidro, se filtra y se concentra in vacuo. Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (9:1) para dar el compuesto del título como un aceite rosa (6.0 g, 87%) que se cristalizó en el congelador.

Preparación 187

Clorohidrato de 2-Clorometil-3-metilpiridina



2-Hidroximetil-3-metilpiridina: Se calienta una mezcla de ácido 3-metilpicolínico (1.0 g, 7.3 mmol), carbonato de potasio (4.1 g, 29.7 mmol), y yodometano (4.4 g, 31.0 mmol) en acetona (35 mL) durante la noche bajo reflujo. Se filtra, se lava el residuo con EtOAc, y se concentra in vacuo. Se pasa a través de un tapón corto de gel de sílice eluyendo con hexano/EtOAc (1:1) para proporcionar 2-metoxicarbonil-3-metilpiridina como un líquido amarillo pálido (630 mg, 57%). A una solución de 2-metoxicarbonil-3-metilpiridina en THF anhidro (10 mL) a 0°C, se agrega con una solución agitada de hidruro de aluminio litio 1M en THF (5 mL, 5 mmol), y se continua agitando durante 30 min a 0°C. Se permite que la mezcla se caliente a temperatura ambiente y se apaga cuidadosamente con NaOH 0.5M acuoso. Se calienta la mezcla a 60°C durante 40 min, se enfría a temperatura ambiente, se extrae con EtOAc, se seca sobre Na_2SO_4 anhidro y se concentra in vacuo.

Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (4:3) para dar el intermediario deseado (90 mg, 18%).

Clorohidrato de 2-Clorometil-3-metilpiridina: A 2-hidroximetil-3-metilpiridina (90 mg, 0.73 mmol) en DCM seco (10 mL) a temperatura ambiente, se agrega con cloruro de tionilo agitado (0.53 mL, 7.3 mmol). Se continua agitando durante la noche, se concentra in vacuo, y se hace azeótropo tres veces con cloroformo. Se tritura el residuo con éter seco, se filtra, y se seca bajo vacío para obtener el compuesto del título como un sólido beige (130 mg, 100%).

Preparación 188

2-Clorometil-6-metilpriidina

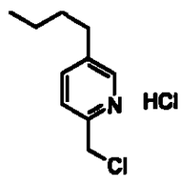


Se agrega con una solución agitada de cloruro de tionilo (0.77 mL, 10.6 mmol) en DCM seco (20 mL) a 2-hidroximetil-6-metilpiridina (1.0 g, 8.12 mmol) en DCM seco (20 mL) a 0°C. Se continua agitando a 0°C durante 1.25 h. Se apaga con isopropanol y se concentra in vacuo. Se disuelve el residuo en DCM, se lava con acuoso saturado $NaHCO_3$, se seca sobre Na_2SO_4 anhidro, y se concentra in

vacuo para dar el compuesto del título. EM (ES+) m/z 142 $(M+H)^+$.

Preparación 189

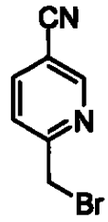
Clorohidrato de 5-Butil-2-clorometilpiridina



Se usa un método similar para la preparación 187, usando ácido fusarico, para dar el compuesto del título. EM (APCI+) m/z 184 $(M+H)^+$.

Preparación 190

6-Bromometilnicotinonitrilo



Se usa un método similar para la preparación 184, usando 5-ciano-2-metilpiridina, para dar el compuesto del título.

Preparación 191

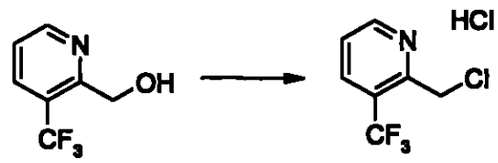
5-Bromometil-piridina-2-carbonitrilo



Se usa un método similar para la preparación 184, usando 5-metil-picolinonitrilo (J. Chem. Soc. 1962, 2637-2658), para dar el compuesto del título.

Preparación 192

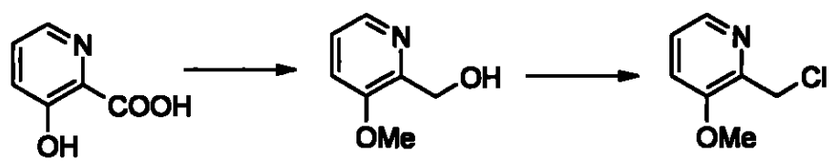
Clorohidrato de 2-Clorometil-3-trifluorometilpiridina



Se usa el método de cloración descrito en la preparación 187, usando 2-hidroximetil-3-trifluorometilpiridina, para dar el compuesto del título. EM (APCI+) m/z 196 $(M+H)^+$.

Preparación 193

2-Clorometil-3-metoxipiridina

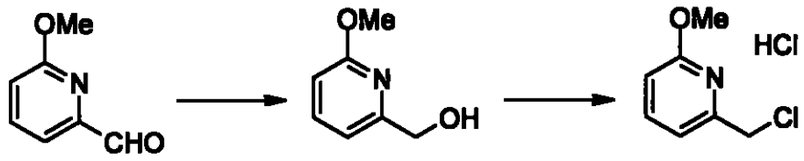


2-Hidroximetil-3-metoxipiridina: Se calienta una mezcla de ácido 3-hidroxipicolínico (5.3 g, 38 mmol), carbonato de potasio (15.8 g, 114 mmol), y yodometano (9.6 mL, 153 mmol) en acetona (100 mL) y DMF (10 mL) durante la noche a 60°C. Se enfría la mezcla de reacción a temperatura ambiente, se vacía en salmuera, se extrae tres veces con éter etílico, se seca sobre $MgSO_4$ anhidro y se concentra in vacuo. Se pasa a través de un tapón corto de gel de sílice eluyendo con éter para proporcionar 3-metoxi-2-metoxicarbonilpiridina como un líquido amarillo pálido (6.3 g, 100%). A una solución de 3-metoxi-2-metoxicarbonil-piridina (2.34 g, 14.0 mmol) en THF seco (25 mL) se agrega lentamente con una solución agitada de hidruro de aluminio y litio 1M en THF (10 mL, 10 mmol) y se continua agitando durante la noche a temperatura ambiente. Se apaga cuidadosamente con decahidrato de sulfato de sodio, se filtra bajo succión y se enjuagan los sólidos con THF adicional. Concentrado in vacuo. Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (3:1) para proporcionar el intermediario deseado como un sólido blanco (350 mg, 18%).

2-Clorometil-3-metoxipiridina: Se usa un método similar para la preparación 188, usando 2-hidroximetil-3-metoxipiridina, para dar el compuesto del título. EM (APCI+) m/z 158 $(M+H)^+$.

Preparación 194

Clorohidrato de 2-Clorometil-6-metoxipiridina

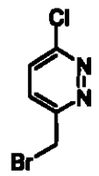


2-Hidroximetil-6-metoxipiridina: Al 6-metoxi-piridina-2-carbaldehído (J. Org. Chem. 1990, 55, 69-73) (11.0 g, 80.3 mmol) en THF húmedo (200 mL) se agrega en porciones con borohidruro de sodio agitado (3.0 g, 79mmol) y se continua agitando durante 1 h a temperatura ambiente. Se agrega salmuera, se extrae la mezcla de reacción dos veces con EtOAc, la capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra in vacuo. Se pasa el residuo a través de un tapón pequeño de gel de sílice eluyendo con hexano/EtOAc (3:1) para proporcionar el intermediario deseado como un líquido claro (9.0 g, 81%).

Clorohidrato de 2-Clorometil-6-metoxipiridina: Se usa el método de cloración descrito en la preparación 187, usando 2-hidroximetil-6-metoxipiridina, para dar el compuesto del título como un sólido amarillo pálido. EM (APCI+) m/z 158 $(M+H)^+$.

Preparación 195

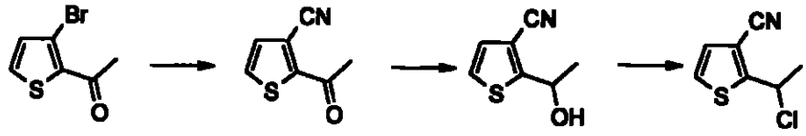
3-Bromometil-6-cloro-piridazina



Se usa un método similar para la preparación 184, usando 3-cloro-6-metilpiridazina, para dar el compuesto del título como un líquido rojo-naranja que se oscurece al reposar.

Preparación 196

(±)-2-(1-Cloroetil)-3-cianotiofeno



2-Acetil-3-cianotiofeno: Se calienta una solución agitada de 2-acetil-3-bromotiofeno (1.49 g, 7.29 mmol) (Chem. Pharm. Bull. 2000, 48, 1558-1566) en NMP seco (72 mL) durante 10 h a 150°C en la presencia de cianuro de cobre (3.26 g, 36.5 mmol). Se diluye la mezcla con agua, se extrae tres veces con éter dietílico, se secan sobre Na_2SO_4 anhidro y se concentra in vacuo. Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (10:1) para dar el intermediario deseado como un aceite oscuro (1.1 g, 99%).

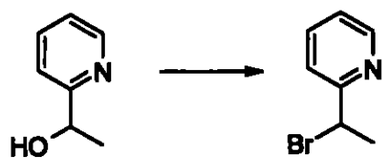
(±)-2-(1-Hidroxietil)-3-cianotiofeno: Se usa un método similar al procedimiento de reducción descrito en la

preparación 194, usando 2-acetil-3-cianotiofeno, para dar el intermediario deseado como un aceite oscuro.

(±)-2-(1-Cloroetil)-3-cianotiofeno: Se usa un método similar para la preparación 188, usando (±)-2-(1-hidroxietil)-3-cianotiofeno, para dar el compuesto del título como un aceite oscuro. Se usa el material crudo sin purificación adicional.

Preparación 197

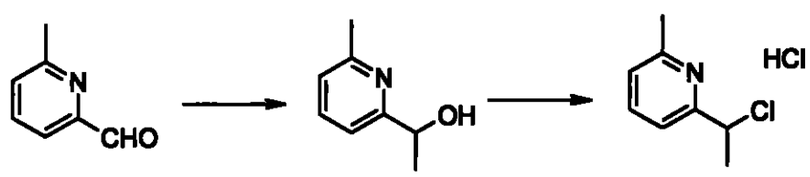
(±)-2-(1-Bromoetil)-piridina



A la (±)-2-(1-hidroxietil)-piridina (Bull. Chem. Soc. Jpn. 1990, 63, 461-465) (10.0 g, 81.3 mmol) en DCM (120 mL) a 0°C, se agrega con trifenilfosfina agitada (22.39 g, 85.365 mmol) seguido por NBS (15.2 g, 85.4 mmol) en porciones. Se calienta la mezcla de reacción a temperatura ambiente y se continua agitando durante 3 h. Se concentra in vacuo y se purifica por cromatografía en gel de sílice eluyendo con hexano/EtOAc (19:1) para dar el compuesto del título.

Preparación 198

Clorohidrato de (±)-2-(1-Cloroetil)-6-metilpiridina

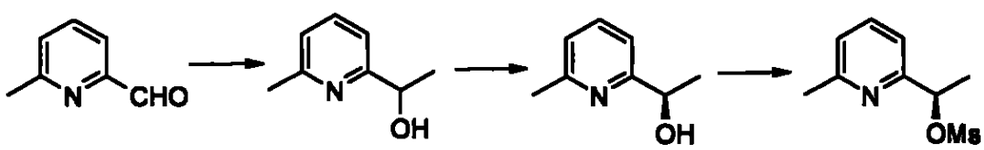


(±)-2-(1-Hidroxietil)-6-metilpiridina: Al 6-metilpiridina-2-carboxaldehído (2.0 g, 16.5 mmol) en THF seco (55 mL) a 0°C bajo nitrógeno, se agrega una solución de bromuro de metil magnesio 3M en éter (6.0 mL, 18.0 mmol,) gota a gota con agitación. Después de 1 h a 0°C, se apaga con NH_4Cl acuoso saturado, se extrae tres veces con EtOAc, se seca sobre Na_2SO_4 anhidro y se concentra in vacuo para dar el intermediario deseado (crudo, 2.3 g).

Clorohidrato de (±)-2-(1-Cloroetil)-6-metilpiridina: A la 2-(1-hidroxietil)-6-metilpiridina cruda (1.6 g, 11.7 mmol) en DCM seco (15 mL) se agrega con cloruro de tionilo agitado (2.0 mL, 27 mmol) y se continua agitando durante la noche. Se concentra in vacuo, se hace azeótropo tres veces con cloroformo seco y se seco bajo alto vacío para proporcionar el compuesto del título como un sólido marrón (1.9 g, 85%). EM (APCI+) m/z 156 $(M+H)^+$.

Preparación 199

Éster de 1-(6-metil-piridin-2-il)-etilo del ácido (R)-Metansulfónico



(±)-1-(6-Metil-piridin-2-il)-etanol: Se usa un método similar para la preparación 198 (Etapa 1), usando 6-metil-2-piridinacarboxaldehído y bromuro de metilmagnesio, para dar el intermediario deseado.

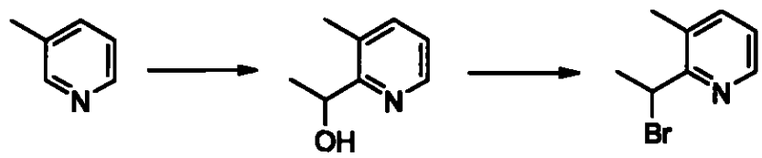
(R)-1-(6-Metil-piridin-2-il)-etanol: Se agita una mezcla de 1-(6-metil-piridin-2-il)-etanol (2.9 g, 21 mmol), polvo de tamiz molecular 4A (3 g), acetato de vinilo (6 mL) y resina acrílica de lipasa de Candida Antartica (0.87 g) en i-Pr_2O (40 mL) a temperatura ambiente durante la noche (J. Org. Chem. 1998, 63, 2481-2487; Synlett 1999, 41-44). Se remueve el residuo sólido por filtración. Se evaporaron las substancias volátiles y se purificaron por cromatografía eluyendo con hexano/EtOAc (7:3 to 1:1) para dar el eluyente rápido éster de 1-(6-metil-piridin-2-il)-etilo del ácido (R)-acético (1.9 g, 50%), y se eluye más lento el (S)-alcohol como un aceite amarillo ligero (1.258 g, 43%). Se disuelve el éster de 1-(6-metil-piridin-2-il)-etilo del ácido (R)-acético (1.72 g, 9.62 mmol) en metanol (50 mL) y se agrega carbonato de potasio (5.3 g, 38.5 mmol) en agua (10 mL). Se agita la mezcla a temperatura ambiente durante 4 h. Se diluye con salmuera, se extrae tres veces con EtOAc, se seca sobre Na_2SO_4

anhidro, se filtra a través de una almohadilla corta de gel de sílice y se concentra in vacuo para dar el intermediario deseado como un aceite incoloro (1.17 g, 89%).

Éster de 1-(6-metil-piridin-2-il)-etilo del ácido (R)-Metansulfónico: A una solución agitada de (R)-1-(6-metil-piridin-2-il)-etanol (175 mg, 1.28 mmol) y trietilamina (355 µl, 2.56 mmol) en DCM (5 mL) a 0°C se agrega cloruro de metansulfonilo (148 µl, 1.92 mmol). Se agita a 0°C durante 30 minutos y se apaga la mezcla de reacción con $NaHCO_3$ acuoso saturado a la misma temperatura. Se extrae la mezcla tres veces con EtOAc, se seca sobre Na_2SO_4 anhidro y se concentra in vacuo. Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (8:2) para dar el compuesto del título como un aceite incoloro (274 mg, 100%).

Preparación 200

(±)-2-(1-Bromoetil)-3-metil-piridina



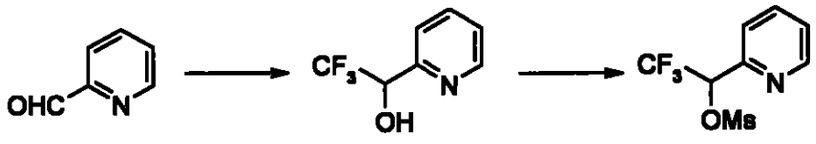
(±)-1-(3-Metil-piridin-2-il)-etanol: Se disuelve N,N-dimetiletanolamina (70.45 mmol) en hexano (90 mL) a 0°C,

se agrega 2.5M n-butil litio en hexano (140.9 mmol,) y se agita durante 30 minutos a esta temperatura. Se agrega una solución de 3-picolina (35.23 mmol) en hexano (10 mL) y se continua agitando a 0°C durante 1 h. Se enfría la mezcla resultante a -78°C, se agrega acetaldehído (70.45 mmol) y se continua agitando a -78°C durante 1 h. Se diluye con agua, se calienta a temperatura ambiente, se extrae tres veces con EtOAc, se seca sobre Na_2SO_4 anhidro y se concentra in vacuo. Se purifica por cromatografía eluyendo con hexano/EtOAc (85:15) para dar el intermediario deseado como un aceite amarillo ligero.

(±)-2-(1-Bromoetil)-3-metil-piridina: Se usa un método similar para la preparación 197, usando 1-(3-fluoro-piridin-2-il)-etanol, para dar el compuesto del título.

Preparación 201

(±)-2-[1-Metansulfoniloxi-(2,2,2-trifluoroetil)]piridina



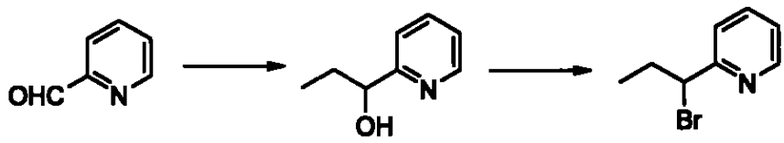
(±)-2-[1-Hidroxi-(2,2,2-trifluoroetil)]-piridina: A una solución agitada de 2-piridina carboxaldehído (2.09 g, 19.5 mmol) y (trifluorometil)trimetilsilano (3.33 g, 23.4 mmol) en

THF (30 mL) a 0°C se agrega fluoruro de tetrabutilamonio 1M en THF (956 µl, 0.956 mmol). Se continua agitando durante 30 min a 0°C y luego a temperatura ambiente durante 2 h. Se agrega HCl 1M acuoso (20 mL) y se agita 2 h a temperatura ambiente. Se diluye con NaOH acuoso 1M a pH 8, se extrae la mezcla tres veces con EtOAc, se secan sobre Na_2SO_4 anhidro, y se concentra in vacuo. Se purifica por cromatografía eluyendo con hexano/EtOAc (8:2) para dar el intermediario deseado como un aceite amarillo (3.22 g, 93%).

(±)-2-[1-Metansulfoniloxi-(2,2,2-trifluoroetil)]piridina: Se usa un método similar para la preparación 199 (Etapa 3), usando (±)-2-[1-hidroxi-(2,2,2-trifluoroetil)]piridina, para dar el compuesto del título.

Preparación 202

(±)-2-(1-Bromopropil)piridina



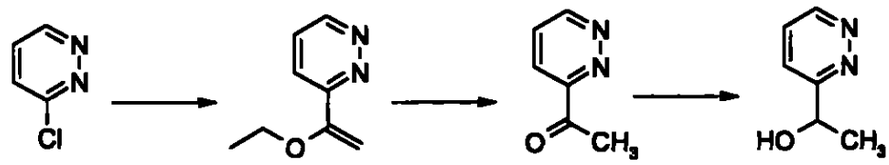
(±)-1-Piridin-2-il-propan-1-ol: A una solución agitada de 2-piridina carboxaldehído (4.0 g, 37.34 mmol) en THF (50 mL) a 0°C, se agrega bromuro de etil magnesio 3M en éter

(18.7 mL, 56.0 mmol), se continua agitando durante 30 min a 0°C y luego a temperatura ambiente durante 2 h. Se agrega agua (200 mL), se extrae tres veces con EtOAc, se secan sobre Na_2SO_4 anhidro, se filtra a través de una almohadilla corta de gel de sílice y se concentra in vacuo para dar el intermediario deseado como un aceite amarillo (3.39 g, 66%).

(±)-2-(1-Bromopropil)piridina: Se usa un método similar para la preparación 197, usando 1-piridin-2-il-propan-1-ol, para dar el compuesto del título.

Preparación 203

(±)-1-Piridazin-3-il-etanol



3-(1-Etoxivinil)piridazina: Se calienta cloruro de piridazina-3 (WO 0107416) (2 g, 17.5 mmol) con tributil-(1-etoxivinil)tin (7.1 mL, 21.1 mmol) y diclorobis(trifenilfosfina)paladio(II) (1.1 g, 1.6 mmol) en DMF (18 mL) a 110°C durante 13 h. La mezcla fría, se diluye con éter (175 mL) y se agrega una solución de fluoruro de potasio (5.43 g, 94 mmol) en agua (10 mL). Después de 1 h, se

filtra la mezcla a través de Celite®, y se lava el filtrado con salmuera. Los extractos orgánicos combinados se secan sobre Na_2SO_4 y se evaporan. Purificación por cromatografía en gel de sílice eluyendo con EtOAc:hexano (0:1 to 6:4) para obtener el intermediario deseado (1.7 g, 65%). CLAR t_R=3.7 min (Zorbax Eclipse XBD-C8 4.6 x 150 mm, columna de 5 micrones, 1.5 mL/min de 90/10 a 10/90 0.1% TFA en agua/acetonitrilo durante 10 min. Detector es a 230 y 254 nm.).

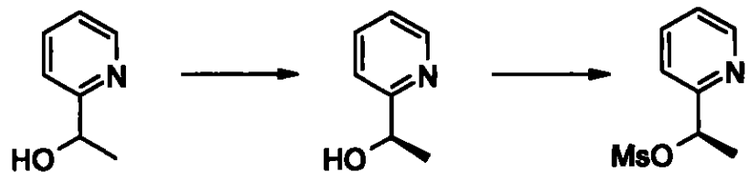
1-Piridazin-3-il-etanona: Se agita 3-(1-etoxivinil)piridazina (1.7 g, 11.3 mmol) en acetona (6.3 mL) y HCl 2.5N acuoso (3.1 mL) durante 2 h a temperatura ambiente y se evapora. Se disuelve el residuo en DCM y se lava la capa orgánica con $NaHCO_3$ acuoso saturado, la capa orgánica se seca sobre Na_2SO_4 y se evapora para obtener el intermediario deseado (1.4 g, 99%). CLAR t_R=1.9 min (Zorbax Eclipse XBD-C8 4.6 x 150 mm, columna de 5 micrones, 1.5 mL/min de 90/10 hasta 10/90 0.1% TFA en agua/acetonitrilo durante 10 min. Los detectores a 230 y 254 nm.).

(±)-1-Piridazin-3-il-etanol: A la 1-Piridazin-3-il-etanona (1.4 g, 11.2 mmol) en metanol (112 mL) se agrega borohidruro de sodio (0.85 g, 22.5 mmol) a 0°C y se agita durante 1 h a temperatura ambiente. Se evapora la mezcla y se purifica por

cromatografía en gel de sílice eluyendo con EtOAc:hexano (1:1 hasta 1:0) y metanol:EtOAc (0:1 hasta 1:9) para obtener el compuesto del título (1.3 g, 93%).

Preparación 204

Éster de metnasulfonato de (R)-(-)-1-(2-Piridinil)etanol



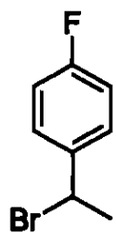
(R)-1-(Piridin-2-il)-etanol: Se agita una mezcla de (±)-1-(piridin-2-il)-etanol (21.2 mmol), polvo de tamiz molecular 4A (3 g), acetato de vinilo (6 mL) y resina acrílica de lipasa Candida Antartica (0.87 g) en i-Pr_2O (40 mL) a temperatura ambiente durante la noche (J. Org. Chem. 1998, 63, 2481-2487; Synlett 1999, 41-44). Se remueve el residuo sólido por filtración. Se evaporan las substancias volátiles y se purificaron por cromatografía eluyendo con hexano/EtOAc (7:3 hasta 1:1) para dar el eluyente rápido éster de 1-(piridin-2-il)-etil del ácido (R)-acético como aceite incoloro (50%) y se eluye más lento (S)-alcohol como un aceite amarillo ligero (43%). Se disuelve éster de 1-(piridin-2-il)-etilo del ácido (R)-acético (9.620 mmol) en metanol (50 mL) y se agrega carbonato de potasio (38.48 mmol) en agua (10 mL). Se agita la mezcla a temperatura ambiente

durante 4 h. Se diluye con salmuera, se extrae tres veces con EtOAc, se secan sobre Na_2SO_4 anhidro, se filtra a través de una almohadilla corta de gel de sílice y se concentra in vacuo para dar el intermediario deseado como un aceite incoloro (89%).

Éster de metansulfonato de (R)-(-)-1-(2-Piridinil)etanol: A una solución agitada de (R)-1-(piridin-2-il)-etanol (1.28 mmol) y trietilamina (2.56 mmol) en DCM (5 mL) a 0°C se agrega cloruro de metansulfonilo (1.92 mmol). Se agita a 0°C durante 30 minutos y se apaga la mezcla de reacción con $NaHCO_3$ acuoso saturado a la misma temperatura. Se extrae tres veces con EtOAc, se seca sobre Na_2SO_4 anhidro, y se concentra in vacuo. Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (4:1) para dar el compuesto del título como un aceite incoloro (100 %). EM (APCI+) m/z 202 $(M+H)^+$; $[\alpha]_D^{25} = -73.5°$ (c 1, $CHCl_3$).

Preparación 205

Bromuro de (±)-1-(4-Fluorofenil)etilo

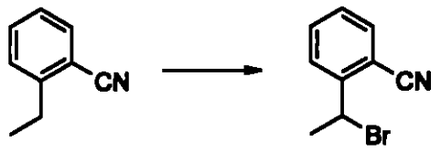


Método A: Se agrega tetrabromuro de carbono (646 mg, 1.95 mmol) a una solución de trifenilfosfina (511 mg, 1.95 mmol) y alcohol (±)-4-fluoro-α-metilbencílico (260 mg, 1.86 mol) en DMF seco (20 mL) a 0°C bajo nitrógeno. Se agita la reacción durante 2 h para dar el compuesto del título. No se requiere purificación adicional.

Método B: Se agrega HBr (460 µL de 48% v/v en agua, 4.28 mmol) a una solución de alcohol (±)-4-fluoro-α-metilbencílico (300 mg, 2.14 mmol) en DCM seco (10 mL) a temperatura ambiente bajo una atmósfera de nitrógeno. Se agita durante 2.5 h. El volumen se reduce in vacuo para dar el compuesto del título. Se diluye con DCM (1 mL) y se usa sin purificación adicional.

Preparación 206

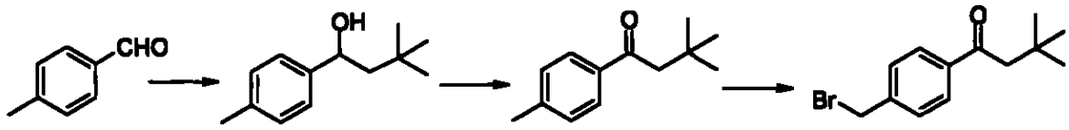
(±)-2-(1-Bromoetil)benzonitrilo



Se usa un método similar para la preparación 184, usando 2-etilbenzonitrilo, para dar el compuesto del título como un líquido claro.

Preparación 207

1-(4-Bromometilfenil)-3,3-dimetilbutan-1-ona



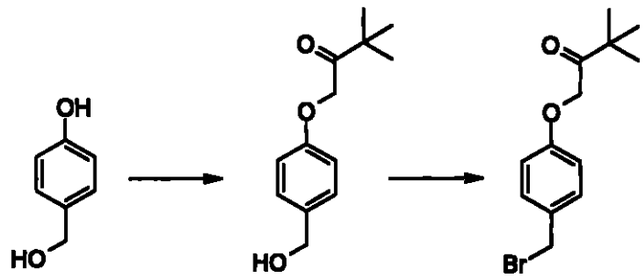
(±)-3,3-Dimetil-1-p-toluilbutan-1-ol: A una solución agitada de 4-metilbenzaldehído (1.51 g, 12.6 mmol) en THF (30 mL) a 0°C, Se agrega cloruro de magnesio neopentilo (33.0 mL, 16.34 mmol, 0.5-1M en éter) y se continua agitando a 0°C durante 1 h. Se diluye con NH_4Cl acuoso saturado, se extrae tres veces con EtOAc, se secan sobre Na_2SO_4 anhidro, y se concentra in vacuo. Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (95:5) para dar el intermediario deseado como un aceite incoloro (2.15 g, 89%).

3,3-Dimetil-1-p-toluil-butan-1-ona: A una solución agitada de (±)-3,3-dimetil-1-p-toluil-butan-1-ol (2.15 g, 11.3 mmol) en hexano (30 mL) se agrega dióxido de manganeso (2.94 g, 33.8 mmol) y se calienta la mezcla durante la noche a 65°C. Se enfría a temperatura ambiente, se filtran las sales de manganeso, y se concentra in vacuo para dar el intermediario deseado como un aceite incoloro (2.2 g, 100%).

1-(4-Bromometilfenil)-3,3-dimetilbutan-1-ona: Se usa un método similar para la preparación 184, usando 3,3-dimetil-1-p-toluilbutan-1-ona, para dar el compuesto del título.

Preparación 208

1-(4-Bromometilfenoxi)-3,3-dimetilbutan-2-ona



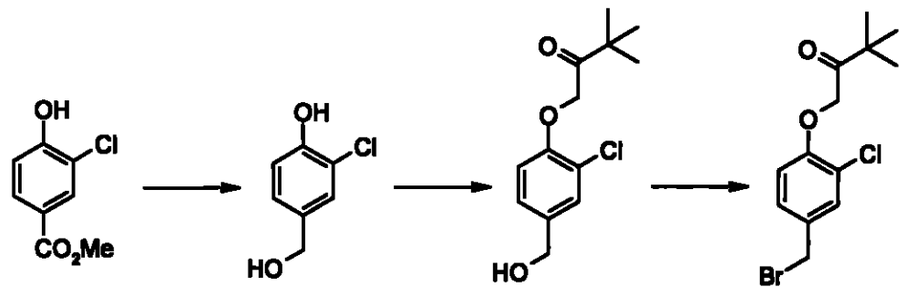
1-(4-Hidroximetilfenoxi)-3,3-dimetilbutan-2-ona: Se mezcla carbonato de potasio (2.764 g, 20 mmol), alcohol 4-hidroxi-bencílico (1.49 g, 12 mmol) en etanol absoluto (100 mL), se agrega 1-bromopinacolona (1.791 g, 10 mmol) gota a gota. Se calienta la mezcla bajo reflujo durante 12 h. Se agrega agua para disolver el sólido, y remover más el etanol in vacuo. Se extrae la mezcla con EtOAc tres veces. Las capas orgánicas combinadas, se lavan con salmuera, se secan sobre Na_2SO_4, se filtran y se concentran. Se purifica el residuo por cromatografía en gel de sílice eluyendo con EtOAc:hexano (1:2) para proporcionar el intermediario deseado como un aceite incoloro (1.08 g, 48%). EM (ES+) m/z: 205 $(M+H-H_2O)^+$.

1-(4-Bromometilfenoxi)-3,3-dimetilbutan-2-ona: Se agrega tribromuro de fosforo (1.45 g, 5.34 mmol) lentamente a una

solución de 1-(4-hidroximetil-fenoxi)-3,3-dimetilbutan-2-ona (1.08 g, 4.85 mmol) en THF anhidro bajo nitrógeno a 0°C. Se agita a 0°C durante 1 h y luego se enjuaga a temperatura ambiente. Se agita durante la noche. Se diluye con EtOAc, se lava con $NaHCO_3$ acuoso saturado, salmuera, se seca sobre Na_2SO_4, se filtra y se concentra. Se purifica el residuo por cromatografía en gel de sílice eluyendo con EtOAc:hexano (1:6) para proporcionar el compuesto del título (1.152 g, 83%). EM (ES+) m/z: 205 $(M-Br)^+$.

Preparación 209

1-(4-Bromometil-3-clorofenoxi)-3,3-dimetilbutan-2-ona



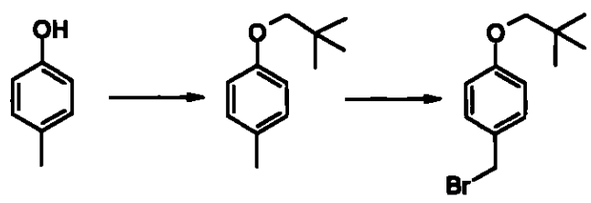
Alcohol 3-Cloro-4-hidroxibencílico: Se agrega una solución de DIBAL-H en tolueno (1.0 M, 35 mL) a una solución de 3-cloro-4-hidroxibenzoato de metilo (1.9 g, 10 mmol) a 0°C bajo nitrógeno. Se agita la reacción a 0°C y gradualmente se calienta a temperatura ambiente durante la noche. Se apaga la reacción con adición lenta de HCl 0.1N acuoso, se agrega más ácido para romper el sólido de tipo gel en dos capas

transparentes. Se separaron la capa orgánica, y se extrae la capa acuosa con EtOAc tres veces. Las capas orgánicas combinadas, se lavan con salmuera, se secan sobre Na_2SO_4, se filtran y se concentran para dar un sólido blanco. EM (ES-) m/z 157 $(M-H)^-$.

1-(4-Bromometil-3-clorofenoxi)-3,3-dimetil-butan-2-ona: Se usa un método similar para la preparación 208 para convertir alcohol 3-cloro-4-hidroxi-bencílico al compuesto del título (1.144 g, 64% dos etapas). EM (ES+) m/z 319.0 $(M+H)^+$.

Preparación 210

1-Bromometil-4-(2,2-dimetil-propoxi)-benceno



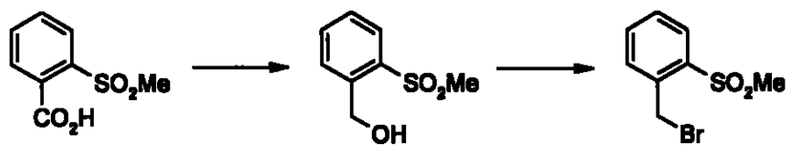
1-(2,2-Dimetil-propoxi)-4-metil-benceno: A una solución de p-cresol (526 mg, 4.87 mmol) en THF (50 mL), se agrega con agitación diisopropil azodicarboxilato (2.16 mL, 10.7 mmol) seguido por trifenilfosfina (306 mg, 11.7 mmol) y alcohol neopentílico (5.15 g, 58.4 mmol). Se calienta a 60°C durante 3 h, se enfría a temperatura

ambiente y se concentra in vacuo. Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc para dar el intermediario deseado como un aceite incoloro.

1-Bromometil-4-(2,2-dimetil-propoxi)-benceno: Se usa un método similar para la preparación 184, usando 1-(2,2-dimetil-propoxi)-4-metilbenceno, para dar el compuesto del título.

Preparación 211

1-Bromometil-2-metansulfonilbenceno

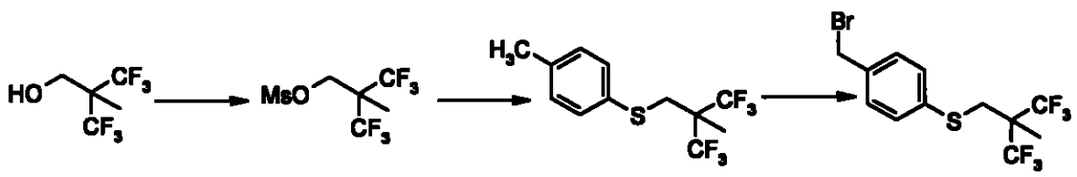


(2-Metansulfonilfenil)metanol: A una solución agitada de ácido 2-metansulfonil-benzoico (2.7 g, 13.5 mmol) en THF seco (60 mL) a 0°C, se agrega una solución de borano en THF (27.0 mL, 0.5 M, 13.5 mmol). Se permite que la mezcla se caliente a temperatura ambiente y se continua agitando durante 2 días. Se apaga el exceso de borano por la adición lenta de metanol, se agrega salmuera, se extrae tres veces con EtOAc, se seca sobre Na_2SO_4 anhidro y se concentra in vacuo para proporcionar el intermediario deseado crudo como un aceite claro, espeso (2.4 g, 97 %).

1-Bromometil-2-metansulfonilbenceno: A una solución agitada de (2-metansulfonil-fenil)metanol (735 mg, 3.99 mmol) en DCM seco (2 mL) a 0°C, se agrega una solución de tribromuro de fósforo 1M en DCM (6.0 mL, 6.0 mmol) y se continua agitando durante 1 h. Se diluye con $NaHCO_3$ acuoso saturado, se extrae tres veces con éter etílico, se secan sobre $MgSO_4$ anhidro y se concentra in vacuo. Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (12:1) para proporcionar el compuesto del título como un sólido blanco (950 mg, 97 %).

Preparación 212

1-Bromometil-4-(3,3,3-trifluoro-2-metil-2-trifluorometilpropiltio)benceno



éster de 3,3,3-trifluoro-2-metil-2-trifluorometil-propilo del ácido metansulfónico: Al 2,2-bis(triflorometil)propanol (4.34 g, 22.1 mmol) en DCM (100 mL) a 0°C se agrega con trietilamina agitada (6.2 mL, 44 mmol) seguido por cloruro de metansulfonilo (2.6 mL, 33 mmol). Después de 15 min a 0°C se diluye con agua y se extrae tres veces con EtOAc. Se seca sobre Na_2SO_4 anhidro y se concentra in vacuo para dar el

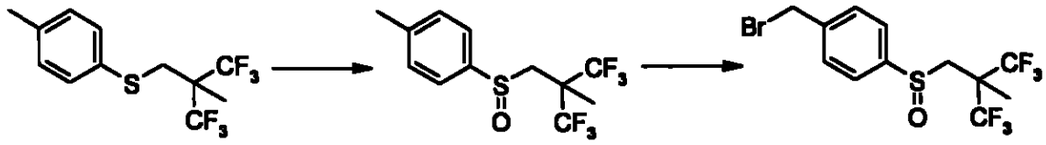
intermediario deseado crudo como un aceite amarillo (6.16 g, 100 %).

1-Metil-4-(3,3,3-trifluoro-2-metil-2-trifluorometilpropiltio)benceno: En un tubo sellado se disuelve 4-metilbencenotiol (4.13 g, 33.2 mmol) en DMF (20 mL) a temperatura ambiente. Se agrega en porciones con hidruro de sodio agitado (899 mg, 37.5 mmol) seguido por yoduro de tetrabutilamonio (82 mg, 0.22 mmol) y una solución de éster de 3,3,3-trifluoro-2-metil-2-trifluorometilpropilo del ácido metansulfónico (6.16 g, 22.5 mmol) en DMF (10 mL). Se agita a 150°C durante la noche, La mezcla fría a temperatura ambiente y se diluye cuidadosamente con agua. Se extrae tres veces con EtOAc, se seca sobre Na_2SO_4 anhidro, y se concentra in vacuo. Purificación por cromatografía en gel de sílice eluyendo con hexano para dar el intermediario deseado como un aceite amarillo (4.5 g, 62 %).

1-Bromometil-4-(3,3,3-trifluoro-2-metil-2-trifluorometilpropiltio)benceno: Se usa un método similar para la preparación 184, usando 1-metil-4-(3,3,3-trifluoro-2-metil-2-trifluorometilpropiltio)benceno, para dar el compuesto del título.

Preparación 213

1-Bromometil-4-(3,3,3-trifluoro-2-metil-2-trifluorometilpropano-1-sulfinil)-benceno



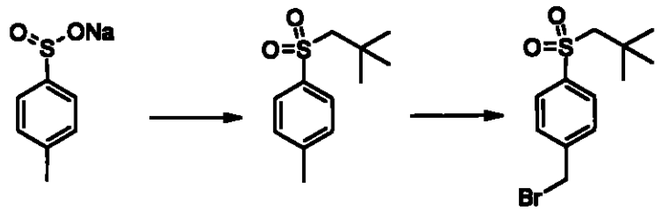
1-Metil-4-(3,3,3-trifluoro-2-metil-2-trifluorometilpropano-1-sulfinil)-benceno: Al 1-metil-4-(3,3,3-trifluoro-2-metil-2-trifluorometilpropiltio)benceno (4.5 g, 14.9 mmol) en ácido acético (15 mL) a temperatura ambiente, se agrega con agitación peróxido de hidrógeno acuoso (15 mL, 30% en agua) y se agita durante 1 h. La reacción se diluye con agua, se extrae tres veces con EtOAc, se seca sobre Na_2SO_4 anhidro, y se concentra in vacuo. Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (9:1) para dar el intermediario deseado como un aceite incoloro (4.125 g, 88 %).

1-Bromometil-4-(3,3,3-trifluoro-2-metil-2-trifluorometilpropano-1-sulfinil)-benceno: al 1-metil-4-(3,3,3-trifluoro-2-metil-2-trifluorometilpropano-1-sulfinil)-benceno (4.13 g, 13.0mmol) en tetracloruro de carbono (50 mL) se agrega NBS (2.31 g, 13.0 mmol), peróxido de benzoilo (314 mg, 1.30 mmol) y se agita durante la noche

a reflujo. Se enfría a temperatura ambiente, se diluye con agua y se extrae tres veces con EtOAc. Se seca sobre Na_2SO_4 anhidro y se concentra in vacuo. Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (9:1) para dar el compuesto del título como aceite incoloro (2.3 g, 55 %).

Preparación 214

1-Bromometil-4-(2,2-dimetilpropano-1-sulfonil)benceno



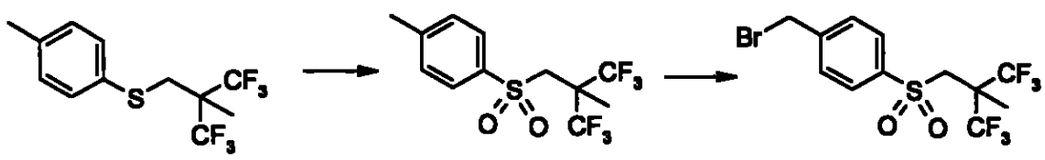
1-(2,2-Dimetil-propano-1-sulfonil)-4-metil-benceno: En un tubo sellado, se disuelve sal de sodio del ácido p-toluensulfínico (5.71 g, 32.1 mmol) en DMF (20 mL) y agua (10 mL). Se agrega bromuro de neo-pentilo (6.3 mL, 48 mmol) y yoduro de tetrabutilamonio (592 mg, 1.60 mmol) y se calienta la mezcla a 145°C durante la noche. Se enfría la reacción a temperatura ambiente, se diluye con agua y se extrae 3 veces con EtOAc. Se seca sobre Na_2SO_4 anhidro y se concentra in vacuo. Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (9:1) para dar el

intermediario deseado como un aceite incoloro (3.3 g, 45 %).

1-Bromometil-4-(2,2-dimetilpropano-1-sulfonil)benceno: Se usa un método similar para la preparación 213 (Etapa 2), usando 1-(2,2-dimetilpropano-1-sulfonil)-4-metil-benceno, para dar el compuesto del título.

Preparación 215

1-Bromometil-4-(3,3,3-trifluoro-2-metil-2-trifluorometilpropano-1-sulfonil)-benceno



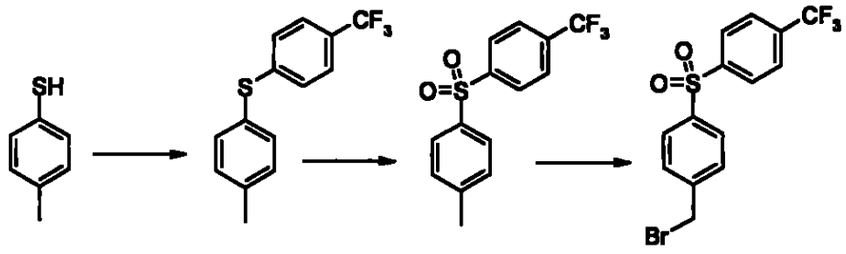
1-Metil-4-(3,3,3-trifluoro-2-metil-2-trifluorometilpropano-1-sulfonil)benceno: al 1-metil-4-(3,3,3-trifluoro-2-metil-2-trifluorometilpropiltio)benceno (3.47 g, 11.49 mmol) en ácido trifluoroacético (15 mL) a temperatura ambiente se agrega con peróxido de hidrógeno acuoso agitado (15 mL, 30% en agua) y se agita durante 1 h. Después de remover el ácido trifluoroacético in vacuo, se diluye con acuoso saturado $NaHCO_3$. Se extrae tres veces con EtOAc, se seca sobre Na_2SO_4 anhidro, y se concentra in vacuo. Purificación por

cromatografía en gel de sílice eluyendo con hexano/EtOAc (9:1) para dar el intermediario deseado como un aceite incoloro (2.8 g, 74 %).

1-Bromometil-4-(3,3,3-trifluoro-2-metil-2-trifluorometilpropano-1-sulfonil)-benceno: Se usa un método similar para la preparación 213 (Etapa 2), usando 1-metil-4-(3,3,3-trifluoro-2-metil-2-trifluorometilpropano-1-sulfonil)benceno, para dar el compuesto del título.

Preparación 216

1-Bromometil-4-(4'-trifluorometil)-fenilsulfonilbenceno



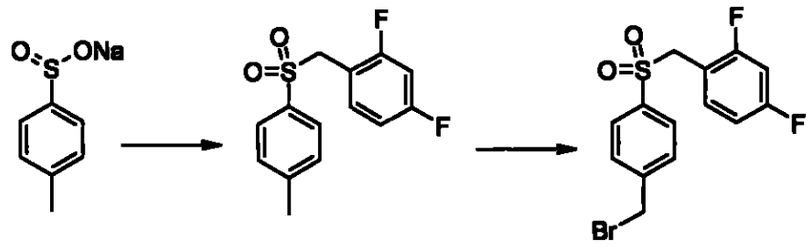
1-Metil-4-(4-trifluorometil)-feniltio-benceno: Se calienta una mezcla de 4-metilbencenotiol (7.67 g, 61.8 mmol), 1-bromo-4-trifluorometil-benceno (4.63 g, 20.6 mmol), 2,2,6,6-tetrametil-3,5-heptanodiona (379 mg, 2.06 mmol), carbonato de cesio (20.1 g, 61.8 mmol) y CuCl (102 mg, 1.03 mmol) en NMP (30 mL) a 150°C durante 3 h. La mezcla fría a temperatura ambiente, se diluye con agua, se extrae tres veces con EtOAc, la capa orgánica se seca sobre Na_2SO_4 anhidro, y se concentra

in vacuo. Se recristaliza el residuo a partir de hexano/EtOAc para dar el intermediario deseado como un sólido blanco (3.87 g, 70%).

1-Bromometil-4-(4-trifluorometil)-fenilsulfonil-benceno: Se usa un método similar para la preparación 215, usando 1-metil-4-(4-trifluorometil)-feniltiobenceno, para dar el compuesto del título.

Preparación 217

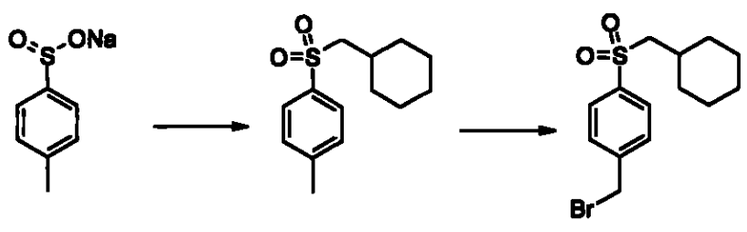
1-(4-Bromometilbencenosulfonilmetil)-2,4-difluorobenceno



Se usa un método similar para la preparación 214, usando bromuro de 2,4-difluorobencilo, para dar el compuesto del título.

Preparación 218

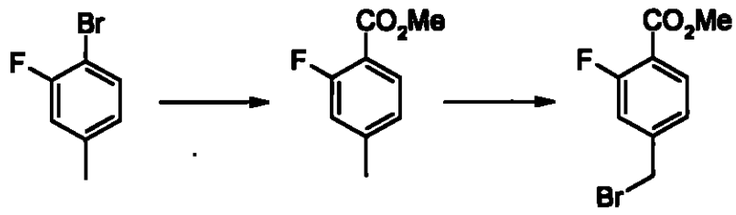
1-Bromometil-4-ciclohexilmetansulfonil-benceno



Se usa un método similar para la preparación 214, usando bromuro de ciclohexilmetilo, para dar el compuesto del título.

Preparación 219

4-bromometil-2-fluorobenzoato de metilo

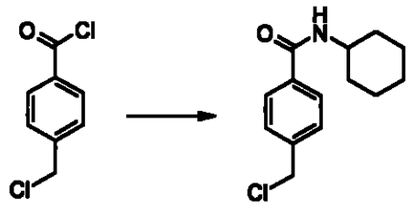


2-fluoro-4-metil-benzoato de metilo: Se mezcla 1-bromo-2-fluoro-4-metilbenceno (15 g, 79.4 mmol), acetato de paladio (712 mg, 3.17 mmol), 1,3-bis(difenilfosfino)-propano (2.94 g, 7.14 mmol), trietilamina (16.1 g, 159 mmol) en metanol (150 mL) y DMF (100 mL). Se desgasifica la mezcla bajo vacuo y se presuriza a 65 psi con monóxido de carbono. Se agita la reacción a 110 °C por 2 días. Se retira el metanol in vacuo, se diluye la mezcla con agua, y se extrae tres veces con EtOAc. Se secan sobre Na_2SO_4 anhidro y se concentra in vacuo. La purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (9:1) para dar el intermediario deseado como un sólido blanco (7.40 g, 55%).

Metil 4-bromometil-2-fluoro-benzoato: Se usa un método similar para la preparación 184, usando 2-fluoro-4-metilbenzoato de metilo, para dar el compuesto del título como un sólido blanco.

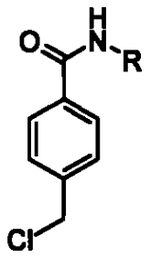
Preparación 220

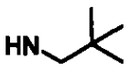
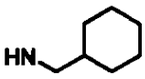
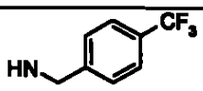
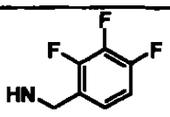
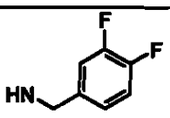
4-Clorometil-N-ciclohexilbenzamida

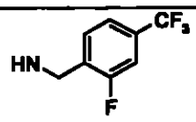
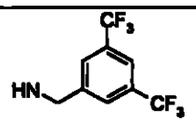
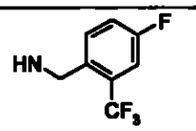
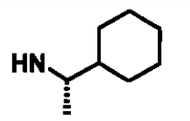
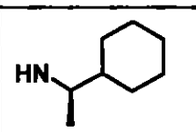
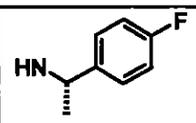
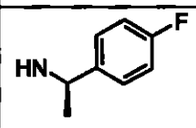


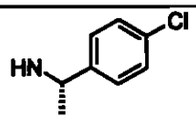
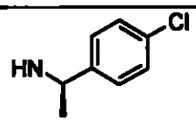
Al cloruro de 4-clorometilbenzoilo (1.03 g, 5.47 mmol) en DCM (20 mL) a 0°C, se agrega con trietilamina agitada (0.839 mL, 6.02 mmol) seguido por ciclohexilamina (0.688 mL, 6.02 mmol), y se continua agitando durante 15 min. La mezcla de reacción se diluye con ácido clorhídrico 1M acuoso, se extrae tres veces con EtOAc, se lava con agua y $NaHCO_3$ acuoso saturado. Los extractos orgánicos combinados se secan sobre Na_2SO_4 anhidro y se concentran in vacuo para dar el compuesto del título como un sólido blanco (1.31 g, 95%).

Los compuestos de las preparaciones 221-235 pueden prepararse esencialmente como se describe en la preparación 220 al usar cloruro de 4-clorometilbenzoilo y la amina apropiada.



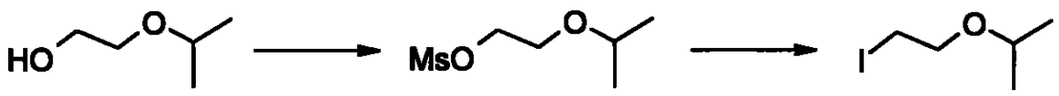
Prep.	NH-R	Compuesto
221		4-Clorometil-N-(2,2-dimetil-propil)-benzamida
222		N-tert-Butil-4-clorometil-benzamida
223		4-Clorometil-N-ciclohexilmetil-benzamida
224		4-Clorometil-N-(4-trifluorometil-benzil)-benzamida
225		4-Clorometil-N-(2,3,4-trifluoro-benzil)-benzamida
226		4-Clorometil-N-(3,4-difluoro-benzil)-benzamida

227		4-Clorometil-N-(2-fluoro-4-trifluorometil-benzil)-benzamida
228		N-(3,5-Bis-trifluorometil-benzil)-4-clorometil-benzamida
229		4-Clorometil-N-(4-fluoro-2-trifluorometil-benzil)-benzamida
230		(S)-4-Clorometil-N-(1-ciclohexil-etil)-benzamida
231		(R)-4-Clorometil-N-(1-ciclohexil-etil)-benzamida
232		(S)-4-Clorometil-N-[1-(4-fluoro-fenil)-etil]-benzamida
233		(R)-4-Clorometil-N-[1-(4-fluoro-fenil)-etil]-benzamida

234		(S)-4-Clorometil-N-[1-(4-cloro-fenil)-etil]-benzamida
235		(R)-4-Clorometil-N-[1-(4-clorofenil)-etil]-benzamida

Preparación 236

2-(2-Iodoetoxi)propano

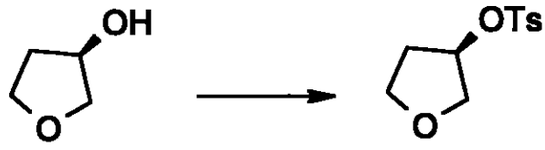


éster de 2-isopropoxietilo del ácido metansulfónico: A una solución agitada de 2-isopropoxietanol (2.0 mL, 17.37 mmol) en DCM (100 mL) a temperatura ambiente se agrega cloruro de metansulfonilo (1.48 mL, 18.08 mmol). Se agrega trietilamina (2.70 mL, 19.37 mmol) lentamente seguido por DMAP (catalítico). Se continua agitando durante la noche y se concentra in vacuo. Se agrega éter dietílico y se filtra. Se lava el filtrado con HCl 1N acuoso, salmuera, y $NaHCO_3$ acuoso saturado. Se seca sobre $MgSO_4$ anhidro y se concentra in vacuo para dar el intermediario deseado (2.97 g, 94%).

2-(2-Iodoetoxi)propano: A una solución agitada de éster de 2-isopropoxi-etilo del ácido metansulfónico (2.95 g, 16.2 mmol) en acetona (200 mL) a temperatura ambiente se agrega yoduro de sodio (7.28 g, 19.4 mmol) y se continua agitando durante la noche. Se concentra in vacuo, se agrega éter dietílico y se filtran, y se concentra in vacuo para dar el compuesto del título como un líquido amarillo pálido (3.12 g, 90%).

Preparación 237

Éster de tetrahidrofuran-3-ilo del ácido (R)-Tolueno-4-sulfónico

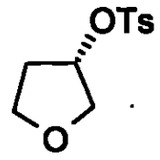


Al (R)-tetrahidro-furan-3-ol (2.0 g, 22.7 mmol), trietilamina (3.8 mL, 27.3 mmol), DMAP (277 mg, 2.26 mmol), y óxido de plata (5.26 g, 22.7 mmol) en DCM seco (30 mL) a 0°C bajo nitrógeno, se agrega en porciones con cloruro de p-toluenosulfonilo agitado (4.76 g, 25.0 mmol). Se calienta a temperatura ambiente durante la noche, se filtra a partir de sales de plata, y se concentra in vacuo. Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (7:1) para dar

el compuesto del título como un líquido claro (4.7 g, 85%).

Preparación 238

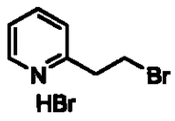
Éster de tetrahidrofuran-3-ilo del ácido (S)-Tolueno-4-sulfónico



Se usa un método similar para la preparación 237, usando (S)-tetrahidro-furan-3-ol, para dar el compuesto del título como un líquido claro.

Preparación 239

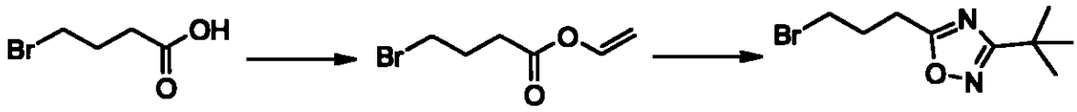
Bromohidrato de 2-(2-Bromoetil)-piridina



Se usa un método similar al procedimiento de bromación descrito en la preparación 186 (Etapa 2), usando 2-piridinaetanol, para dar el compuesto del título. Se recristaliza a partir de 2-propanol para dar un sólido café ligero.

Preparación 240

5-(3-Bromopropil)-3-tert-butil-[1,2,4]oxadiazol

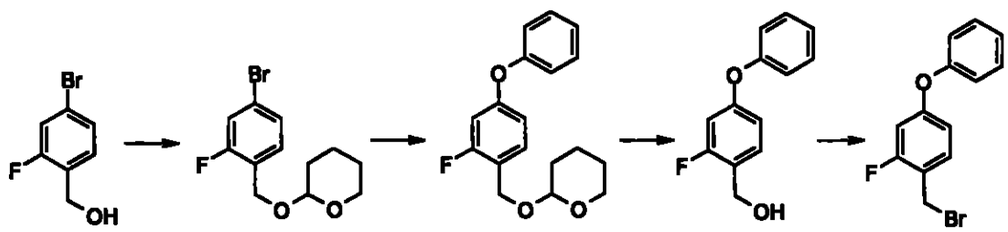


éster de vinilo del ácido 4-Bromobutírico: al ácido 4-bromobutírico (1.0 g, 6.0 mmol) en acetato de vinilo (54 mL) se agrega con acetato de paladio (II) agitado (188 mg, 0.84 mmol) y se continua agitando durante la noche a temperatura ambiente. Se filtra y se concentra in vacuo para proporcionar el intermediario deseado crudo.

5-(3-Bromopropil)-3-tert-butil-[1,2,4]oxadiazol: Se usa un método similar para la preparación 178, usando éster de vinilo del ácido 4-bromobutírico, para dar el compuesto del título.

Preparación 241

1-Bromometil-2-fluoro-4-fenoxibenceno



2-(4-Bromo-2-fluoro-benciloxi)-tetrahidro-pirano: Se mezcla bajo una atmósfera de nitrógeno alcohol 4-bromo-2-

fluorobencílico (4.1 g, 20 mmol), dihidropirano (2 g, 24 mmol), monohidrato del ácido p-toluensulfónico (100 mg, 0.52 mmol), y DCM anhidro (70 mL). Se agita durante 16 h a temperatura ambiente. Se diluye con DCM, se lava secuencialmente con $NaHCO_3$ acuoso saturado luego salmuera. Se separa la capa orgánica, se seca sobre Na_2SO_4 y se concentra in vacuo. Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (1:0 and 9:1) para obtener el intermediario deseado como un aceite claro (4.36 g, 75%). EM (ES+) m/z: 312 $(M+Na)^+$.

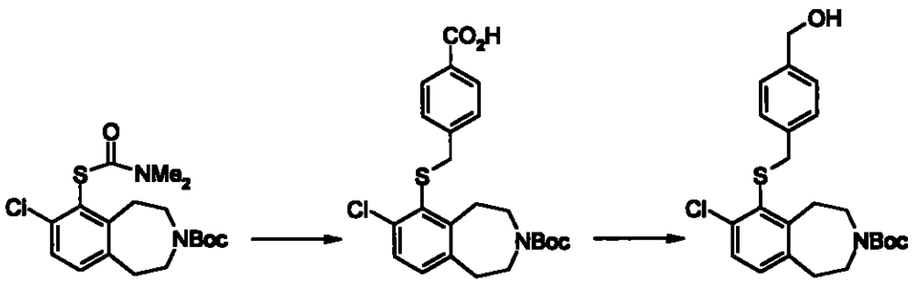
2-(2-Fluoro-4-fenoxi-benciloxi)-tetrahidro-pirano: Se mezcla bajo una atmósfera de argón 2-(4-bromo-2-fluorobenciloxi)-tetrahidropirano (2.9 g, 10 mmol), fenol (1.9 g, 20 mmol), 2,2,6,6-tetrametilheptano-3,5-diona (184.3 mg, 1.0 mmol), carbonato de cesio (6.5 g, 20 mmol) y NMP anhidro (20 mL). Se desgasifica el matraz y se llena con argón. Se agrega cloruro de cobre (I) (495 mg, 5 mmol) rápidamente. Se desgasifica el matraz tres veces luego se llena con argón. Se calienta a 120°C durante 3 h. Se enfría a temperatura ambiente. Se diluye con EtOAc y se filtra. Se concentra in vacuo y se purifica por cromatografía en gel de sílice para obtener el intermediario deseado (2.05 g, 68%). EM (ES+) m/z: 325 $(M+Na)^+$.

(2-Fluoro-4-fenoxi-fenil)-metanol: Se mezcla bajo atmósfera de nitrógeno 2-(2-fluoro-4-fenoxi-benciloxi)-tetrahidropirano (2.05g, 6.8 mmol), metanol (60 mL) y monohidrato del ácido p-toluensulfónico (260 mg, 1.35 mmol). Se agita a temperatura ambiente durante 16 h. Se diluye con EtOAc. Se lava con $NaHCO_3$ acuoso saturado. Se separa la capa orgánica, se seca sobre Na_2SO_4 y se concentra in vacuo para dar el intermediario deseado (1.41 g, 95%). EM (ES+) m/z: 201 $(M-OH)^+$.

1-Bromometil-2-fluoro-4-fenoxi-benceno: Se disuelve bajo atmósfera de nitrógeno (2-fluoro-4-fenoxifenil)-metanol (1.41 g, 6.5 mmol) en THF anhidro (60 mL). Se enfría a 0°C en un baño de hielo. Se agrega tribromuro de fósforo (2.11 g, 7.8 mmol). Se agita frío durante 1 h, luego se remueve el baño de hielo y se agita a temperatura ambiente durante 16 h. Se apaga la reacción con $NaHCO_3$ acuoso saturado. Se extrae tres veces la fase acuosa con EtOAc. Las fracciones orgánicas combinadas, se lavan con salmuera, se secan sobre Na_2SO_4 y se concentran in vacuo. Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (9:1). Se evapora el solvente para obtener el compuesto del título (1.31 g, 72%).

Preparación 242

3-tert-Butoxicarbonil-7-cloro-6-(4-hidroximetil-benciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



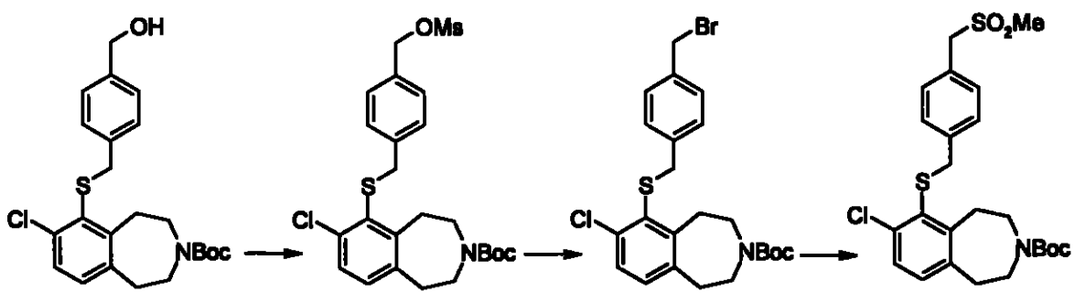
3-tert-Butoxicarbonil-6-(4-carboxi-benciltio)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina: A una solución de 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina (1.0 g, 2.6 mmol) en metanol (15 mL) bajo nitrógeno, se agrega con hidróxido de potasio agitado (4.5 g, 80.3 mmol) a temperatura ambiente. Se calienta a 55-60°C durante 2 h, se enfría a temperatura ambiente, y se agrega 4-bromometilbenzoato de metilo (1.2 g, 5.2 mmol). CCD después de 20 minutos mostró la formación del producto; sin embargo, después de 4 horas a temperatura ambiente ambos CCD y CL/EM indicaron que se completa la hidrólisis del éster y el carbamato. Se diluye con NH_4Cl acuoso saturado, se extrae tres veces con EtOAc, se secan sobre $MgSO_4$ anhidro, y se concentra in vacuo. Se

disuelve el material crudo en THF (10 mL), se trata con di-tert-butil-bicarbonato (2 equiv) y $NaHCO_3$ acuoso saturado (10 mL), y se agita durante la noche. Se extrae tres veces con EtOAc, se seca sobre $MgSO_4$ anhidro y se concentra in vacuo para dar el intermediario deseado como un aceite que se usó sin purificación adicional [2.32 g, 50% pureza con $(Boc)_2O$]. EM (ES+) m/z 348 $(M+H-Boc)^+$.

3-tert-Butoxicarbonil-7-cloro-6-(4-hidroximetil-benciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina: A una solución de 3-tert-butoxicarbonil-6-(4-carboxibenciltio)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina (1.85 g, 50% pureza, 2.06 mmol) en THF anhidro (40 mL) bajo nitrógeno, se agrega con borano 1M agitado en THF (4.2 mL) a 0°C. Se calienta a temperatura ambiente y se agita 2-3 h. Se apaga por la adición cuidadosa de agua (3 mL), se diluye con $NaHCO_3$ acuoso saturado, se extrae tres veces con éter etílico, se seca sobre $MgSO_4$ anhidro, y se concentra in vacuo. Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (5:1) para proporcionar el compuesto del título como un sólido blanco (485 mg, 54 %).

Preparación 243

3-tert-Butoxicarbonil-7-cloro-6-(4-metansulfonilmetilbenciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



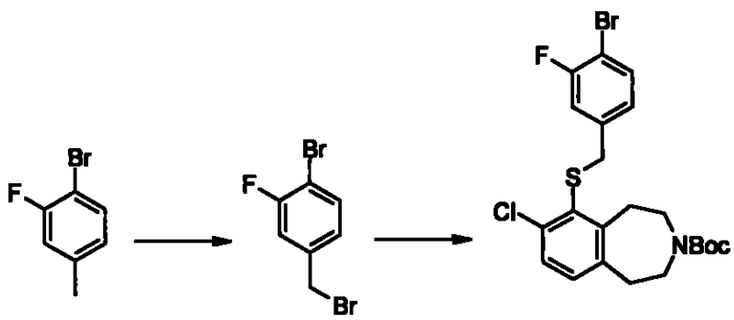
3-tert-Butoxicarbonil-7-cloro-6-(4-metansulfoniloximetil-benciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina: A una solución agitada de 3-tert-butoxicarbonil-7-cloro-6-(4-hidroximetil-benciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (170 mg, 0.391 mmol) en DCM anhidro bajo nitrógeno, se agrega cloruro de metansulfonilo (33 µL, 0.426 mmol) y trietilamina (61 µL, 0.44 mmol) y se continua agitando durante 2 h. Se diluye con agua (5 mL) y se extrae tres veces con DCM. Se lavan los extractos orgánicos combinados con salmuera, se secan sobre Na_2SO_4 anhidro, y se concentran in vacuo para obtener el intermediario deseado que se usó sin purificación adicional.

3-tert-Butoxicarbonil-6-(4-bromometil-benciltio)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Se disuelve el 3-tert-butoxicarbonil-7-cloro-6-(4-metansulfoniloximetil-benciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina cruda en acetona anhidro (3 mL), se trata con bromuro de litio anhidro (335 mg, 3.89 mmol) y se continua agitando durante la noche. Se agrega agua, se extrae la mezcla de reacción tres veces con éter etílico, se lava con salmuera, se seca sobre $MgSO_4$ anhidro, y se concentra in vacuo para obtener el intermediario deseado que se usó sin purificación adicional.

3-tert-Butoxicarbonil-7-cloro-6-(4-metansulfonilmetil-benciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina: A la 3-tert-butoxicarbonil-6-(4-bromometil-benciltio)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina cruda en DMF anhidro (1 mL) bajo nitrógeno, se agrega con metansulfinato de sodio agitado (400 mg, 3.9 mmol), y se continua agitando durante 30 minutos a temperatura ambiente seguido por 2 h a 40°C. Se agrega agua, se extrae tres veces con EtOAc, se lava con salmuera, se seca sobre $MgSO_4$ anhidro, y se concentra in vacuo. Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (3:1) para dar un aceite claro que se solidifica en reposo hasta dar un sólido blanco (118 mg, 61%).

Preparación 244

6-(4-Bromo-3-fluorobenciltio)-3-tert-butoxicarbonil-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina

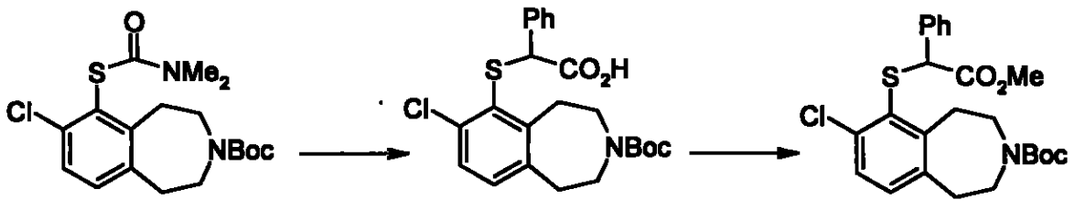


1-Bromo-4-bromometil-2-fluorobenceno: Se usa un método similar para la preparación 184, usando 4-bromo-3-fluorotolueno, para dar el intermediario deseado como un sólido blanco.

6-(4-Bromo-3-fluorobenciltio)-3-tert-butoxicarbonil-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Se usa un método similar para la preparación 177, usando 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 1-bromo-4-bromometil-2-fluorobenceno, para dar el compuesto del título como un sólido blanco.

Preparación 245

(±)-3-tert-Butoxicarbonil-7-cloro-6-(1-metoxicarbonil-1-fenil-metilltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



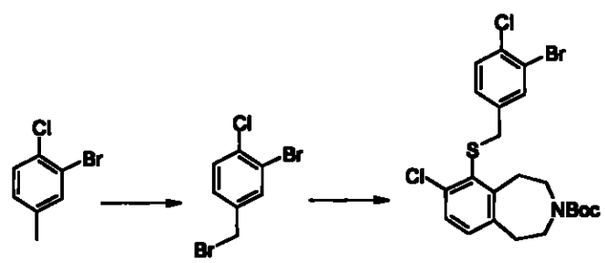
(±)-3-tert-Butoxicarbonil-6-(1-carboxi-1-fenil-metilltio)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina: A una solución de 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina (1.23 g, 3.2 mmol) en metanol (20 mL) bajo nitrógeno, se agrega con hidróxido de potasio agitado (5.36 g, 95.5 mmol) a temperatura ambiente. Se calienta a 55-60°C durante 2 h, se enfría a temperatura ambiente, y se agrega α-bromofenilacetato de metilo (600 µL, 3.81 mmol). Después de 30 min, se diluye con NH_4Cl acuoso saturado, se extrae tres veces con EtOAc, se seca sobre $MgSO_4$ anhidro, y se concentra in vacuo. Se disuelve el material crudo en THF (10 mL), se trata con di-tert-butil-bicarbonato (2 equiv) y $NaHCO_3$ acuoso saturado (10 mL), y se agita durante la noche. Se extrae tres veces con EtOAc, se seca sobre $MgSO_4$ anhidro y se concentra in vacuo para dar el

intermediario deseado como un aceite que se usó sin purificación (1.1 g, 77%).

(±)-3-tert-Butoxicarbonil-6-(1-metoxicarbonil-1-fenil-metilltio)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Se trata una solución de 3-tert-butoxicarbonil-6-(1-carboxi-1-fenil-metiltio)-7-cloro-2,3,4,5-tetrahidrobenzo[d]azepina (200 mg, 0.447 mmol) en DMF anhidro (2 mL) con yoduro de metilo (317 mg, 2.237 mmol) y carbonato de potasio (310 mg, 2.237 mmol) durante 1.5 h a temperatura ambiente. Se agrega agua y se extrae la fase acuosa tres veces con EtOAc. La fase orgánica se seca sobre $MgSO_4$ y se concentra para obtener el compuesto del título que se usó sin purificación adicional.

Preparación 246

6-(3-Bromo-4-cloro-benciltio)-3-tert-butoxicarbonil-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina

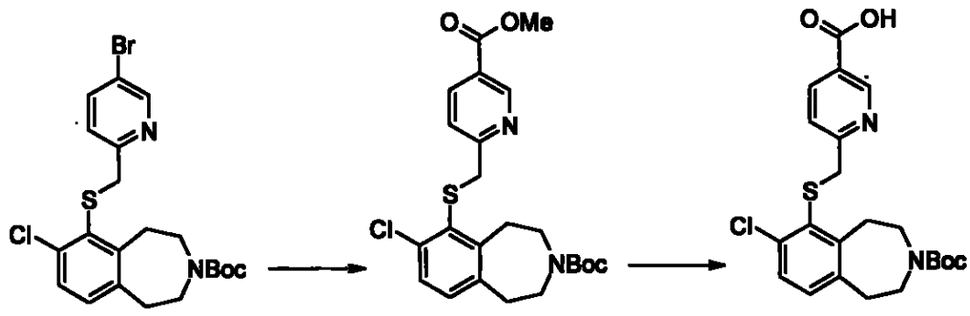


2-Bromo-4-bromometil-1-cloro-benceno: Se usa un método similar para la preparación 184, usando 3-bromo-4-clorotolueno, para dar el intermediario deseado.

6-(3-Bromo-4-cloro-benciltio)-3-tert-butoxicarbonil-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Se usa un método similar para la preparación 177, usando 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoilsulfanil-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 2-bromo-4-bromometil-1-cloro-benceno, para dar el compuesto del título.

Preparación 247

3-tert-Butoxicarbonil-6-(5-carboxi-piridin-2-ilmetiltio)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina



3-tert-Butoxicarbonil-7-cloro-6-(5-metoxicarbonil-piridin-2-ilmetiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Se disuelve 3-tert-butoxicarbonil-6-(5-bromopiridin-2-ilmetiltio)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina (2.13 g, 4.40 mmol), acetato de paladio (35 mg, 0.156 mmol), 1,1'-bis(difenilfosfino)ferroceno (150 mg, 0.271 mmol) y trietilamina (1.30 mL) en metanol (10 mL) y DMF (5 mL).

Se desgasifica y luego se calienta bajo un globo llenado con monóxido de carbono a 75°C durante 10 h. Se remueve el metanol in vacuo, y se diluye la mezcla con agua. Se extrae tres veces con EtOAc, se secan sobre Na_2SO_4 anhidro, y se concentra in vacuo. Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (7:1) para dar el intermediario deseado como un aceite claro (1.86 g, 91%). EM (APCI+) m/z 463 $(M+H)^+$, 363 $(M+H-Boc)^+$.

3-tert-Butoxicarbonil-6-(5-carboxi-piridin-2-ilmetiltio)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Se disuelve 3-tert-butoxicarbonil-7-cloro-6-(5-metoxicarbonil-piridin-2-ilmetiltio)-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina (1.86 g, 4.03 mmol) en metanol (25 mL). Se agrega hidróxido de litio acuoso 1M (12 mL) y se agita a temperatura ambiente durante la noche. Se remueve metanol in vacuo, y se diluye la mezcla con HCl 0.5M acuoso frío hasta pH 4. Se agrega salmuera y se extrae tres veces con EtOAc. Se secan sobre Na_2SO_4 anhidro, y se concentra in vacuo para dar el compuesto del título como un sólido blanco opaco (1.78 g, 95%). EM (APCI+) m/z 449 $(M+H)^+$, 349 $(M+H-Boc)^+$.

Preparación 248

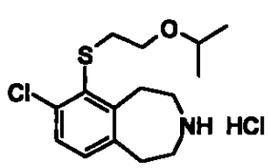
6-(4-Bromo-tiofen-2-ilmetiltio)-3-tert-butoxicarbonil-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina

3-Bromo-5-bromometil-tiofeno: Se usa el procedimiento de bromación descrito en la preparación 211 (Etapa 2), usando (3-bromotiofen-2-il)metanol (Síntesis 1983, 1, 73-75), para dar el intermediario deseado como un líquido café claro.

6-(4-Bromo-tiofen-2-ilmetiltio)-3-tert-butoxicarbonil-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Se usa un método similar para la preparación 177, usando 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 3-bromo-5-bromometil-tiofeno, para dar el compuesto del título como una goma.

Ejemplo 315

Clorohidrato de 7-Cloro-6-(2-isopropoxietiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

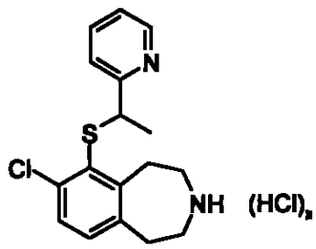


A una mezcla 4:1 de 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y

3-tert-butoxicarbonil-7,9-dicloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina (200 mg, 0.52 mmol) en metanol (5 mL) bajo nitrógeno, se agrega hidróxido de potasio (0.9 g, 16.1 mmol) a temperatura ambiente. Cuando la mezcla se volvió homogénea, se calienta a 55-60°C durante 2-3 h, hasta que la CCD mostró la desaparición del material de partida. Se enfría a temperatura ambiente, se agrega cloruro de amonio saturado acuoso, se extrae tres veces con éter dietílico, se seca sobre $MgSO_4$ anhidro, y se concentra in vacuo. Se disuelve la 3-tert-butoxicarbonil-7-cloro-6-mercapto-2,3,4,5-tetrahidro-1H-benzo[d]azepina cruda en THF anhidro (5 mL) bajo nitrógeno y se agrega con t-butóxido de potasio 1.0 M agitado en THF (1.0 mL) a temperatura ambiente. Después de 10 min, Se agrega 2-(2-iodoetoxi)propano (223 mg, 1.04 mmol), y se permite que la reacción se continue durante la noche. Se diluye con cloruro de amonio saturado acuoso, se extrae la mezcla tres veces con éter dietílico, se seca sobre $MgSO_4$ anhidro, y se concentra in vacuo. Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (12:1) para proporcionar 3-tert-butoxicarbonil-7-cloro-6-(2-isopropoxi-etiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite claro (127 mg, 63 %). Se usa un método similar al procedimiento general 1-4 para dar el compuesto del título como un sólido blanco. EM (ES+) m/z: 300 $(M+H)^+$.

Ejemplo 316

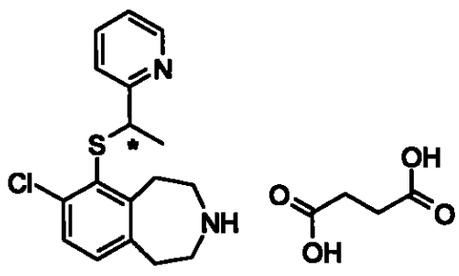
Clorohidrato de (±)-7-Cloro-6-(1-piridin-2-il-etiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al procedimiento general 7, usando 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y (±)-2-(1-bromoetil)-piridina para dar, después de la desprotección por un método similar al procedimiento general 1-4, el compuesto del título como un sólido blanco. EM (APCI+) m/z: 319 $(M+H)^+$.

Ejemplo 317

Succinato de (-)-7-Cloro-6-(1-piridin-2-il-etiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

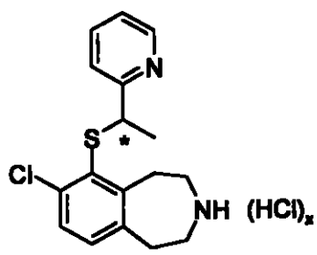


Se separaron los enantiómeros de la (±)-7-cloro-6-(1-piridin-2-il-etiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina por cromatografía de fase normal quiral (columna Chiralpak AD 8x30 cm, eluyendo con 0.2% DMEA en metanol). Se toma el segundo isómero eluido y se purifica por cromatografía en gel de sílice eluyendo con DCM/amoniaco 2M en metanol (100:1 hasta 80:20).

Se usa el procedimiento general 2-1 para dar el compuesto del título como un sólido blanco (4.27 g, 33%). EM (ES+) m/z: 319 $(M+H)^+$; ee = 99.4%; $[\alpha]^{20}_D$ -179° (c 0.5, CH_3OH).

Ejemplo 318

Clorohidrato de (-)-7-Cloro-6-(1-piridin-2-il-etiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

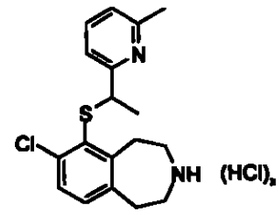


Se usa un método similar al procedimiento general 7, excepto que la alquilación se lleva a cabo a 0°C, para hacer reaccionar 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina con

éster de metansulfonato de (R)-(-)-1-(2-piridinil)etanol. Se usa un método similar al procedimiento general 1-4 para dar el compuesto del título como un sólido blanco. EM (APCI+) m/z: 319 $(M+H)^+$; ee = 98.6% [CLAR quiral: columna Chiralpak AD-H 0.46x15 cm, eluyendo con 15:85 etanol/heptano].

Ejemplo 319

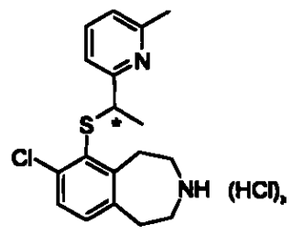
Clorohidrato de (±)-7-Cloro-6-[1-(6-metilpiridin-2-il)-etiltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al ejemplo 315, usando 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y clorohidrato de (±)-2-(1-cloroetil)-6-metilpiridina para dar, después de la desprotección por un método similar al procedimiento general 1-4, el compuesto del título como un sólido marrón. EM (ES+) m/z: 333 $(M+H)^+$.

Ejemplo 320

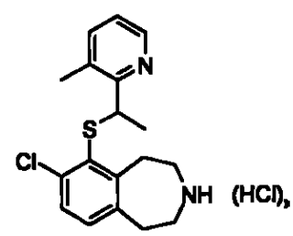
Clorohidrato de 7-Cloro-6-[1-(6-metilpiridin-2-il)-etiltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina, Isómero 1



Se usa un método similar para la preparación 177, excepto que la alquilación se lleva a cabo a 0°C, para hacer reaccionar 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina con éster de 1-(6-metil-piridin-2-il)-etilo del ácido (R)-metansulfónico. Se usa un método similar al procedimiento general 1-5, preparación básica, y un método similar al procedimiento general 2-2 para dar el compuesto del título como un sólido blanco. EM (APCI+) m/z: 333 $(M+H)^+$; ee >97%, t_R = 6.53 min. (CLAR quiral: Chiralpak OJ 120Å 4.6x250 mm, 45 °C; eluyente: 20% isopropanol con 0.05% trietilamina en SFC, relación de flujo 2 mL/min, Detector UV a 234 nm).

Ejemplo 321

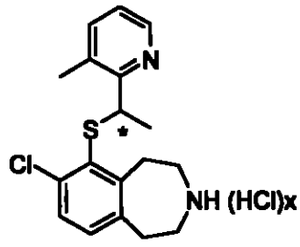
Clorohidrato de (±)-7-Cloro-6-[1-(3-metilpiridin-2-il)-etiltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar para la preparación 177 para hacer reaccionar 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina con (±)-2-(1-bromoetil)-3-metil-piridina. Se usa un método similar al procedimiento general 1-5, preparación básica, y un método similar al procedimiento general 2-2 para dar el compuesto del título como un sólido blanco. EM (APCI+) m/z: 333 $(M+H)^+$.

Ejemplo 322

Clorohidrato de (-)-7-Cloro-6-[1-(3-metilpiridin-2-il)-etiltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina

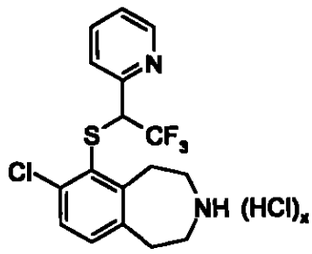


Se separaron los enantiómeros de (±)-7-cloro-[1-(3-metil-piridin-2-il)-etiltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina por cromatografía de fase normal quiral (columna Chiralpak AD 8x30 cm, eluyendo con 85:15 heptano:0.2% DMEA en etanol). Se toma el segundo isómero eluyente y se purifica por cromatografía de columna SCX.

Se usó el procedimiento general 2-2 para dar el compuesto del título como un sólido blanco (60 mg, 43%). EM (ES+) m/z: 333 $(M+H)^+$; $[\alpha]^{20}_D$ -232° (c 0.5, CH_3OH).

Ejemplo 323

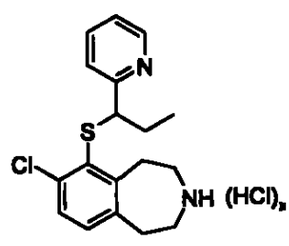
Clorohidrato de (±)-7-Cloro-6-(2,2,2-trifluoro-1-piridin-2-il-etiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar para la preparación 177 para hacer reaccionar 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina con (±)-2-[1-metansulfoniloxi-(2,2,2-trifluoroetil)]-piridina. Se usa un método similar al procedimiento general 1-5, preparación básica, y un método similar al procedimiento general 2-2 para dar el compuesto del título como un sólido blanco. EM (APCI+) m/z: 373 $(M+H)^+$.

Ejemplo 324

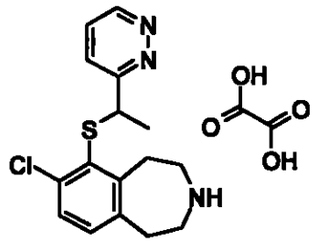
Clorohidrato de (±)-7-Cloro-6-(1-piridin-2-il-propiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar a la preparación 177 para hacer reaccionar 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina con (±)-2-(1-bromopropil)piridina. Se usa un método similar al procedimiento general 1-5, preparación básica, y un método similar al procedimiento general 2-2 para dar el compuesto del título como un sólido blanco. EM (APCI+) m/z: 333 $(M+H)^+$.

Ejemplo 325

Oxalato de (±)-7-Cloro-6-[1-(Piridazin-3-il)-etiltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina

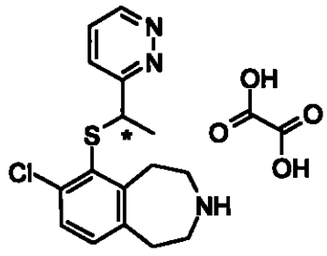


Se disuelve (±)-1-Piridazin-3-il-etanol (38 mg, 0.31 mmol) en cloruro de tionilo (0.14 mL) a 0°C y se agita durante 1 h a temperatura ambiente. Se evapora la mezcla, se agrega tolueno y se evapora nuevamente. Se trata este residuo con el tiolato preparado a partir de éster de tert-butilo del ácido 7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina-3-carboxílico (0.1 g, 0.25 mmol) de conformidad al procedimiento general 7 en la presencia

de carbonato de potasio (0.3 g, 2.25 mmol) en DMF (3 mL) a 80°C durante 16 h. Se usa un método similar al procedimiento general 1-5, preparación básica, y un método similar al procedimiento general 2-5 para dar el compuesto del título (38 mg, 37%). EMAR calculado para $C_{16}H_{19}ClN_3S$ 320.0988, encontrado 320.0970.

Ejemplo 326

Oxalato de (+)-7-Cloro-6-[1-(Piridazin-3-il)-etiltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



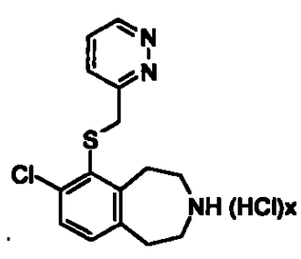
Se disuelve (±)-1-Piridazin-3-il-etanol (0.29 g, 2.35 mmol) en cloruro de tionilo (1.0 mL) a 0°C y se agita durante 1 h a temperatura ambiente. Se evapora la mezcla, se agrega tolueno y se evapora nuevamente. Se trata este residuo con el tiolato preparado a partir de éter de tert-butilo del ácido 7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina-3-carboxílico (0.72 g, 1.88 mmol) de conformidad al procedimiento general 7 en la presencia de carbonato de potasio (2.60 g, 18.8 mmol) y

yoduro de tetrabutilamonio (7 mg, 0.02 mmol) en DMF (20 mL) a 80°C durante 28 h. Se separaron los enantiómeros por CLAR preparativa (Waters Symmetry C18 4.6 x 150 mm, columna de 3.5 micrones, 1 mL/min de 90:10 hasta 50:50:0.1% TFA en agua:ACN durante 25 min. Detector está a 254 nm) para obtener 3-tert-butoxicarbonil-7-cloro-6-[1-(Piridazin-3-il)-etiltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina, isómero 1.

Se usa un método similar al procedimiento general 1-5, preparación básica, y un método similar al procedimiento general 2-5 para dar el compuesto del título (56 mg, 7%). CLAR t_R = 3.0 min (Chiralpak AD-H 4.6x150 mm, columna de 3 micrones, 1.0 mL/min de 99.8:0.2 metanol/dimetietilamina isocrática; detector a 225 nm); EMAR calculado para $C_{16}H_{19}ClN_3S$ 320.0988, encontrado 320.1001. $[\alpha]^{20}_D$ +160° (c 0.5, CH_3OH).

Ejemplo 327

Clorohidrato de 7-Cloro-6-(Piridazin-3-ilmetiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

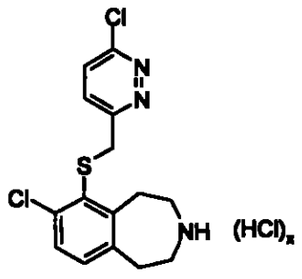


Se hace reaccionar 3-clorometil-piridazina (preparado como se describe en WO 99/54333, WO 98/49166) (1.8 g, 11.0 mmol) con 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina (2.2 g, 5.7 mmol) de conformidad al procedimiento general 7 en la presencia de yoduro de tetrabutilamonio (0.1 g, 0.27 mmol) a temperatura ambiente durante 3 h.

Se usa un método similar al procedimiento general 1-4 para dar el compuesto del título como un polvo marron (1.9 g, 98 %): EMAR calculado para $C_{15}H_{16}ClN_3S$ 306.0832, encontrado 306.0829.

Ejemplo 328

Clorohidrato de 7-Cloro-6-(6-cloro-Piridazin-3-ilmetiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

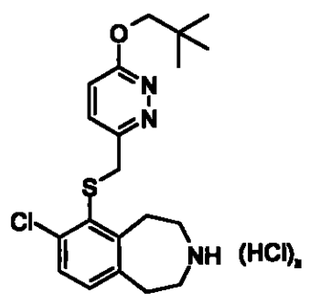


Se usa un método similar para la preparación 177, usando 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 3-bromometil-6-cloropiridazina para dar 3-tert-butoxicarbonil-7-cloro-6-(6-cloro-Piridazin-

3-ilmetiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina. Se usa un método similar al procedimiento general 1-4 para dar el compuesto del título como un polvo blanco opaco. EM (APCI+) m/z: 340 $(M+H)^+$.

Ejemplo 329

Clorohidrato de 7-Cloro-6-[6-(2,2-dimetilpropoxi)-Piridazin-3-ilmetiltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina

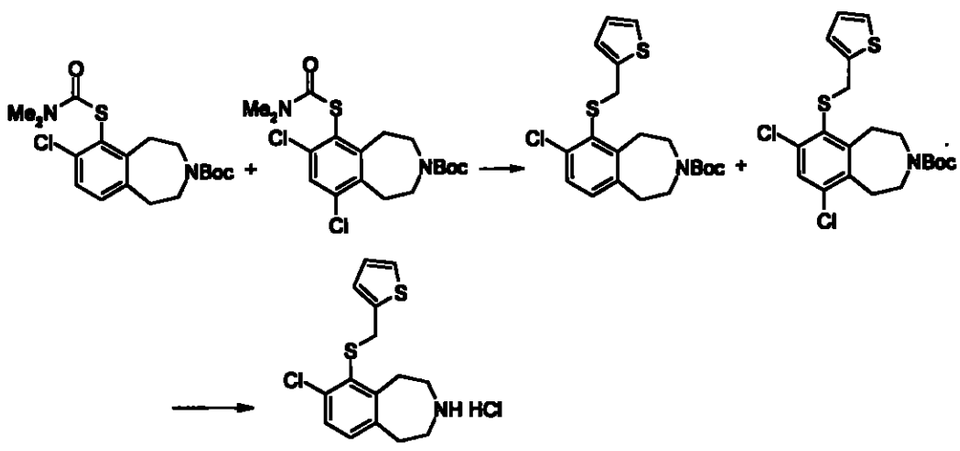


A una solución agitada de alcohol neopentílico (105 mg, 1.19 mmol) en THF (5 mL) a temperatura ambiente se agrega hidruro de sodio (31 mg, 95%, 1.19 mmol) y se continua agitando durante 3 h a temperatura ambiente. Se agrega una solución de 3-tert-butoxicarbonil-7-cloro-6-(6-cloro-Piridazin-3-ilmetiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (315 mg, 0.59 mmol) en THF (1 mL) y se continua agitando durante la noche a temperatura ambiente y luego a 60°C durante 1 h. Se diluye con agua, se extrae la mezcla de reacción tres veces con EtOAc, se seca sobre Na_2SO_4 anhidro, y se concentra in vacuo. Purificación por cromatografía en gel

de sílice eluyendo con hexano/EtOAc (6:1) para dar 3-tert-butoxicarbonil-7-cloro-6-[6-(2,2-dimetil-propoxi)-Piridazin-3-ilmetiltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite claro (81 mg, 28%). EM (APCI+) m/z: 492 $(M+H)^+$, 392 $(M+H-Boc)^+$. Se usa un método similar al procedimiento general 1-4 para dar el compuesto del título como un polvo blanco. EM (APCI+) m/z: 392 $(M+H)^+$, m/z: 322 $(M+H-C_5H_{11})^+$.

Ejemplo 330

Clorohidrato de 7-Cloro-6-(tiofen-2-ilmetiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



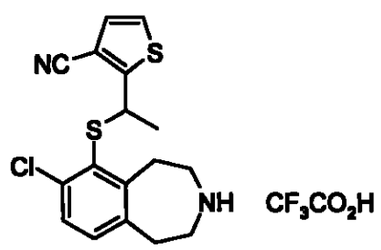
A una mezcla 4:1 de 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 3-tert-butoxicarbonil-7,9-dicloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-benzo[d]azepina (108 mg, 0.281 mmol) en metanol (3 ml), se agrega hidróxido de potasio peletizado (504 mg, 9.0 mmol) y se calienta la mezcla 2 h a 50°C. Se

enfría la reacción a temperatura ambiente, se agrega 2-clorometiltiofeno (186 µL, 1.406 mmol), y se continua agitando durante 30 min. Se diluye con EtOAc y agua. Se separaron las capas y se extrae la capa acuosa tres veces con EtOAc, se seca sobre Na_2SO_4 anhidro, y se concentra in vacuo. Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (19:1) para dar 3-tert-butoxicarbonil-7-cloro-6-(tiofen-2-ilmetiltio)-2,3,4,5-tetrahidro-benzo[d]azepina como un aceite incoloro (36 mg, 31%).

Se usa un método similar al procedimiento general 1-5, usando 3-tert-butoxicarbonil-7-cloro-6-(tiofen-2-ilmetiltio)-2,3,4,5-tetrahidro-benzo[d]azepina para dar, después de preparación básica y un método similar al procedimiento general 2-2, el compuesto del título como un sólido blanco. EM (ES+) m/z: 310 $(M+H)^+$.

Ejemplo 331

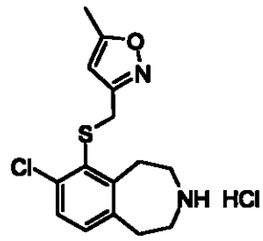
Trifluoroacetato de (±)-7-Cloro-6-(3-cianotiofen-2-ilmetiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar para la preparación 177, usando 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y (±)-2-(1-cloroetil)-3-cianotiofeno para dar, después de la desprotección usando un método similar al Procedimiento general 1-5, el compuesto del título como un sólido blanco. EM (APCI+) m/z: 349 $(M+H)^+$.

Ejemplo 332

Clorohidrato de 7-Cloro-6-(5-metilisoxazol-3-ilmetiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

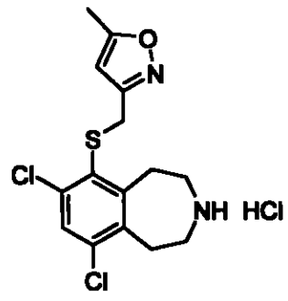


A una mezcla 4:1 de 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 3-tert-butoxicarbonil-7,9-dicloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina (200 mg, 0.521 mmol) en metanol (3.3 mL) bajo nitrógeno se agrega hidróxido de potasio (0.9 g, 16.1 mmol) a temperatura ambiente. Cuando la mezcla se volvió homogénea, se calienta a 55-60°C durante 2-3 h, hasta que el CCD mostró la desaparición del material de partida. Se enfría a temperatura ambiente, se agrega 3-(clorometil)-5-metilisoxazol (82 mg, 0.62 mmol) y se

continua agitando durante 30 min. Se agrega cloruro de amonio saturado acuoso, se extrae la mezcla tres veces con éter dietílico, se seca sobre $MgSO_4$ anhidro, y se concentra in vacuo. Se trata una solución del material crudo obtenido en DCM (2 mL) con cloruro de hidrógeno 2M en éter (exceso) y se continua agitando hasta que el CCD mostró el consumo del material de partida. Se concentra in vacuo, se purifica por CCD preparativa eluyendo con 19:1 DCM/amonio saturado en metanol, y se convierte al clorohidrato por seguir un método similar al procedimiento general 2-2 para dar el compuesto del título como un sólido blanco. EM (APCI+) m/z: 309 $(M+H)^+$.

Ejemplo 333

Clorohidrato de 7,9-Dicloro-6-(5-metilisoxazol-3-ilmetiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

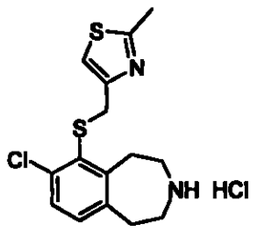


Se obtiene la base libre del compuesto del título como un producto menor del ejemplo 332, después de CCD preparativa eluyendo con 19:1 DCM/amonio saturado en metanol. Se usa un

método similar al procedimiento general 2-2 para dar el compuesto del título como un sólido blanco. EM (APCI+) m/z: 343 $(M+H)^+$.

Ejemplo 334

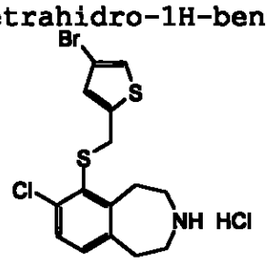
Clorohidrato de 7-Cloro-6-(2-metiltiazol-4-ilmetiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al ejemplo 332, usando 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y clorohidrato de 4-clorometil-2-metiltiazol para dar, después de la desprotección por el procedimiento general 1-4, el compuesto del título como un sólido blanco. EM (APCI+) m/z: 325 $(M+H)^+$.

Ejemplo 335

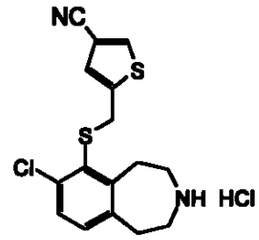
Clorohidrato de 6-(4-Bromotiofen-2-ilmetiltio)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al procedimiento general 1-4, usando 6-(4-bromotiofen-2-ilmetiltio)-3-tert-butoxicarbonil-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina para dar el compuesto del título como un sólido blanco. EM (APCI+) m/z: 390 $(M+H)^+$.

Ejemplo 336

Clorohidrato de 7-Cloro-6-(4-cianotiofen-2-ilmetiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se desgasifica una solución agitada de 6-(4-bromotiofen-2-ilmetiltio)-3-tert-butoxicarbonil-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina (183 mg, 0.37 mmol), cianuro de zinc (50 mg, 0.42 mmol) y tetraquistrifenilfosfina paladio(0) (30 mg, 0.026 mmol) en DMF seco. Se purga con nitrógeno seco, y se calienta a 120°C durante 6 h. Se diluye con agua, se extrae tres veces con EtOAc, se seca sobre $MgSO_4$ anhidro y se concentra in vacuo. Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (10:1) para dar 3-tert-butoxicarbonil-7-cloro-6-(4-cianotiofen-2-ilmetiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como

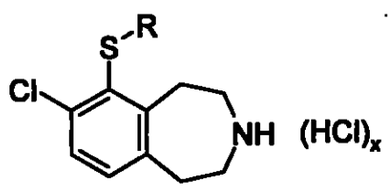
un aceite (85 mg, 52%). EM (APCI+) m/z: 335 $(M+H-Boc)^+$. Se usa un método similar al procedimiento general 1-4 para dar el compuesto del título como un sólido blanco. EM (APCI+) m/z: 335 $(M+H)^+$.

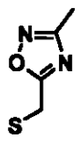
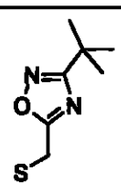
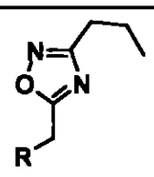
Ejemplo 337

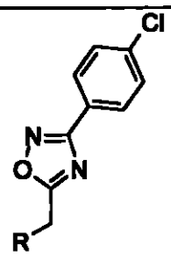
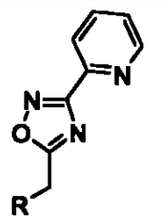
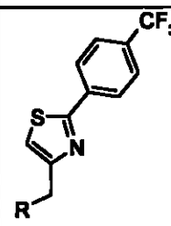
Clorohidrato de 7-Cloro-6-([1,2,4]-oxadiazol-3-ilmetiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

Se usa un método similar para la preparación 177, usando 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 3-clorometil-1,2,4-oxadiazol para dar, después de la desprotección usando un método similar al Procedimiento general 1-4, el compuesto del título como un sólido blanco. EM (ES+) m/z 296 $(M+H)^+$.

Los ejemplos 338-343 pueden prepararse esencialmente como se describe en el ejemplo 337 usando 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 5-clorometil-1,2,4-oxadiazol apropiadamente substituido o 4-clorometil-tiazol. Los datos EM (ES+) se incluyen en la siguiente tabla.



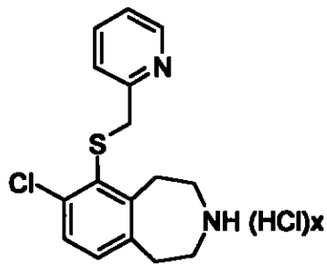
Ej.	SR	Compuesto	EM (ES+) m/z
338		Clorohidrato de 7-Cloro-6-(3-metil-[1,2,4]oxadiazol-5-ilmetiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	310 $(M+H)^+$
339		Clorohidrato de 6-(3-tert-Butil-[1,2,4]oxadiazol-5-ilmetiltio)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina	352 $(M+H)^+$
340		Clorohidrato de 7-Cloro-6-(3-propil-[1,2,4]oxadiazol-5-ilmetiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	338 $(M+H)^+$

341		Clorohidrato de 7-Cloro-6-[3-(4-cloro-fenil)-[1,2,4]oxadiazol-5-ilmetiltio]-2,3,4,5-tetrahidro-1H-benzo[d]azazepina	406 $(M+H)^+$
342		Clorohidrato de 7-Cloro-6-(3-piridin-2-il-[1,2,4]oxadiazol-5-ilmetiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	373 $(M+H)^+$
343		Clorohidrato de 7-Cloro-6-[2-(4-trifluorometilfenil)-tiazol-4-ilmetiltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	455 $(M+H)^+$

Ejemplo 344

Clorohidrato de 7-Cloro-6-(piridin-2-ilmetiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

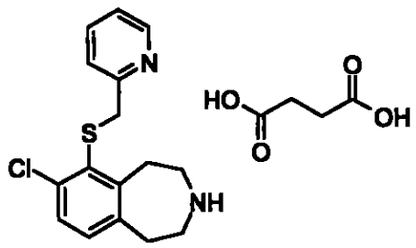
5



Se usa un método similar al Procedimiento general 7, para hacer reaccionar 3-tert-butoxicarbonil-7-cloro-6-dimetilaminocarboniltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina (8 g, 20.8 mmol) con clorohidrato de cloruro de 2-picolilo (3.41 g, 20.8 mmol). La mezcla de reacción se diluye con éter dietílico y se filtra el precipitado. Se concentra el filtrado in vacuo, se disuelve el residuo en éter dietílico (100 mL) y se agrega HCl 1N acuoso (100 mL). Se agita la mezcla durante 16 h a temperatura ambiente. Se separa, se lava la capa acuosa con éter dietílico, se ajusta el pH de la capa acuosa hasta 12 con hidróxido de sodio y se extrae con éter dietílico. Se seca sobre Na_2SO_4 y se concentra in vacuo para dar la base libre del compuesto del título. Se usa el procedimiento general 2-2 para dar el compuesto del título como un sólido blanco (4.91 g, 78%). EM (ES+) m/z: 305 $(M+H)^+$.

Ejemplo 345

Succinato de 7-Cloro-6-(piridin-2-ilmetiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

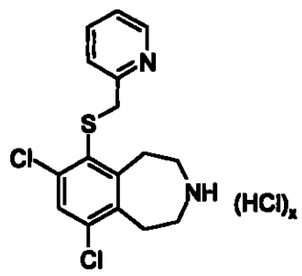


Se disuelve 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina (1 equiv.) en metanol (0.1-0.4 M) y se agrega hidróxido de potasio (8-20 equiv.). Se agita a 60°C durante 4-24 h. Se enfría la mezcla de reacción en un baño de hielo, se agrega clorohidrato de cloruro de picolilo (1-3 equiv.) y se agita la mezcla a temperatura ambiente durante 16-24 h. Se agrega un volumen de tolueno aproximadamente igual al volumen de la mezcla de reacción y se concentra la mezcla resultante a aproximadamente ½ del volumen total resultante y se repitió este proceso una vez más. Se agrega agua hasta que los sólidos se disuelven y se separaron las capas. La capa orgánica se seca sobre Na_2SO_4 y se filtra. Se calienta la solución (que contiene alrededor de 0.25-0.40 M de la base libre del compuesto del título) a 50-75°C y luego se siembra opcionalmente con cristales previamente formados del compuesto del título. Se agrega ácido succínico (1-1.3 equivalentes) en alcohol isopropílico (0.25-0.40M solución) a la solución durante 5-45 min. Se enfría la solución hasta 20-25°C durante 1-3 h y se filtra, se enjuaga con una solución

de tolueno/alcohol isopropílico (1:1). Se seca el sólido resultante bajo vacío a 50-70°C/5 Torr para dar el compuesto del título como un sólido blanco, p.f. 159-160°C. Análisis calculado para $C_{20}H_{23}ClN_2O_4S$: C, 56.80; H, 5.48; N, 6.62. Encontrado: C, 56.56; H, 5.41; N, 6.57.

Ejemplo 346

Clorohidrato de 7,9-Dicloro-6-(piridin-2-ilmetiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

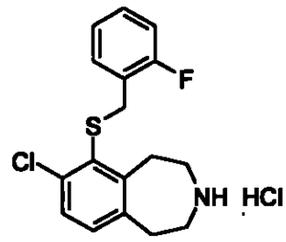


Se obtiene como producto menor de la reacción de la mezcla 4:1 de 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 3-tert-butoxicarbonil-7,9-dicloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-benzo[d]azepina con bromohidrato de 2-bromometilpiridina, se usa un método similar al Procedimiento general 7. Se trata una solución de la mezcla cruda en DCM con cloruro de hidrógeno 4M en dioxano (exceso) durante la noche. Se concentra in vacuo y se purifica por CCD preparativa eluyendo con 19:1 DCM/amonio saturado en metanol. Se usa un método similar al procedimiento general 2-2 para

dar el compuesto del título como un sólido blanco opaco. EM (APCI+) m/z: 339 $(M+H)^+$.

Ejemplo 347

Clorohidrato de 7-Cloro-6-(2-fluorobenciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

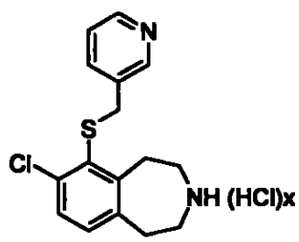


A una mezcla de 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 3-tert-butoxicarbonil-7,9-dicloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-benzo[d]azepina (102 mg, 0.267 mmol) en metanol (2 ml), se agrega hidróxido de potasio peletizado (450 mg, 8.02 mmol) y se calienta la mezcla 3 h a 60°C. Se enfría a temperatura ambiente, se agrega cloruro de amonio saturado acuoso solución, se extrae tres veces con EtOAc, se seca sobre Na_2SO_4 anhidro, y se concentra in vacuo. Se disuelve el tiofenol crudo así obtenido en DCM seco (2 mL) bajo nitrógeno, y se agrega DBU (80 □L, 0.54 mmol) y bromuro de 2-fluorobencilo (65 □L, 0.54 mmol) con agitación. Se agita durante la noche a temperatura ambiente, se diluye con agua, se extrae tres veces con EtOAc, se seca sobre Na_2SO_4 anhidro, y se concentra in vacuo. Purificación por cromatografía en gel de sílice eluyendo

con hexano/EtOAc (9:1) para dar 3-tert-butoxicarbonil-7-cloro-6-(2-fluorobenciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite amarillo (31 mg, 25%). Se usa un método similar al procedimiento general 1-4 para dar el compuesto del título como un sólido blanco. EM (ES+) m/z: 322 $(M+H)^+$.

Ejemplo 348

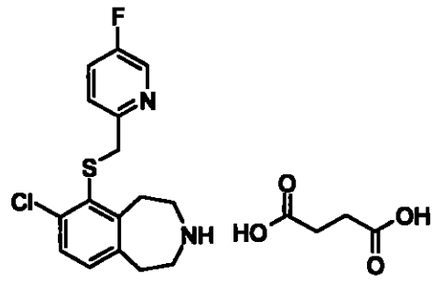
Clorohidrato de 7-Cloro-6-(piridin-3-ilmetiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al ejemplo 347, usando 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y bromohidrato de 3-(bromometil)piridina para dar, después de la desprotección por un método similar al procedimiento general 1-4, el compuesto del título como un sólido blanco. EM (ES+) m/z: 305 $(M+H)^+$.

Ejemplo 349

Succinato de 7-Cloro-6-(5-fluoropiridin-2-ilmetiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



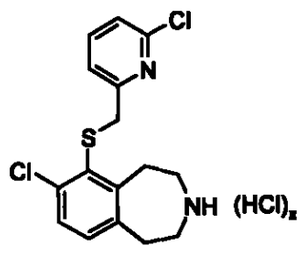
Se disuelve 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina (527 mg, 1.4 mmol) y hidróxido de potasio (1.1 g, 20.5 mmol) en metanol (10 mL) y se calienta la solución a reflujo durante 2 h. Se enfría la mezcla de reacción a temperatura ambiente y se removió el solvente in vacuo. Se mezcla el residuo con EtOAc (50 ml), y se lava la mezcla espesa con NH_4Cl saturado. Se colecta y la fase orgánica se seca sobre Na_2SO_4, se removió el solvente bajo presión reducida para obtener el intermediario de tiofenol como un aceite. Se disuelve el aceite en DMSO (10 ml), se agrega trietilamina (1.1 ml, 8.2 mmol) y éster de 5-fluoro-piridin-2-ilmetilo del ácido metansulfónico (500mg, 2.4 mmol). Se calienta la mezcla de reacción a 60°C durante 1 h. Se monitoreo la reacción por CLAR y CCD. Se enfría la reacción a temperatura ambiente, se agrega 1:1 hexano/EtOAc (80 ml) y se lava la capa orgánica con 5% de NaCl (3 X 30 ml). Se colecta la capa orgánica, se concentra, y se purifica por cromatografía

en gel de sílice eluyendo con hexano/EtOAc (9:1 hasta 1:1) para obtener 3-tert-butoxicarbonil-7-cloro-6-(5-fluoro-piridin-2-ilmetiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (519 mg, 89%). EM (ES+) m/z: 423 $(M+H)^+$.

Se usa el procedimiento general 1-4 para desproteger 3-tert-butoxicarbonil-7-cloro-6-(5-fluoro-piridin-2-ilmetiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (510 mg, 1.2 mmol). Se purifica por cromatografía SCX seguido por cromatografía en gel de sílice eluyendo con DCM/amoniaco 2M en metanol (99:1 hasta 90:10). Se usa el procedimiento general 2-1 para dar el compuesto del título (370 mg, 70%). EM (ES+) m/z: 323 $(M+H)^+$.

Ejemplo 350

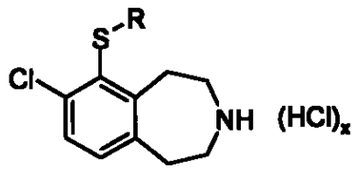
Clorohidrato de 7-Cloro-6-(6-cloropiridin-2-ilmetiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

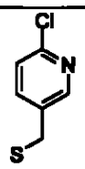


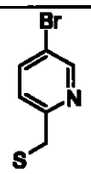
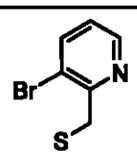
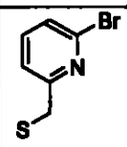
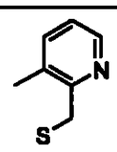
Se usa un método similar para la preparación 177, usando 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 2-bromometil-6-cloropiridina

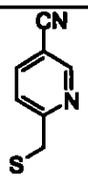
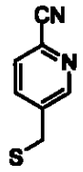
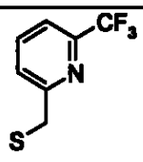
clorohidrato para dar, después de la desprotección por un método similar al procedimiento general 1-4, el compuesto del título como un sólido blanco opaco. EM (APCI+) m/z: 339 $(M+H)^+$.

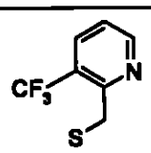
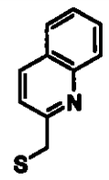
Los ejemplos 351-360 pueden prepararse esencialmente como se describe en el ejemplo 350 al usar 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y clorometilpiridina aproximadamente substituida, bromometilpiridina o clorometilquinolina. Los datos EM (ES+) se incluyen en la siguiente tabla.



Ej.	SR	Compuesto	EM (ES+ o APCI+)
351		Clorohidrato de 7-Cloro-6-(6-cloro-piridin-3-ilmetiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	339 $(M+H)^+$

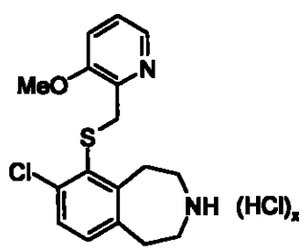
352		Clorohidrato de 6-(5-Bromo-piridin-2-ilmetiltio)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina	385 $(M+H)^+$
353		Clorohidrato de 6-(3-Bromo-piridin-2-ilmetiltio)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina	385 $(M+H)^+$
354		Clorohidrato de 6-(6-Bromo-piridin-2-ilmetiltio)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina	385 $(M+H)^+$
355		Clorohidrato de 7-Cloro-6-(3-metil-piridin-2-ilmetiltio)-	319 $(M+H)^+$

		2,3,4,5-tetrahidro-1H-benzo[d]azepina	
356		Clorohidrato de 7-Cloro-6-(5-ciano-piridin-2-ilmetiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	330 $(M+H)^+$
357		Clorohidrato de 7-Cloro-6-(6-ciano-piridin-3-ilmetiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	330 $(M+H)^+$
358		Clorohidrato de 7-Cloro-6-(6-trifluorometil-piridin-2-ilmetiltio)-	373 $(M+H)^+$

		2,3,4,5-tetrahidro-1H-benzo[d]azepina	
359		Clorohidrato de 7-Cloro-6-(3-trifluorometil-piridin-2-ilmetiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	373 $(M+H)^+$
360		Clorohidrato de 7-Cloro-6-(quinolin-2-ilmetiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	355 $(M+H)^+$

Ejemplo 361

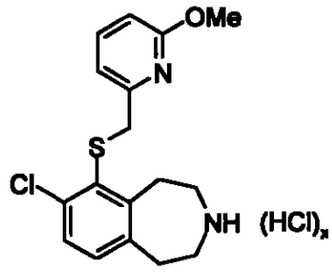
Clorohidrato de 7-Cloro-6-(3-metoxipiridin-2-ilmetiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al ejemplo 315, usando 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 2-clorometil-3-metoxipiridina para dar, después de la desprotección por un método similar al procedimiento general 1-4, el compuesto del título como un sólido blanco (71 mg). EM (APCI+) m/z: 335 $(M+H)^+$.

Ejemplo 362

Clorohidrato de 7-Cloro-6-(6-metoxipiridin-2-ilmetiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

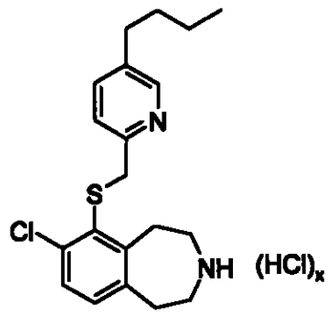


Se usa un método similar al ejemplo 330, usando 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y clorohidrato de 2-clorometil-6-metoxipiridina para dar, después de la desprotección por un método similar al procedimiento general 1-4, el compuesto del

título como un sólido blanco (120 mg). EM (APCI+) m/z: 335 $(M+H)^+$.

Ejemplo 363

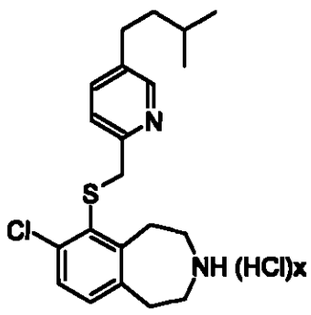
Clorohidrato de 6-(5-Butilpiridin-2-ilmetiltio)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al ejemplo 315, usando 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y clorohidrato de 5-butil-2-clorometilpiridina para dar el compuesto del título como un sólido blanco. EM ($APCI^+$) m/z: 330 $(M+H)^+$.

Ejemplo 364

Clorohidrato de 7-Cloro-6-[5-(3-metilbutil)-piridin-2-ilmetiltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



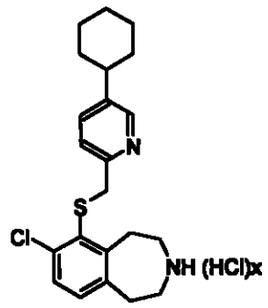
A 6-(5-bromo-piridin-2-ilmetiltio)-3-tert-butoxicarbonil-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina (219 mg, 0.452 mmol) y aducto de diclorometano de dicloro[1,1'-bis(difenilfosfino)ferroceno]paladio(II) (18 mg, 0.022 mmol) bajo nitrógeno seco se agrega con agitación una solución de bromuro de 3-metilbutilzinc 0.5M en THF (4.6 mL, 2.3 mmol). Se desgasifica, se purga con nitrógeno seco, y se agita durante la noche a temperatura ambiente. Se diluye con EtOAc, se lava con agua, se seca sobre $MgSO_4$ anhidro y se concentra in vacuo. Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (5:1) da 3-tert-butoxicarbonil-7-cloro-6-[5-(3-metil-butil)-piridin-2-ilmetiltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite (160 mg, 75%). EM (APCI+) m/z: 475 $(M+H)^+$. Se usa un método similar al procedimiento general 1-4 para dar el compuesto del título como un sólido marrón. EM (APCI+) m/z: 375 $(M+H)^+$.

Ejemplo 365

Clorohidrato de 7-Cloro-6-[5-(2,2-dimetilpropil)-piridin-2-ilmetiltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Clorohidrato de 7-Cloro-6-(5-ciclohexilpiridin-2-ilmetiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



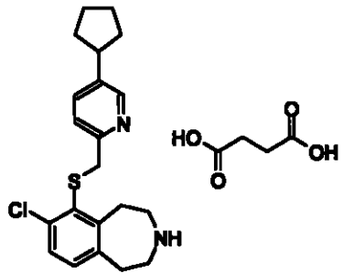
A una mezcla de 6-(5-bromopiridin-2-ilmetiltio)-3-tert-butoxicarbonil-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina (146 mg, 0.30 mmol) y un aducto de diclorometano de dicloro[1,1'-bis(difenilfosfino)ferroceno]paladio(II) (12 mg, 0.015 mmol) bajo nitrógeno seco se agrega con una solución agitada de bromuro de ciclohexilzinc 0.5 M en THF (3.0 mL, 1.5 mmol). Se desgasifica, se purga con nitrógeno seco, y se agita durante la noche a 60°C. Se enfría a temperatura ambiente, se diluye con EtOAc, se lava con agua, se seca sobre $MgSO_4$ anhidro y se concentra in vacuo. Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (5:1) para dar 3-tert-butoxicarbonil-7-cloro-6-(5-ciclohexil-piridin-2-ilmetiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite (46 mg, 32%). EM (APCI+) m/z: 487 $(M+H)^+$. Se usa un método similar al procedimiento general 1-4 para dar el compuesto del título como un sólido blanco. EM (APCI+) m/z: 387 $(M+H)^+$.

A una solución agitada de cloruro de magnesio neopentilo 1.0 M en éter dietílico (50 mL, 50 mmol) a -78°C bajo nitrógeno, se agrega por medio de una jeringa una solución de 0.5 M cloruro de zinc en THF (100 mL, 50 mmol). Se calienta gradualmente a temperatura ambiente y se transfiere por medio de una jeringa de esta solución (25 mL, ~8.33 mmol) a una solución agitada de 3-tert-butoxicarbonil-6-(5-bromo-piridin-2-ilmetiltio)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina (300 mg, 0.62 mmol) en THF (2 mL) a temperatura ambiente. Se agrega un aducto de diclorometano de dicloro[1,1'-bis(difenilfosfino)ferroceno]paladio(II) (50 mg, 0.061 mmol) y se calienta a 65°C durante 6 h. Se enfría a temperatura ambiente, se diluye con EtOAc, se lava con agua, se seca sobre $MgSO_4$ anhidro y se concentra in vacuo. Se purifica por cromatografía en gel de sílice eluyendo con hexano/EtOAc (6:1) para dar 3-tert-butoxicarbonil-7-cloro-6-[5-(2,2-dimetil-propil)-piridin-2-ilmetiltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite (69 mg, 24%). EM (APCI+) m/z: 501 $(M+H)^+$. Se usa un método similar al procedimiento general 1-4 para dar el compuesto del título como un polvo blanco. EM (APCI+) m/z: 375 $(M+H)^+$.

Ejemplo 366

Ejemplo 367

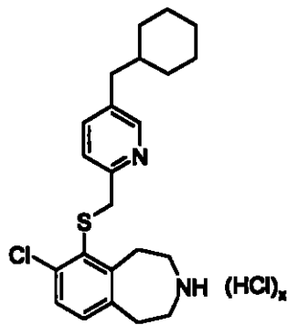
Succinato de 7-Cloro-6-(5-ciclopentilpiridin-2-ilmetiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al ejemplo 366 para hacer reaccionar 6-(5-bromo-piridin-2-ilmetiltio)-3-tert-butoxicarbonil-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina con una solución de bromuro de ciclopentilzinc en THF. Se usa un método similar al procedimiento general 1-4, preparación básica, y un método similar al procedimiento general 2-1 para dar el compuesto del título como un sólido marrón. EM (APCI+) m/z: 373 $(M+H)^+$.

Ejemplo 368

Clorohidrato de 7-Cloro-6-(5-ciclohexilmetilpiridin-2-ilmetiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

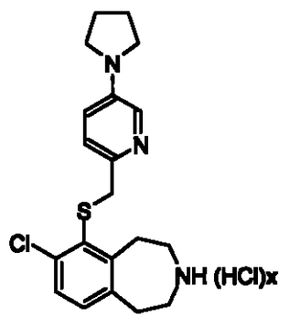


butoxicarbonil-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina (242 mg, 0.501 mmol), tert-butóxido de sodio (96 mg, 1.0 mmol), 18-corona-6 (13 mg, 0.050 mmol) y piperidina (496 µL, 5.01 mmol) en tolueno (3 mL). Se limpia la mezcla con nitrógeno y se calienta durante la noche. Se enfría a temperatura ambiente, se diluye con agua y se extrae tres veces con EtOAc. Se seca sobre Na_2SO_4 anhidro y se concentra in vacuo. Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (9:1) para dar 3-tert-butoxicarbonil-7-cloro-6-(3,4,5,6-tetrahidro-2H-[1,3']bipiridinil-6'-ilmetiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite amarillo (179 mg, 73%).

Se usa un método similar al procedimiento general 1-5, usando 3-tert-butoxicarbonil-7-cloro-6-(3,4,5,6-tetrahidro-2H-[1,3']bipiridinil-6'-ilmetiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina para dar, después de preparación básica y un método similar al procedimiento general 2-2, el compuesto del título como un sólido amarillo. EM (ES+) m/z: 388 $(M+H)^+$.

Ejemplo 370

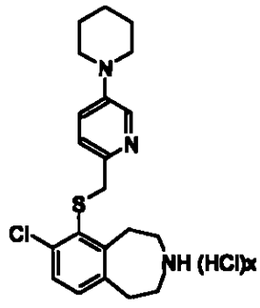
Clorohidrato de 7-Cloro-6-(5-pirrolidin-1-il-piridin-2-ilmetiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al ejemplo 366 para hacer reaccionar 6-(5-bromo-piridin-2-ilmetiltio)-3-tert-butoxicarbonil-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina con bromuro de ciclohexilmetilzinc. Se usa un método similar al procedimiento general 1-5, preparación básica, y un método similar al procedimiento general 2-2 para dar el compuesto del título como un sólido blanco. EM (APCI+) m/z: 401 $(M+H)^+$.

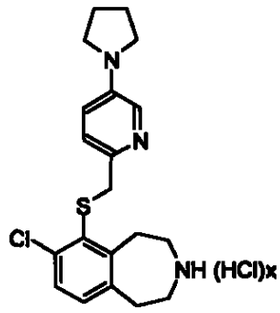
Ejemplo 369

Clorohidrato de 7-Cloro-6-(3,4,5,6-tetrahidro-2H-[1,3']bipiridinil-6'-ilmetiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



En un tubo sellado, se agrega tris(dibencilidenacetona)dipaladio(O) (3.44 mg, 0.00376 mmol) y 2,2'-bis(difenilfosfino)-1,1'-binaftilo (4.98 mg, 0.00752 mmol) a una mezcla de 6-(5-bromopiridin-2-ilmetiltio)-3-tert-

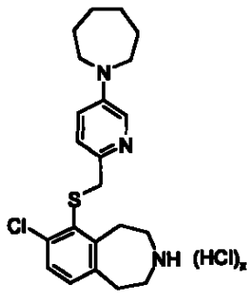
Clorohidrato de 7-Cloro-6-(5-pirrolidin-1-il-piridin-2-ilmetiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al ejemplo 369, usando 6-(5-bromopiridin-2-ilmetiltio)-3-tert-butoxicarbonil-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina y pirrolidina para dar el compuesto del título como un sólido amarillo pálido. EM (ES+) m/z: 374 $(M+H)^+$.

Ejemplo 371

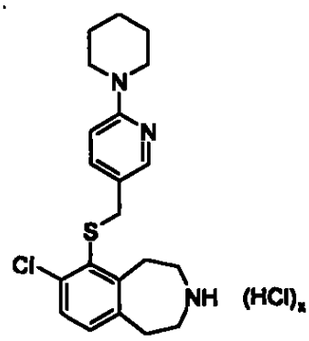
Clorohidrato de 6-(5-Azepan-1-il-piridin-2-ilmetiltio)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al ejemplo 369, usando 6-(5-bromopiridin-2-ilmetiltio)-3-tert-butoxicarbonil-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina y homopiperidina para dar el compuesto del título como un sólido amarillo. EM (ES+) m/z 402 $(M+H)^+$.

Ejemplo 372

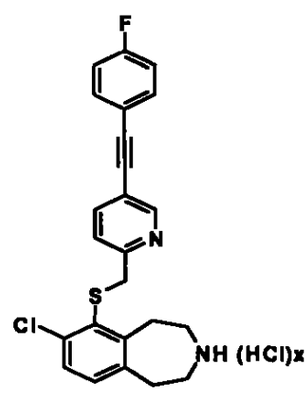
Clorohidrato de 7-Cloro-6-(3,4,5,6-tetrahidro-2H-[1,2']bipiridinil-5'-ilmetiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al ejemplo 369, usando 3-tert-butoxicarbonil-7-cloro-6-(6-cloropiridin-3-ilmetiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina y piperidina, para dar el compuesto del título como un sólido blanco. EM (ES+) m/z: 388 $(M+H)^+$.

Ejemplo 373

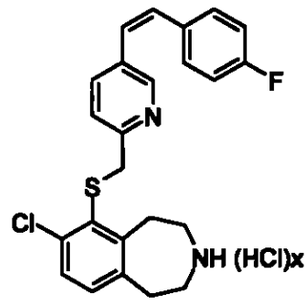
Clorohidrato de 7-Cloro-6-[5-(4-fluorofeniletinil)-piridin-2-ilmetiltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se disuelve 3-tert-butoxicarbonil-6-(5-bromopiridin-2-ilmetiltio)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina (1.0 g, 2.07 mmol), tetraquiistrifenilfosfina paladio(0) (120 mg, 0.104 mmol), yoduro de cobre (20 mg, 0.105 mmol), trietilamina (2.60 mL) y 1-etinil-4-fluorobenceno (500 mg, 4.16 mmol) en DMF (8 mL). Se desgasifica la mezcla, se purga con nitrógeno, y se calienta a 65°C durante 3 días. Se diluye la mezcla con agua, se extrae tres veces con EtOAc, se seca sobre Na_2SO_4 anhidro y se concentra in vacuo. Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (50:1) para dar 3-tert-butoxicarbonil-7-cloro-6-[5-(4-fluorofeniletinil)-piridin-2-ilmetiltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina como una espuma color marrón (1.02 g, 95%). EM (APCI+) m/z: 523 $(M+H)^+$, 423 $(M+H-Boc)^+$. Se usa un método similar al procedimiento general 1-4 para dar el compuesto del título como un polvo marrón. EM (APCI+) m/z: 423 $(M+H)^+$.

Ejemplo 374

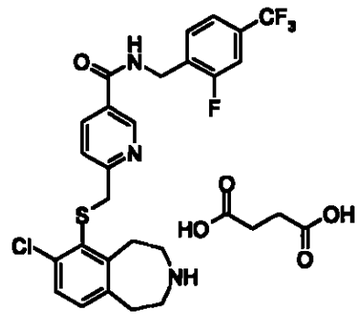
Clorohidrato de (Z)-7-Cloro-6-{5-[2-(4-fluorofenil)vinil]-piridin-2-ilmetiltio}-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se disuelve 3-tert-butoxicarbonil-7-cloro-6-[5-(4-fluorofeniletinil)-piridin-2-ilmetiltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina (1.0 g, 1.9 mmol), catalizador Lindlar (240 mg), y quinolina (0.8 mL) en metanol (30 mL). Se desgasifica, se purga con nitrógeno, y se agita bajo un globo de hidrógeno durante 36 h. Se filtra la mezcla y se lava el catalizador con metanol adicional. Se concentra el filtrado in vacuo. Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (8:1) para dar (Z)-3-tert-butoxicarbonil-7-cloro-6-{5-[2-(4-fluoro-fenil)-vinil]-piridin-2-ilmetiltio}-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite claro (630 mg, 63%). EM (APCI+) m/z: 525 $(M+H)^+$, 425 $(M+H-Boc)^+$. Se usa un método similar al procedimiento general 1-4 para dar el compuesto del título como un sólido amarillo pálido. EM (APCI+) m/z: 425 $(M+H)^+$.

Ejemplo 375

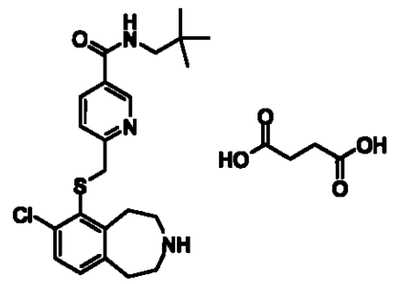
Succinato de 7-cloro-6-[5-(2-fluoro-4-trifluorometilbencilcarbamoil)-piridin-2-ilmetiltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se disuelve 3-tert-butoxicarbonil-6-(5-carboxipiridin-2-ilmetiltio)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina (300 mg, 0.67 mmol) en DMF (5.0 mL). Se trata secesivamente con HATU (305 mg, 0.802 mmol), N,N-diisopropiletilamina (140 µL, 0.804 mmol) y 2-fluoro-4-(trifluorometil)bencilamina (260 mg, 1.34 mmol). Se agita durante la noche a 40°C. Se diluye la mezcla con agua, se extrae tres veces con EtOAc, se seca sobre Na_2SO_4 anhidro y se concentra in vacuo. Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (3:1) para dar 3-tert-butoxicarbonil-7-cloro-6-[5-(2-fluoro-4-trifluorometil-bencilcarbamoil)-piridin-2-ilmetiltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina como una espuma (409 g, 98%). Se usa un método similar al procedimiento general 1-4 para dar, después de preparación básica y un método similar al procedimiento general 2-1, el compuesto del título como un sólido blanco opaco. EM (APCI+) m/z: 524 $(M+H)^+$.

Ejemplo 376

Succinato de 7-Cloro-6-[5-(2,2-dimetilpropilcarbamoil)-piridin-2-ilmetiltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina

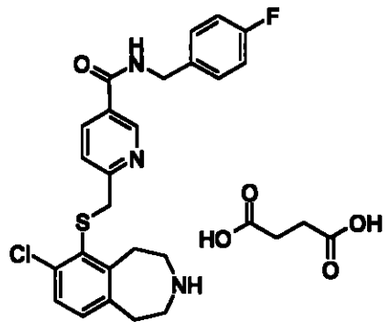


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Se usa un método similar al ejemplo 375, usando 3-tert-butoxicarbonil-6-(5-carboxi-piridin-2-ilmetiltio)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina y neopentilamina, para dar el compuesto del título como un sólido blanco opaco. EM (APCI+) m/z: 418 $(M+H)^+$.

Ejemplo 377

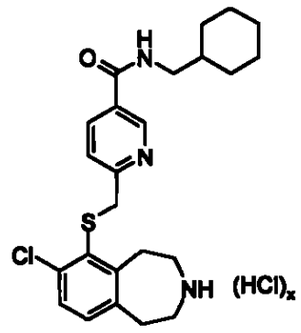
Succinato de 7-Cloro-6-[5-(4-fluoro-bencilcarbamoil)-piridin-2-ilmetiltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al ejemplo 375, usando 3-tert-butoxicarbonil-6-(5-carboxi-piridin-2-ilmetiltio)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 4-fluorobencilamina, para dar el compuesto del título como un sólido blanco opaco. EM (APCI+) m/z: 456 $(M+H)^+$.

Ejemplo 378

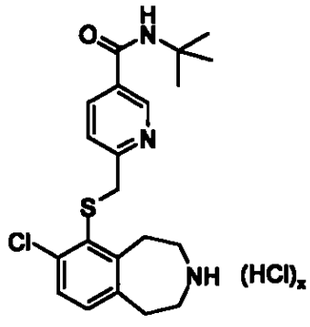
Clorohidrato de 7-Cloro-6-[5-(ciclohexilmetilcarbamoil)-piridin-2-ilmetiltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al ejemplo 375, usando 3-tert-butoxicarbonil-6-(5-carboxi-piridin-2-ilmetiltio)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina y aminometilciclohexano para dar, después de la desprotección por el Procedimiento general 1-4, el compuesto del título como un sólido blanco. EM (APCI+) m/z: 444 $(M+H)^+$.

Ejemplo 379

Clorohidrato de 6-(5-tert-Butilcarbamoil-piridin-2-ilmetiltio)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al ejemplo 375, usando 3-tert-butoxicarbonil-6-(5-carboxi-piridin-2-ilmetiltio)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina y tert-butilamina para dar, después de la desprotección por el Procedimiento general 1-4, el compuesto del título como un sólido blanco opaco. EM (APCI+) m/z: 404 $(M+H)^+$.

Ejemplo 380

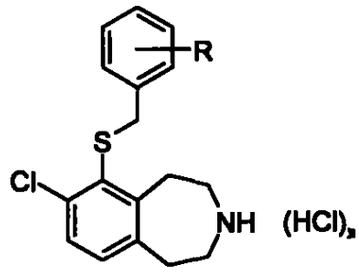
Clorohidrato de 7-Cloro-6-(4-trifluorometoxibenciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



A una mezcla 4:1 de 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 3-tert-butoxicarbonil-7,9-dicloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina (102 mg, 0.27 mmol) en metanol (1.7 mL) bajo nitrógeno, se agrega hidróxido de potasio (0.9 g, 16.1 mmol) a temperatura ambiente. Cuando la mezcla se volvió homogénea, se calienta a 55-60°C durante 2-3 h, hasta que el

CCD mostró la desaparición del material de partida. Se enfría a temperatura ambiente, se agrega una solución de cloruro de amino acuoso saturado, se extrae tres veces con éter dietílico, se seca sobre $MgSO_4$ anhidro y se concentra in vacuo. Se disuelve la 3-tert-butoxicarbonil-7-cloro-6-mercapto-2,3,4,5-tetrahidro-1H-benzo[d]azepina cruda en DCM anhidro (2 mL) bajo nitrógeno. Se agrega con agitación DBU (80 µL, 0.532 mmol) y bromuro de 4-(trifluorometoxi)bencilo (77 µL, 0.53 mmol) a temperatura ambiente y se permite que la reacción continue durante la noche. Se diluye con una solución de cloruro de amino acuoso saturado, se extrae tres veces con éter dietílico, se seca sobre $MgSO_4$ anhidro y se concentra in vacuo. Se trata una solución de 3-tert-butoxicarbonil-7-cloro-6-(4-trifluorometoxi-benciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina cruda en DCM (2 mL) con cloruro de hidrógeno 2M en éter (exceso) y se continua agitando hasta que el CCD muestra el consumo del material de partida. Se concentra in vacuo y se tritura el sólido obtenido con éter/pentano (10:90). Se purifica por CCD preparativa eluyendo con 19:1 DCM/amonio saturado en metanol y se convierte al clorohidrato siguiendo un método similar al procedimiento general 2-2 para dar el compuesto del título como un sólido blanco (48 mg, 43%). EM (APCI+) m/z: 388 $(M+H)^+$.

Los ejemplos 381-383 pueden prepararse esencialmente como se describen en el ejemplo 380 al usar 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y el bromuro de bencilo apropiadamente substituido. El ejemplo 382 puede purificarse después de la desprotección por CLAR preparativa de fase inversa [Columna: YMC ODS-AQ 120Å 20x250mm [S10-20µm], eluyente: gradiente desde 95:5 hasta 5:95 A/B, relación de flujo: 15 mL/min; solvente A: agua, 0.1% TFA, 1% isopropanol; solvente B: acetonitrilo, 0.05% TFA, 1% isopropanol]. Los datos EM (ES+) se incluyen en la siguiente tabla.

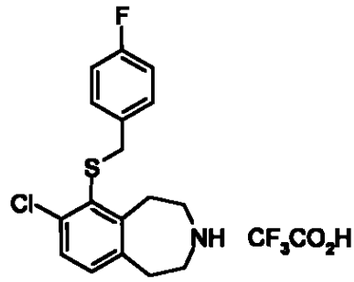


Ej.	R	Compuesto	EM (ES+) m/z
381	2-Cl	Clorohidrato de 7-Cloro-6-(2-cloro-benciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	338 $(M+H)^+$
382	2-	Clorohidrato de 7-	329 $(M+H)^+$

	CN	Cloro-6-(2-ciano-benciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	
383	4-Ph	Clorohidrato de 7-Cloro-6-(4-fenil-benciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	380 $(M+H)^+$

Ejemplo 384

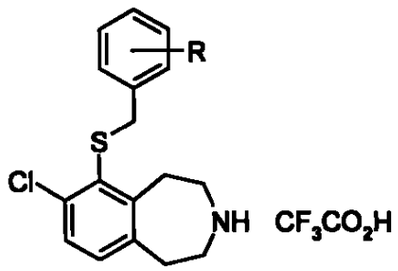
Trifluoroacetato de 7-Cloro-6-(4-fluoro-benciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al ejemplo 380 para hacer reaccionar 3-tert-butoxilcarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]-azepina con bromuro de 4-fluorobencilo. Se purifica por CLAR preparativa de fase inversa [Columna: YMC ODS-AQ 120Å 20 x

250mm [S10-20µm], eluyente: gradiente desde 95:5 hasta 5:95 A/B, relación de flujo: 15 mL/min; solvente A: agua, 0.1% TFA, 1% isopropanol; solvente B: acetonitrilo, 0.05% TFA, 1% isopropanol] para dar el compuesto del título como un sólido blanco. EM (ES+) m/z: 322 $(M+H)^+$.

Los ejemplos 385-386 pueden prepararse esencialmente como se describe en el ejemplo 384 al usar 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y bromuro de bencilo apropiadamente substituido. Los datos EM (ES+) se incluyen en la siguiente tabla.

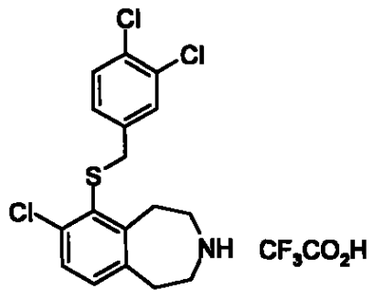


Ej.	R	Compuesto	EM (ES+) m/z
385	4-Cl	Trifluoroacetato de 7-Cloro-6-(4-cloro-benciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	338 $(M+H)^+$

386	4-CN	Trifluoroacetato de 7-Cloro-6-(4-ciano-benciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	329 $(M+H)^+$

Ejemplo 387

Trifluoroacetato de 7-Cloro-6-(3,4-diclorobenciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



A una mezcla 4:1 de 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 3-tert-butoxicarbonil-7,9-dicloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina (200 mg, 0.521 mmol) en metanol (3.3 mL) bajo nitrógeno se agrega hidróxido de potasio (0.9 g, 16.07 mmol) a temperatura ambiente. Cuando la mezcla se volvió homogénea, se calienta a 55-60°C durante 2-3 h, hasta que el CCD mostró la desaparición del material de

partida. Se enfría a temperatura ambiente, se agrega una solución de cloruro de amonio acuoso saturado, se extrae tres veces con éter dietílico, se seca sobre $MgSO_4$ anhidro y se concentra in vacuo. Se disuelve la 3-tert-butoxicarbonil-7-cloro-6-mercapto-2,3,4,5-tetrahidro-1H-benzo[d]azepina cruda en DCM anhidro (5 mL) bajo nitrógeno. Se agrega PS-DIEA (Argonaut, 3.83 mmol/g, 410 mg, 1.57 mmol) y bromuro de 3,4-diclorobencilo (100 µL, 0.586 mmol) a temperatura ambiente y se permite que la reacción continue durante la noche. Se filtra la mezcla de reacción para dar la resina y se enjuaga con DCM (2 mL), metanol (2 mL), DCM (2 mL), y metanol (2 mL). Se concentra in vacuo. Se trata una solución de la 3-tert-butoxicarbonil-7-cloro-6-(3,4-dicloro-benciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina cruda en DCM (2 mL) con cloruro de hidrógeno 2M en éter (exceso) y se continua agitando hasta que el CCD muestra el consumo del material de partida. Se concentra in vacuo y se tritura el sólido obtenido con éter:pentano (10:90). Se purifica por CLAR preparativa de fase inversa (Columna: Xterra Prep RP18 19x250mm; Solvente A: 10 mM carbonato de amonio acuoso, Solvente B: acetonitrilo; 30-100% B durante 20 minutos; relación de flujo 25 mL/min) para dar el compuesto del título como un sólido blanco (97 mg, 38%). EM (APCI+) m/z: 374 $(M+H)^+$.

Los ejemplos 388-393 pueden prepararse esencialmente como se describe en el ejemplo 387 al usar 3-tert-

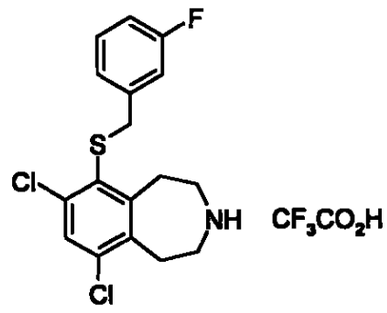
butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y bromuro de bencilo apropiadamente substituido. Los datos EM (ES+) se incluyen en la siguiente tabla.

Ej.	R	Compuesto	EM (ES+ o APCI+)
388	3-Cl	Trifluoroacetato de 7-Cloro-6-(3-cloro-benciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	338 $(M+H)^+$
389	3-F	Trifluoroacetato de 7-Cloro-6-(3-fluoro-benciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	322 $(M+H)^+$
390	3,4-diF	Trifluoroacetato de 7-Cloro-6-(3,4-difluoro-	340 $(M+H)^+$

		benciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	
391	3,5-diF	Trifluoroacetato de 7-Cloro-6-(3,5-difluoro-benciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	340 $(M+H)^+$
392	3,4,5-triF	Trifluoroacetato de 7-Cloro-6-(3,4,5-trifluoro-benciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	358 $(M+H)^+$
393	3-OCF_3	Trifluoroacetato de 7-Cloro-6-(3-trifluorometoxibenciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	388 $(M+H)^+$

Ejemplo 394

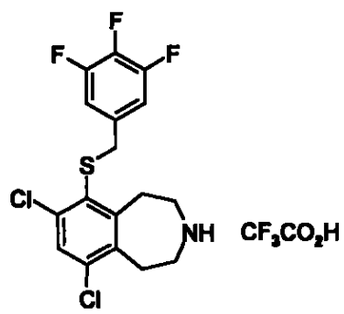
Trifluoroacetato de 7,9-Dicloro-6-(3-fluorobenciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se obtiene como producto menor de la reacción de la mezcla 4:1 de 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 3-tert-butoxicarbonil-7,9-dicloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-benzo[d]azepina con bromuro de 3-fluorobencilo, se usa un método similar al Ejemplo 387. Se desprotege y se aisla el compuesto del título como un sólido blanco después de CLAR preparativa de fase inversa. EM (ES+) m/z: 356 $(M+H)^+$.

Ejemplo 395

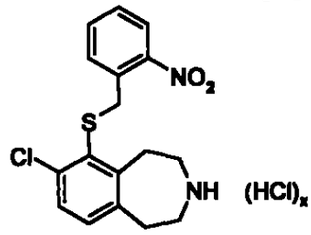
Trifluoroacetato de 7,9-Dicloro-6-(3,4,5-trifluorobenciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se obtiene como producto menor de la reacción de la mezcla 4:1 de 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 3-tert-butoxicarbonil-7,9-dicloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-benzo[d]azepina con bromuro de 3,4,5-trifluorobencilo, se usa un método similar al Ejemplo 387. Se desprotege y se aisla el compuesto del título como un sólido blanco después de CLAR preparativa de fase inversa. EM (APCI+) m/z: 392 $(M+H)^+$.

Ejemplo 396

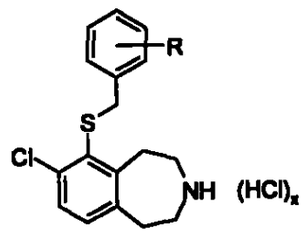
Clorohidrato de 7-Cloro-6-(2-nitro-benciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al ejemplo 387, usando 3-tert-butoxilcarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]-azepina y bromuro de 2-nitrobencilo para dar, después de la cromatografía eluyendo con hexano/EtOAc (10:1) y desprotección por el procedimiento general 1-4, el compuesto del título

como un polvo blanco opaco. EM (APCI+) m/z: 349 $(M+H)^+$.

Los ejemplos 397-399 pueden prepararse esencialmente como se describen en el ejemplo 396 al usar 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y bromuro de bencilo apropiadamente substituido. Los datos EM (ES+) se incluyen en la siguiente tabla.

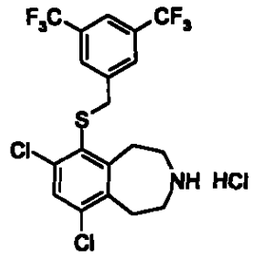


Ej.	R	Compuesto	EM (ES+ o APCI+)
397	2-OCF_3	Clorohidrato de 7-Cloro-6-(2-trifluorometoxibenciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	388 $(M+H)^+$
398	3-OPh	Clorohidrato de 7-Cloro-6-	396 $(M+H)^+$

		(3-fenoxibenciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	
399	3,5-diCF_3	Clorohidrato de 7-Cloro-6-(3,5-bistrifluorometilbenciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	440 $(M+H)^+$

Ejemplo 400

Clorohidrato de 7,9-Dicloro-6-(3,5-bis-trifluorometilbenciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (2148393)

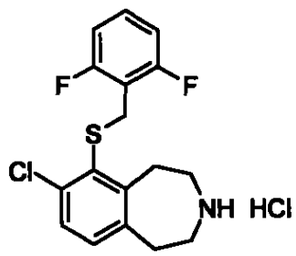


Se obtiene como producto menor de la reacción de la mezcla 4:1 de 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 3-tert-butoxicarbonil-7,9-dicloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-benzo[d]azepina con bromuro de 3,5-bis-trifluorometilbencilo, se usa un método similar al Ejemplo

396. Se desprotege la mezcla cruda y se purifica por CLAR preparativa de fase inversa (Columna: Xterra Prep RP18 19x250mm; solvente A: 10 mM carbonato de amonio acuoso; solvente B: acetonitrilo; 30-100% B durante 20 minutos; relación de flujo 25 mL/min). Se usa un método similar al procedimiento general 2-2 para dar el compuesto del título como un sólido blanco. EM (APCI+) m/z: 474 $(M+H)^+$.

Ejemplo 401

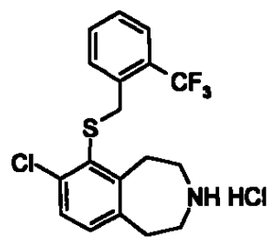
Clorohidrato de 7-Cloro-6-(2,6-difluorobenciltio-)2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al ejemplo 330, usando 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y bromuro de 2,6-difluorobencilo para dar, después de la desprotección por el Procedimiento general 1-4, el compuesto del título.

Ejemplo 402

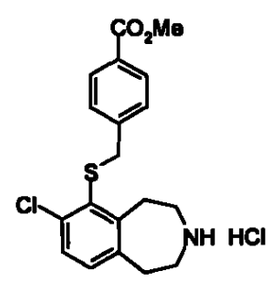
Clorohidrato de 7-Cloro-6-(2-trifluorometilbenciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al ejemplo 347 para hacer reaccionar 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina con bromuro de 2-trifluorometilbencilo. Se usa un método similar al procedimiento general 1-4 para dar el compuesto del título como un sólido color marrón ceroso. EM (APCI+) m/z: 372 $(M+H)^+$.

Ejemplo 403

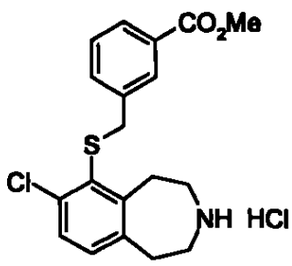
Clorohidrato de 7-Cloro-6-(4-metoxicarbonilbenciltio)-2,3,4,5-tetrahidro-benzo[d]azepina



Se usa un método similar para la preparación 177, usando 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 4-(bromometil)benzoato de metilo para dar, después de la desprotección por el procedimiento general 1-4, el compuesto del título como un sólido blanco. EM (ES+) m/z: 362 $(M+H)^+$.

Ejemplo 404

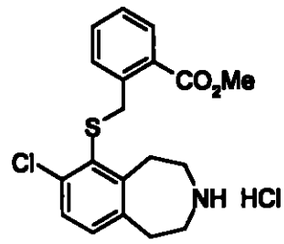
Clorohidrato de 7-Cloro-6-(3-metoxicarbonilbenciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al ejemplo 347 para hacer reaccionar 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina con metil 3-(bromometil)benzoato. Se usa un método similar al procedimiento general 1-5, preparación básica, y un método similar al procedimiento general 2-2 para dar el compuesto del título. EM (APCI+) m/z: 362 $(M+H)^+$.

Ejemplo 405

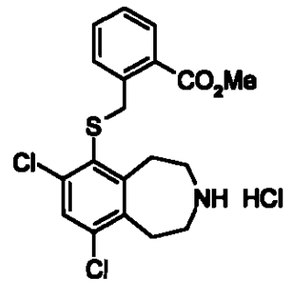
Clorohidrato de 7-Cloro-6-(2-metoxicarbonilbenciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al ejemplo 347, usando la mezcla 4:1 de 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 3-tert-butoxicarbonil-7,9-dicloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-benzo[d]azepina con 2-(bromometil)benzoato de metilo. Se usa un método similar al procedimiento general 1-4 y se purifica por CLAR preparativa de fase inversa (Columna: Xterra Prep RP18 19x250mm; solvente A: 10 mM carbonato de amonio acuoso, solvente B: acetonitrilo; 30-100% B durante 20 minutos; relación de flujo 25 mL/min). Se usa un método similar al procedimiento general 2-2, para dar el compuesto del título como un sólido blanco. EM (ES+) m/z: 362 $(M+H)^+$.

Ejemplo 406

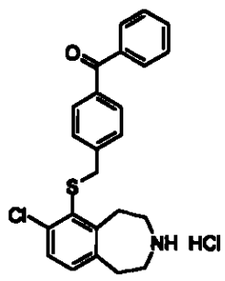
Clorohidrato de 7,9-Dicloro-6-(2-metoxicarbonilbenciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se obtiene la base libre del compuesto del título como un producto menor del ejemplo 405, después de CLAR preparativa de fase inversa (Columna: Xterra Prep RP18 19x250mm; solvente A: carbonato de amonio acuoso 10 mM; solvente B: acetonitrilo; 30-100% B durante 20 minutos; relación de flujo 25 mL/min). Se usa un método similar al procedimiento general 2-2 para dar el compuesto del título como un sólido blanco. EM (ES+) m/z: 396 $(M+H)^+$.

Ejemplo 407

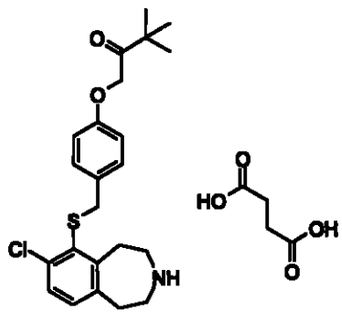
Clorohidrato de 6-(4-Benzoilbenciltio)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al ejemplo 380 para hacer reaccionar 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina con 4-(bromometil)benzofenona. Se purifica por CLAR preparativa de fase inversa (Columna: Xterra Prep RP18 19x250mm; Solvente A: 10 mM carbonato de amonio acuoso, Solvente B: acetonitrilo; 30-100% B durante 20 minutos; relación de flujo 25 mL/min). Se usa un método similar al procedimiento general 2-2 para dar el compuesto del título como un sólido blanco. EM (ES+) m/z: 408 $(M+H)^+$.

Ejemplo 408

Succinato de 7-Cloro-6-[4-(3,3-dimetil-2-oxo-butoxi)-benciltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



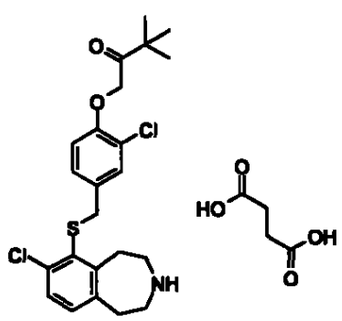
Se usa un método similar al procedimiento general 7, usando 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina (577 mg, 1.5 mmol) y 1-(4-bromometilfenoxi)-3,3-dimetilbutan-2-ona (556 mg, 1.95 mmol) para dar, después

de cromatografía en gel de sílice eluyendo con EtOAc/hexano (1:5), 3-tert-butoxicarbonil-7-cloro-6-[4-(3,3-dimetil-2-oxo-butoxi)-benciltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite incoloro (669 mg, 86%). EM (ES+) m/z: 518 $(M+H)^+$.

Se usa un método similar al procedimiento general 1-5 para desproteger 3-tert-butoxicarbonil-7-cloro-6-[4-(3,3-dimetil-2-oxo-butoxi)-benciltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina (669 mg, 1.29 mmol). Purificación por cromatografía en gel de sílice eluyendo con DCM/2M amonio en metanol (92:8) para dar la base libre del compuesto del título como un aceite incoloro (349 mg, 64%). EM (ES+) m/z: 418 $(M+H)^+$. Se usa un método similar al procedimiento general 2-1 para dar el compuesto del título.

Ejemplo 409

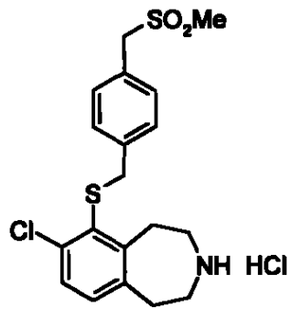
Succinato de 7-Cloro-6-[3-cloro-4-(3,3-dimetil-2-oxo-butoxi)-benciltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al ejemplo 408, usando 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 1-(4-bromometil-3-clorofenoxi)-3,3-dimetilbutan-2-ona para dar el compuesto del título. EM (ES+) m/z: 452 $(M+H)^+$.

Ejemplo 410

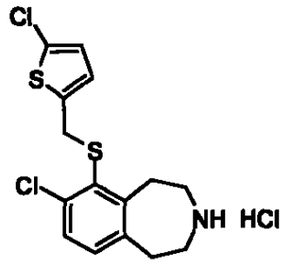
Clorohidrato de 7-Cloro-6-(4-metansulfonilmetil-benciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al procedimiento general 1-4, usando 3-tert-butoxicarbonil-7-cloro-6-(4-metansulfonilmetil-benciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina para dar el compuesto del título como un sólido blanco. EM (ES+) m/z: 396 $(M+H)^+$.

Ejemplo 411

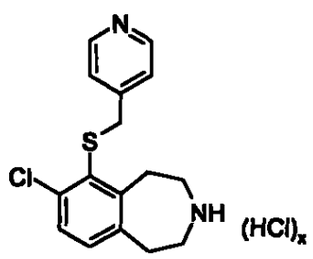
Clorohidrato de 7-Cloro-6-(5-cloro-tiofen-2-ilmetiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al ejemplo 387, usando 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 2-cloro-5-(clorometil)tiofeno para dar, después de la formación de clorohidrato por el procedimiento general 2-2, el compuesto del título como un sólido café. EM (APCI+) m/z: 344 $(M+H)^+$.

Ejemplo 412

Clorohidrato de 7-Cloro-6-(piridin-4-ilmetiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

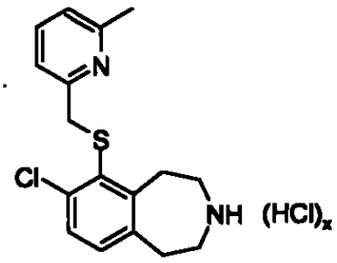


Se usa un método similar al ejemplo 387, usando 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y bromohídrato de 4-bromometilpiridina para dar, después de la formación de

clorohidrato por el procedimiento general 2-2, el compuesto del título como un sólido blanco. EM (APCI+) m/z: 305 $(M+H)^+$.

Ejemplo 413

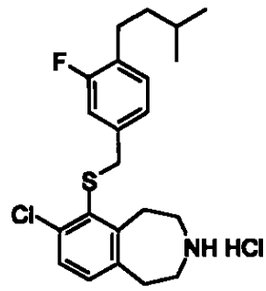
Clorohidrato de 7-Cloro-6-(6-metil-piridin-2-ilmetiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al ejemplo 387, usando 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 2-clorometil-6-metilpriidina para dar, después de cromatografía en gel de sílice eluyendo con hexano/EtOAc (4:1) y desprotección por el procedimiento general 1-4, el compuesto del título como un sólido blanco. EM (ES+) m/z: 319 $(M+H)^+$.

Ejemplo 414

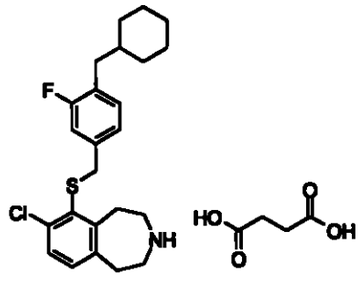
Clorohidrato de 7-Cloro-6-[3-fluoro-4-(3-metilbutil)-benciltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



A la 6-(4-bromo-3-fluorobenciltio)-3-tert-butoxicarbonil-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina (0.210 mg, 0.42 mmol) y un aducto de diclorometano de dicloro[1,1'-bis(difenilfosfino)-ferroceno]paladio(II) (17 mg, 0.021 mmol) se agrega 0.5 M bromuro de 3-metilbutilzinc en THF (4.2 mL, 2.10 mmol). Se desgasifica, se purga con nitrógeno seco, y se agita durante la noche a 80°C. Se enfría a temperatura ambiente, se diluye con EtOAc, se lava con agua, se seca sobre $MgSO_4$ anhidro y se concentra in vacuo. Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (9:1) para dar 3-tert-butoxicarbonil-7-cloro-6-[3-fluoro-4-(3-metilbutil)-benciltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite amarillo (85 mg, 42%). Se usa un método similar al procedimiento general 1-4 para dar el compuesto del título como un sólido blanco. EM (ES+) m/z: 392 $(M+H)^+$.

Ejemplo 415

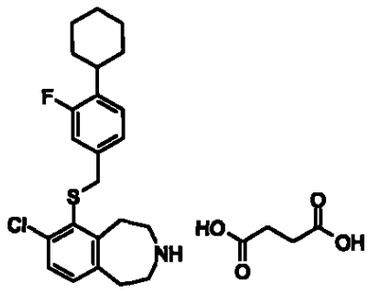
Succinato de 7-Cloro-6-(4-ciclohexilmetil-3-fluorobenciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al ejemplo 414 para hacer reaccionar 6-(4-bromo-3-fluorobenciltio)-3-tert-butoxicarbonil-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina con bromuro de (ciclohexil)metilzinc. Se usa un método similar al procedimiento general 1-4, preparación básica, y un método similar al procedimiento general 2-1, para dar el compuesto del título como un sólido blanco. EM (ES+) m/z: 418 $(M+H)^+$.

Ejemplo 416

Clorohidrato de 7-Cloro-6-(4-ciclohexil-3-fluorobenciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

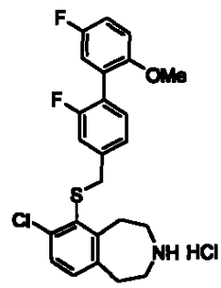


Se usa un método similar al ejemplo 414, usando 6-(4-bromo-3-fluorobenciltio)-3-tert-butoxicarbonil-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina y bromuro de ciclohexilzinc. Se usa un método similar al procedimiento

general 1-4, preparación básica, y un método similar al procedimiento general 2-1, para dar el compuesto del título como un sólido blanco. EM (ES+) m/z: 404 $(M+H)^+$.

Ejemplo 417

Clorohidrato de 7-Cloro-6-(2,5'-difluoro-2'-metoxibifenil-4-ilmetiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

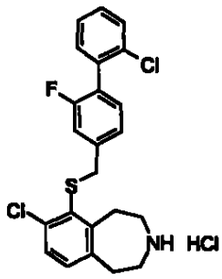


Se desgasifica una mezcla agitada de 6-(4-bromo-3-fluorobenciltio)-3-tert-butoxicarbonil-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina (212 mg, 0.424 mmol), ácido 5-fluoro-2-metoxibenceno borónico (108 mg, 0.636 mmol), carbonato de potasio (292 mg, 2.12 mmol), trifenilfosfina (11 mg, 0.0424 mmol) y cloruro de bis(trifenilfosfina)-paladio(II) (15 mg, 0.0212 mmol) en dioxano (3 mL) y agua (1 mL). Se purga con nitrógeno seco y se calienta a 100°C durante 5 h. Se enfría a temperatura ambiente, se agrega agua, se extrae tres veces con EtOAc, se seca sobre Na_2SO_4 anhidro y se concentra in vacuo. Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (9:1) para dar 3-tert-butoxicarbonil-7-cloro-6-(2,5'-difluoro-2'-metoxi-bifenil-4-ilmetiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite

amarillo (216 mg, 93%). Se usa un método similar al procedimiento general 1-4 para dar el compuesto del título como una espuma amarilla. EM (ES+) m/z: 446 $(M+H)^+$.

Ejemplo 418

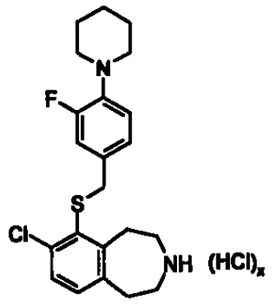
Clorohidrato de 7-Cloro-6-(2'-cloro-2-fluorobifenil-4-ilmetiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al ejemplo 417, usando ácido 2-clorofenilborónico para dar, después de la desprotección por el Procedimiento general 1-4, el compuesto del título como un sólido blanco. EM (ES+) m/z: 432 $(M+H)^+$.

Ejemplo 419

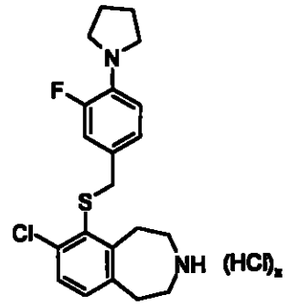
Clorohidrato de 7-Cloro-6-(3-fluoro-4-piperidin-1-il-benciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



En un tubo sellado, se agrega tris(dibencilidenacetona)dipaladio (13 mg, 0.014 mmol) y 2,2'-bis(difenilfosfino)-1,1'-binaftilo (19 mg, 0.029 mmol) a una mezcla de 6-(4-bromo-3-fluorobenciltio)-3-tert-butoxicarbonil-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina (957 mg, 1.91 mmol), tert-butóxido de sodio (367 mg, 3.83 mmol), 18-crown-6 (50 mg, 0.191 mmol) y piperidina (944 µl, 9.57 mmol) en tolueno (10 mL). Se limpia la mezcla con nitrógeno y se calienta durante la noche. Se enfría a temperatura ambiente, se diluye con agua y se extrae tres veces con EtOAc. Se seca sobre Na_2SO_4 anhidro y se concentra in vacuo. Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (9:1) para dar 3-tert-butoxicarbonil-7-cloro-6-(3-fluoro-4-piperidin-1-il-benciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite amarillo (511 mg, 33%). Se usa un método similar al procedimiento general 1-4 para dar el compuesto del título como un sólido blanco. EM (ES+) m/z: 405 $(M+H)^+$.

Ejemplo 420

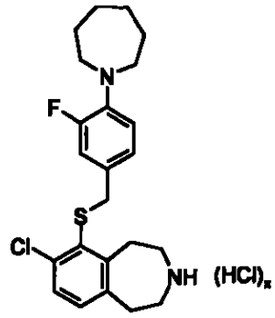
Clorohidrato de 7-Cloro-6-(3-fluoro-4-pirrolidin-1-il-benciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al ejemplo 419 para hacer reaccionar 6-(4-bromo-3-fluorobenciltio)-3-tert-butoxicarbonil-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina con pirrolidina. Se usa un método similar al procedimiento general 1-4 para dar el compuesto del título como un sólido blanco. EM (ES+) m/z: 391 $(M+H)^+$.

Ejemplo 421

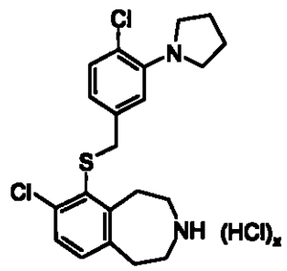
Clorohidrato 6-(4-Azepan-1-il-3-fluorobenciltio)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al ejemplo 419 para hacer reaccionar 6-(4-bromo-3-fluorobenciltio)-3-tert-butoxicarbonil-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina con homopiperidina. Se usa un método similar al procedimiento general 1-4 para dar el compuesto del título como un sólido blanco. EM (ES+) m/z: 419 $(M+H)^+$.

Ejemplo 422

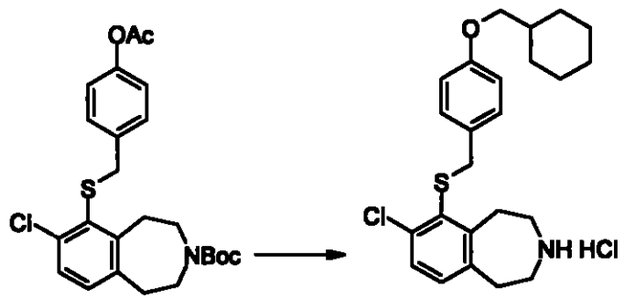
Clorohidrato de 7-Cloro-6-(4-cloro-3-pirrolidin-1-il-benciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al ejemplo 419, usando 6-(3-bromo-4-cloro-benciltio)-3-tert-butoxicarbonil-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina y pirrolidina para dar, después de la desprotección usando un método similar al Procedimiento general 1-4, el compuesto del título como un sólido blanco. EM (ES+) m/z: 407 $(M+H)^+$.

Ejemplo 423

Clorohidrato de 7-Cloro-6-(4-ciclohexilmetoxibenciltio)-3-tert-butoxicarbonil-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar para la preparación 177, usando 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y acetato de 4-(clorometil)fenilo para dar 6-(4-acetoxibenciltio)-3-tert-butoxicarbonil-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un sólido blanco.

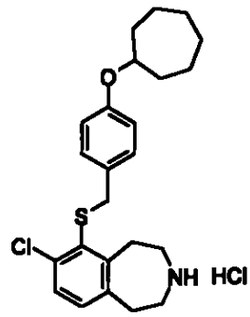
A la 6-(4-acetoxibenciltio)-3-tert-butoxicarbonil-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina (532 mg, 1.15 mmol) en metanol (8 mL) a temperatura ambiente se agrega con una solución agitada de carbonato de potasio (796 mg, 5.77 mmol) en agua (4 mL) y se agita la mezcla durante 2 h. Se diluye con agua, se extrae tres veces con EtOAc, se seca sobre Na_2SO_4 anhidro y se concentra in vacuo. A una porción del fenol cruda así obtenida (204 mg, 0.487 mmol) en THF (5 mL), se agrega con diisopropil azodicarboxilato agitado (216 µl, 1.71 mmol) seguido por trifenilfosfina (306 mg, 1.17 mmol) y ciclohexilmetanol (619 mg, 5.42 mmol). Se calienta a 60°C durante 3 h, se enfría a temperatura ambiente y se concentra in vacuo. Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (9:1) para dar 3-tert-butoxicarbonil-7-cloro-6-(4-ciclohexilmetoxi-benciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite incoloro (176 mg, 70%). Se usa un método similar al procedimiento

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general 1-4 para dar el compuesto del título como un sólido blanco. EM (ES+) m/z: 416 $(M+H)^+$.

Ejemplo 424

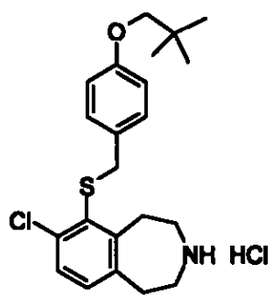
Clorohidrato de 7-Cloro-6-(4-cicloheptiloxibenciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al ejemplo 423 para hacer reaccionar 6-(4-acetoxibenciltio)-3-tert-butoxicarbonil-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina con cicloheptanol. Se usa un método similar al procedimiento general 1-4 para dar el compuesto del título como un sólido blanco. EM (ES+) m/z: 416 $(M+H)^+$.

Ejemplo 425

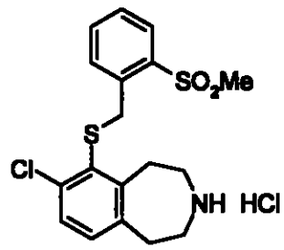
Clorohidrato de 7-Cloro-6-[4-(2,2-dimetilpropoxi)-benciltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar para la preparación 177 para hacer reaccionar 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 1-bromometil-4-(2,2-dimetilpropoxi)-benceno. Se usa un método similar al procedimiento general 1-4 para dar el compuesto del título como un sólido blanco. EM (ES+) m/z: 390 $(M+H)^+$.

Ejemplo 426

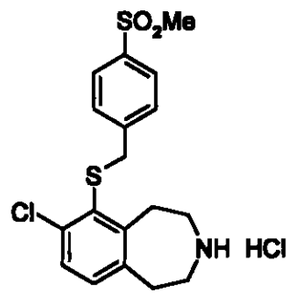
Clorohidrato de 7-Cloro-6-(2-metansulfonilbenciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar para la preparación 177, usando 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 1-bromometil-2-metansulfonil-benceno para dar, después de la desprotección por el Procedimiento general 1-4, el compuesto del título y como un sólido blanco. EM (APCI+) m/z: 382 $(M+H)^+$.

Ejemplo 427

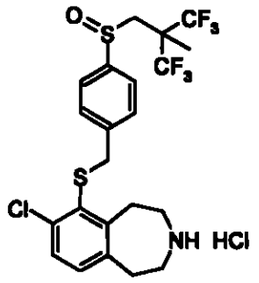
Clorohidrato de 7-Cloro-6-(4-metansulfonilbenciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al ejemplo 380, usando 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y bromuro de 4-metilsulfonilbencilo para dar, después de la formación de clorohidrato por el procedimiento general 2-2, el compuesto del título como un sólido blanco. EM (ES+) m/z: 382 $(M+H)^+$.

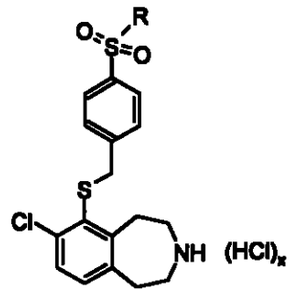
Ejemplo 428

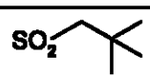
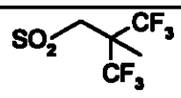
Clorohidrato de 7-Cloro-6-[4-(3,3,3-trifluoro-2-metil-2-trifluorometilpropano-1-sulfinil)-benciltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina

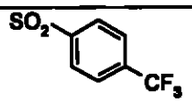
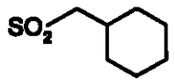


A la 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina (723 mg, 1.88 mmol) en metanol (10 mL) se agrega hidróxido de potasio peletizado (3.34 g, 60.2 mmol) y se agita la mezcla a 50°C durante 2 h. Se enfría a temperatura ambiente, se agrega cloruro de amonio saturado acuoso, se extrae tres veces con EtOAc, se seca sobre Na_2SO_4 anhidro y se concentra in vacuo para dar la 3-tert-butoxicarbonil-7-cloro-6-mercapto-2,3,4,5-tetrahidro-1H-benzo[d]azepina cruda. Se disuelve el compuesto en DMF (5 mL), se agrega carbonato de cesio (920 mg, 2.82 mmol) y 1-bromometil-4-(3,3,3-trifluoro-2-metil-2-trifluorometil-propano-1-sulfinil)-benceno (824 mg, 2.071 mmol) y se agita 2 h a temperatura ambiente. Se diluye con agua, se extrae tres veces con EtOAc, se seca sobre Na_2SO_4 anhidro y se concentra in vacuo. Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (9:1) para dar 3-tert-butoxicarbonil-7-cloro-6-[4-(3,3,3-trifluoro-2-metil-2-trifluorometil-propano-1-sulfinil)-benciltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite amarillo (986 mg, 83%). Se usa un método similar al procedimiento general 1-4 para dar el compuesto del título como una espuma blanca. EM (ES+) m/z: 530 $(M+H)^+$.

Los ejemplos 429-432 pueden prepararse esencialmente como se describe en el ejemplo 428 al usar 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina con bromuro de bencilo apropiadamente substituido. Los datos EM (ES+) se incluyen en la siguiente tabla.

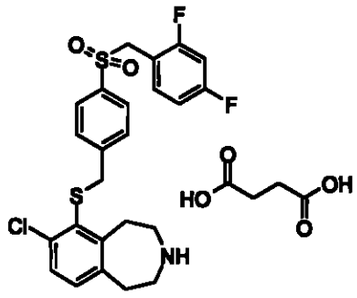


Ej.	SO_2R	Compuesto	EM (ES+ o APCI+)
429		Clorohidrato de 7-Cloro-6-[4-(2,2-dimetil-propano-1-sulfonil)-benciltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	438 $(M+H)^+$
430		Clorohidrato de 7-Cloro-6-[4-(3,3,3-trifluoro-2-metil-2-trifluorometilpropano-1-sulfonil)-benciltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	546 $(M+H)^+$

431		Clorohidrato de 7-Cloro-6-[4-(4-trifluorometil-bencenosulfonil)-benciltio]-1,2,4,5-tetrahidro-benzo[d]azepina	512 $(M+H)^+$
432		Clorohidrato de 7-Cloro-6-(4-ciclohexilmetansulfonil-benciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	464 $(M+H)^+$

Ejemplo 433

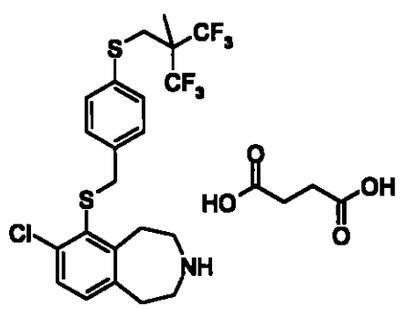
Succinato de 7-Cloro-6-[4-(2,4-difluoro-fenilmetansulfonil)-benciltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al ejemplo 428 para hacer reaccionar 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina con 1-(4-bromometil-bencenosulfonilmetil)-2,4-difluoro-benceno. Se usa un método similar al procedimiento general 1-4, preparación básica, y un método similar al procedimiento general 2-1, para dar el compuesto del título como un sólido blanco. EM (ES+) m/z: 494 $(M+H)^+$.

Ejemplo 434

Succinato de 7-Cloro-6-[4-(3,3,3-trifluoro-2-metil-2-trifluorometilpropiltio)-benciltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina

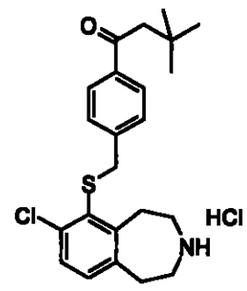


Se usa un método similar al ejemplo 428 para hacer reaccionar 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina

con 1-bromometil-4-(3,3,3-trifluoro-2-metil-2-trifluorometil-propiltio)-benceno. Se usa un método similar al procedimiento general 1-5, preparación básica, y un método similar al procedimiento general 2-1, para dar el compuesto del título como un sólido blanco. EM (APCI$^+$) m/z: 514 $(M+H)^+$.

Ejemplo 435

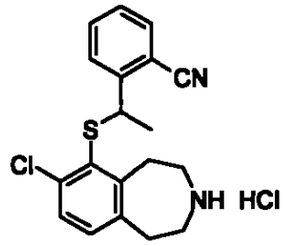
Clorohidrato de 7-Cloro-6-[4-(3,3-dimetilbutiril)-benciltio]-1,2,4,5-tetrahidro-benzo[d]azepina



Se usa un método similar al ejemplo 428 para hacer reaccionar 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina con 1-(4-bromometilfenil)-3,3-dimetilbutan-1-ona. Se usa un método similar al procedimiento general 1-4, preparación básica, y un método similar al procedimiento general 2-2 para dar el compuesto del título como un sólido blanco. EM (APCI$^+$) m/z: 402 $(M+H)^+$.

Ejemplo 436

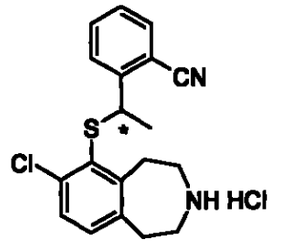
Clorohidrato de (±)-7-Cloro-6-[1-(2-cianofenil)-etiltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar para la preparación 177, usando 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y (±)-2-(1-bromoetil)benzonitrilo para dar, después de la desprotección por el procedimiento general 1-4, el compuesto del título como un sólido blanco. EM (APCI+) m/z: 343 $(M+H)^+$.

Ejemplo 437

Clorohidrato de (-)-7-Cloro-6-[1-(2-cianofenil)-etiltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se disuelve succinato de (±)-7-cloro-6-[1-(2-cianofenil)-etiltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina (326 mg, 1.0 mmol)

en DCM (5 mL) y piridina (0.4 mL, 5 mmol). Se agrega di-tert-butil-dicarbonato (270 mg, 1.2 mmol) y se agita la mezcla durante 16 h a temperatura ambiente. Se lava la mezcla con NaOH 5N acuoso y $NaHCO_3$ acuoso saturado sucesivamente. Se colecta la capa orgánica y se concentra in vacuo. Se purifica el residuo por cromatografía en gel de sílice eluyendo con hexano/EtOAc (1:1) para obtener (±)-3-tert-butoxicarbonil-7-cloro-6-[1-(2-cianofenil)-etiltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina (393 mg, 93%). Se separaron los enantiomeros de (±) 3-tert-butoxicarbonil-7-cloro-6-[1-(2-cianofenil)-etiltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina por cromatografía de fase normal quiral (Columna Chiralpak AD 8x30 cm, eluyendo con heptano/isopropilamina, 95:5).

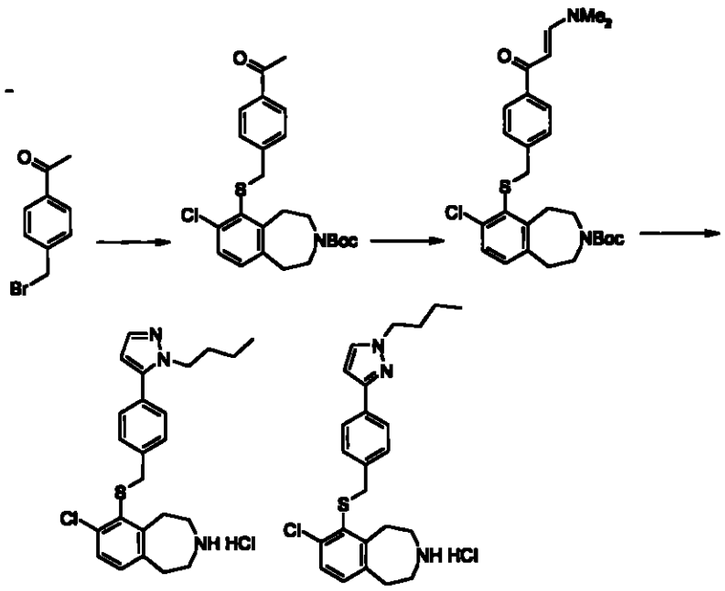
Se toma el segundo isómero eluyente y se desprotege usando el procedimiento general 1-5. Se purifica con cromatografía SCX. Se usa un método similar al procedimiento general 2-2 para obtener el compuesto del titulo (125 mg, 37%). EM (ES+) m/z: 343 $(M+H)^+$. $[\alpha]^{20}_D$ -112° (c 0.5, CH_3OH).

Ejemplos 438 y 439

Clorohidrato de 6-[4-(2-Butil-2H-pirazol-3-il)-benciltio]-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina y Clorohidrato de

1212

6-[4-(1-Butil-1H-pirazol-3-il)-benciltio]-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Bromuro de 4-Acetilbencilo: Se usa un método similar para la preparación 184, usando 4-metilacetofenona, para dar el intermediario deseado como un sólido blanco.

6-(4-Acetilbenciltio)-3-tert-butoxicarbonil-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Se usa un método similar al ejemplo 380, usando 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y bromuro de 4-acetilbencilo para dar, después de la cromatografía eluyendo con hexano/EtOAc (15:1), el intermediario deseado como un sólido blanco. EM (APCI+) m/z 346 $(M+H-Boc)^+$.

3-tert-Butoxicarbonil-7-cloro-6-[4-(3-dimetilaminoacriloil)-benciltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Se calienta una solución de 6-(4-acetilbenciltio)-3-tert-butoxicarbonil-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina (1.0 g, 2.2 mmol) en tolueno (10 mL) a 110°C durante la noche en la presencia de tert-butoxi-bis(dimetilamino)-metano (1.0 mL, 4.84 mmol). Se concentra in vacuo para proporcionar el intermediario deseado como un aceite oscuro (1.2 g, 100%). EM (APCI+) m/z 401 $(M+H-Boc)^+$.

Clorohidrato de 6-[4-(1-Butil-1H-pirazol-3-il)-benciltio]-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina: A una mezcla agitada de 3-tert-butoxicarbonil-7-cloro-6-[4-(3-dimetilaminoacriloil)-benciltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina (240 mg, 0.475 mmol), oxalato de butilhidrazina (102 mg, 0.574 mmol), carbonato de sodio (55 mg, 0.444 mmol) en agua (8 mL) y metanol (10 mL) se agrega ácido acético (ca. 3-6 gotas) hasta pH 5. Se calienta durante la noche a 70°C. Se concentra in vacuo. Se purifica por cromatografía en gel de sílice eluyendo con hexano/EtOAc (10:1) para dar una mezcla del intermediario deseado, 3-tert-butoxicarbonil-6-[4-(2-butil-2H-pirazol-3-il)-benciltio]-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina (65 mg, 32%), EM (APCI+) m/z: 426 $(M+H-Boc)^+$ y 3-tert-butoxicarbonil-6-[4-(1-butil-1H-pirazol-3-il)-benciltio]-7-cloro-2,3,4,5-tetrahidro-

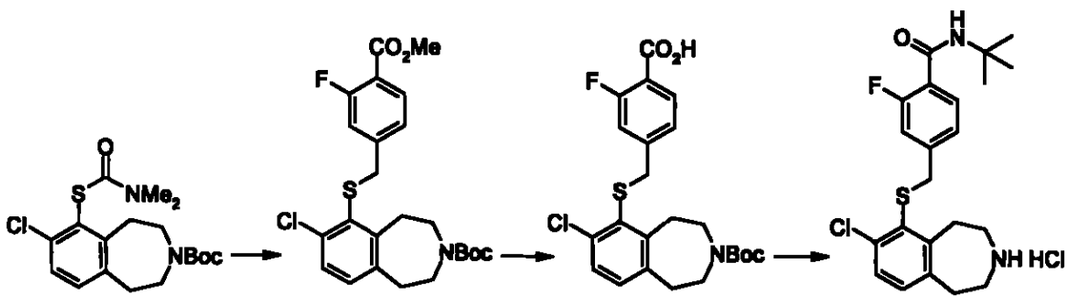
1H-benzo[d]azepina (100 mg, 50%), EM (APCI+) m/z: 426 (M+H-Boc)$^+$.

Se usa un método similar al procedimiento general 1-4, usando 3-tert-butoxicarbonil-6-[4-(2-butil-2H-pirazol-3-il)-benciltio]-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina, para dar 6-[4-(2-butil-2H-pirazol-3-il)-benciltio]-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina (Ejemplo 438) como un sólido blanco. EM (APCI+) m/z: 426 (M+H)$^+$.

Se usa un método similar al procedimiento general 1-4, usando 3-tert-butoxicarbonil-6-[4-(1-butil-1H-pirazol-3-il)-benciltio]-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina, para dar 6-[4-(1-butil-1H-pirazol-3-il)-benciltio]-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina (Ejemplo 439) como un sólido blanco. EM (APCI+) m/z: 426 (M+H)$^+$.

Ejemplo 440

Clorohidrato de 6-(4-tert-Butilcarbamoil-3-fluorobenciltio)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina



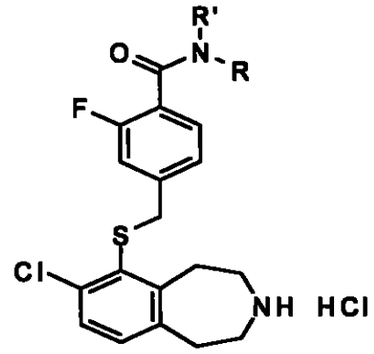
3-tert-Butoxicarbonil-7-cloro-6-(3-fluoro-4-metoxicarbonilbenciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Se usa un método similar al ejemplo 428, usando 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 4-bromometil-2-fluorobenzoato de metilo, para dar el intermediario deseado como un sólido blanco.

3-tert-Butoxicarbonil-6-(4-carboxi-3-fluorobenciltio)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Se calienta una solución agitada de 3-tert-butoxicarbonil-7-cloro-6-(3-fluoro-4-metoxicarbonilbenciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (3.56 g, 7.44 mmol) en THF (50 mL) y agua (40 mL) durante la noche a 65°C en la presencia de hidróxido de potasio (8.30 g, 148.77 mmol). La mezcla se enfría a 0°C, se agrega lentamente una solución 1N de ácido clorhídrico hasta pH 5. Se extrae tres veces con EtOAc, se seca sobre Na_2SO_4 anhidro y se concentra in vacuo para proporcionar el intermediario deseado como un sólido blanco (3.5 g, 99%).

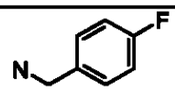
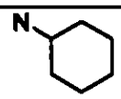
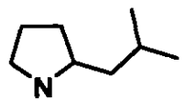
Clorohidrato de 6-(4-tert-Butilcarbamoil-3-fluorobenciltio)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina: A una solución de 3-tert-butoxicarbonil-6-

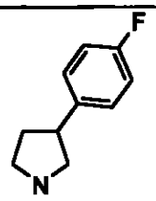
(4-carboxi-3-fluoro-benciltio)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina (1.1 g, 2.36 mmol) en DMF (7 mL), se agrega tert-butilamina (12.05 g, 165.2 mmol), EDC (1.81 g, 9.44 mmol) y HOBt (1.44g, 10.62 mmol) y se agita en un tubo sellado a 70°C durante la noche. Se diluye con EtOAc, se lava con agua, se seca sobre $MgSO_4$ anhidro y se concentra in vacuo. Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (9:1) para dar 3-tert-butoxicarbonil-6-(4-tert-butilcarbamoil-3-fluorobenciltio)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite claro. EM (APCI+) m/z: 421 $(M+H)^+$. Se usa un método similar al procedimiento general 1-4 para dar el compuesto del título como un polvo blanco. EM (APCI+) m/z: 421 $(M+H)^+$.

Los ejemplos 441-447 pueden prepararse esencialmente como se describe en el ejemplo 440 para hacer reaccionar 3-tert-butoxicarbonil-6-(4-carboxi-3-fluorobenciltio)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina con la amina apropiada. Los datos EM (ES+) se incluyen en la siguiente tabla.



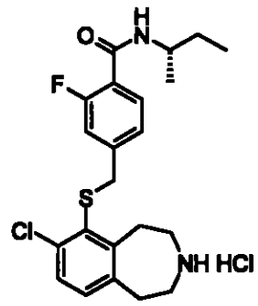
Ej.	N-R	R'	Compuesto	EM (ES+ o APCI+)
441	N-(n-Pr)	H	Clorohidrato de 7-Cloro-6-(3-fluoro-4-n-propilcarbamoil-benciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	407 $(M+H)^+$
442	N-(i-Bu)	H	Clorohidrato de 6-(4-iso-Butilcarbamoil-3-fluoro-benciltio)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina	421 $(M+H)^+$
443	N-(n-Pr)	n-Pr	Clorohidrato de 7-Cloro-6-(4-dipropilcarbamoil-3-fluoro-benciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	449 $(M+H)^+$

444		H	Clorohidrato de 7-Cloro-6-[3-fluoro-4-(4-fluoro-bencilcarbamoil)-benciltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	473 $(M+H)^+$
445		H	Clorohidrato de 7-Cloro-6-(4-ciclohexilcarbamoil-3-fluoro-benciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina	447 $(M+H)^+$
446			Clorohidrato de 7-Cloro-6-[3-fluoro-4-(2-isobutil-pirrolidina-1-carbonil)-benciltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	475 $(M+H)^+$

447		7-Cloro-6-{3-fluoro-4-[3-(4-fluoro-fenil)-pirrolidina-1-carbonil]-benciltio}-2,3,4,5-tetrahidro-1H-benzo[d]azepina-Clorohidrato	513 $(M+H)^+$

Ejemplo 448

Clorohidrato de (S)-(+)-6-(4-sec-Butilcarbamoil-3-fluorobenciltio)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina



3-tert-Butoxicarbonil-7-cloro-6-(4-clorocarbonil-3-fluorobenciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina: A una solución de 3-tert-butoxicarbonil-6-(4-carboxi-3-fluoro-benciltio)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina (1.95 g, 4.21 mmol) en DCM (20 mL) a 0°C bajo nitrógeno, se agregan tres gotas de DMF y cloruro de oxalilo (1.06 g, 8.41 mmol). Se

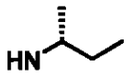
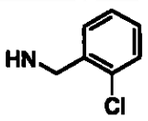
agita durante 2 h y se concentra in vacuo para proporcionar el intermediario deseado como un aceite amarillo (1.93 g, 95%).

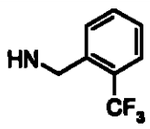
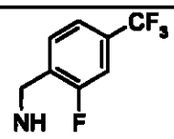
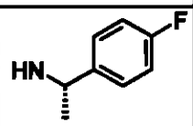
(S)-3-tert-Butoxicarbonil-6-(4-sec-butilcarbamoil-3-fluorobenciltio)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina: A una solución de 3-tert-butoxicarbonil-7-cloro-6-(4-clorocarbonil-3-fluoro-benciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (415 mg, 0.860 mmol) en DCM (10 mL), se agrega (S)-(+)-sec-butilamina (1.0 g, 13.7 mmol) y se agita a temperatura ambiente durante 30 min. Se concentra in vacuo y se purifica por cromatografía en gel de sílice eluyendo con hexano/EtOAc (4:1) para dar el intermediario deseado como un aceite pálido (352 mg, 79%). EM (APCI+) m/z: 421 $(M+H-Boc)^+$.

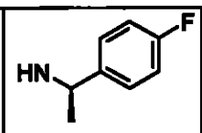
Clorohidrato de (S)-(+)-6-(4-sec-Butilcarbamoil-3-fluorobenciltio)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina: Se usa un método similar al procedimiento general 1-4, usando (+)-3-tert-butoxicarbonil-6-(4-sec-butilcarbamoil-3-fluoro-benciltio)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina, para dar el compuesto del título como un sólido pálido. EM (APCI+) m/z: 421 $(M+H)^+$. $[\alpha]^{20}_D$ +8.7° (c 0.5, CH_3OH).

Los ejemplos 449-454 puede prepararse esencialmente como se describe en el ejemplo 448 para hacer reaccionar 3-tert-butoxicarbonil-6-(4-carboxi-3-fluoro-benciltio)-7-cloro-

2,3,4,5-tetrahidro-1H-benzo[d]azepina con la amina apropiada. La rotación óptica y los datos EM (ES+) se incluyen en la siguiente tabla.

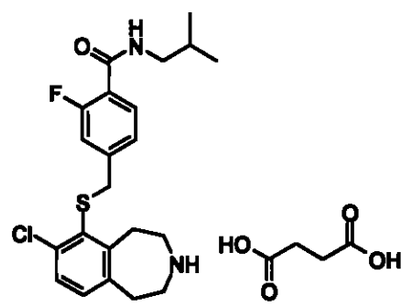
Ej.	NH-R	Compuesto	$[\alpha]^{20}_D$ (c, solvente	EM (ES+) m/z
449		Clorohidrato de (R)-(-)-6-(4-sec-Butilcarbamoil-3-fluoro-benciltio)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina	-7.0° (c 0.5, CH_3OH).	421 $(M+H)^+$
450		Clorohidrato de 7-Cloro-6-[4-(2-cloro-bencilcarbamoil)-3-fluoro-benciltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	-	489 $(M+H)^+$

451		Clorohidrato de 7-Cloro-6-[3-fluoro-4-(2-trifluorometil-bencilcarbamoil)-benciltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina-3-	-	523 $(M+H)^+$
452		Clorohidrato de 7-Cloro-6-[3-fluoro-4-(2-fluoro-4-trifluorometil-bencil-carbamoil)-benciltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	-	541 $(M+H)^+$
453		Clorohidrato de (S)-(-)-7-Cloro-6-{3-fluoro-4-[1-(4-fluoro-fenil)-etil-carbamoil]-benciltio}-2,3,4,5-tetrahidro-1H-benzo-[d]azepina	-25.8° (c 0.5, CH_3OH)	487 $(M+H)^+$

454		Clorohidrato de (R)-(+)-7-Cloro-6-{3-fluoro-4-[1-(4-fluoro-fenil)-etil-carbamoil]-benciltio}-2,3,4,5-tetrahidro-1H-benzo-[d]azepina	+24.9° (c 0.5, CH_3OH)	487 $(M+H)^+$

Ejemplo 455

Succinato de 7-Cloro-6-(3-fluoro-4-isobutilcarbamoil-benciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

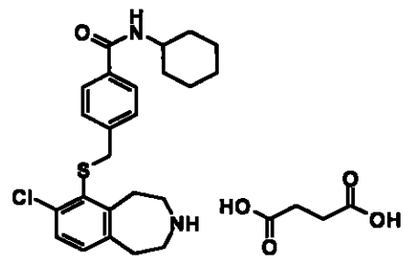


Se usa un método similar al ejemplo 448 para hacer reaccionar 3-tert-butoxicarbonil-6-(4-carboxi-3-fluoro-benciltio)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina con isobutilamina. Se usa un método similar al procedimiento general 1-4, preparación básica, y un método similar al procedimiento general 2-1 para dar el compuesto del título como un sólido blanco. EM (ES+) m/z: 403 $(M+H)^+$.

122A

Ejemplo 456

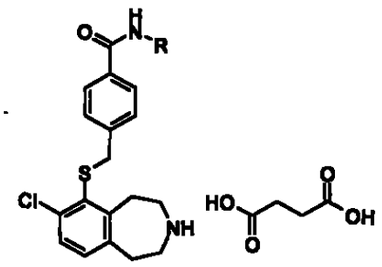
Succinato de 7-Cloro-6-(4-ciclohexilcarbamoilbenciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

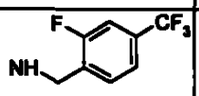
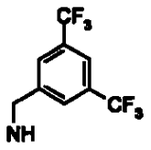


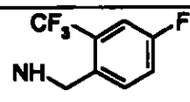
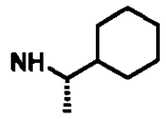
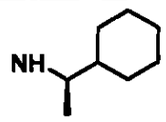
Se usa un método similar para la preparación 177 para hacer reaccionar 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina con 4-clorometil-N-ciclohexilbenzamida. Se usa un método similar al procedimiento general 1-5, preparación básica, y un método similar al procedimiento general 2-1 para dar el compuesto del título como un sólido blanco. EM (ES+) m/z: 429 $(M+H)^+$.

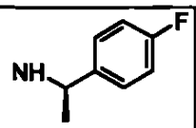
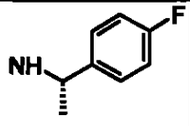
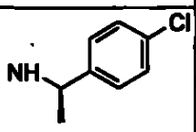
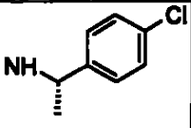
Los ejemplos 457-465 pueden prepararse esencialmente como se describe en el ejemplo 456 al usar 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y cloruro de bencilo apropiadamente substituido. La rotación óptica y los datos EM (ES+) se incluyen en la siguiente tabla.

1225



Ej.	NH-R	Compuesto	$[\alpha]^{20}_D$ (c, solvente)	EM (ES+ o APCI+)
457		Succinato de 7-Cloro-6-[4-(2-fluoro-4-trifluorometil-bencilcarbamoil)-benciltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	-	523 $(M+H)^+$
458		Succinato de [4-(3,5-Bis-trifluorometil-bencilcarbamoil)-benciltio]-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina	-	573 $(M+H)^+$

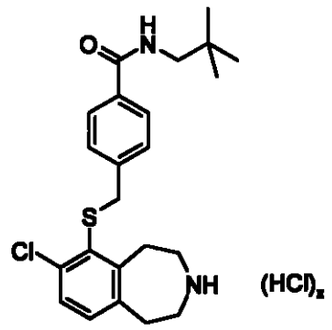
459		Succinato de 7-Cloro-6-[4-(4-fluoro-2-trifluorometil-bencilcarbamoil)-benciltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	-	523 $(M+H)^+$
460		Succinato de (S)-(+)-7-Cloro-6-[4-(1-ciclohexil-etilcarbamoil)-benciltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	+11.2° (c 0.5, CH_3OH)	457 $(M+H)^+$
461		Succinato de (R)-(-)-7-Cloro-6-[4-(1-ciclohexil-etilcarbamoil)-benciltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	-11.3° (c 0.5, CH_3OH)	457 $(M+H)^+$

462		Succinato de (R)-(+)-7-Cloro-6-{4-[1-(4-fluoro-fenil)-etilcarbamoil]-benciltio}-2,3,4,5-tetrahidro-1H-benzo[d]azepina	+2.2° (c 0.5, CH_3OH)	469 $(M+H)^+$
463		Succinato de (S)-(-)-7-Cloro-6-{4-[1-(4-fluoro-fenil)-etilcarbamoil]-benciltio}-2,3,4,5-tetrahidro-1H-benzo[d]azepina	-1.6° (c 0.5, CH_3OH)	469 $(M+H)^+$
464		Succinato de (R)-(-)-7-Cloro-6-{4-[1-(4-cloro-fenil)-etilcarbamoil]-benciltio}-2,3,4,5-tetrahidro-1H-benzo[d]azepina	-5.8° (c 0.5, CH_3OH)	485 $(M+H)^+$
465		Succinato de (S)-(+)-7-Cloro-6-{4-[1-(4-cloro-fenil)-etilcarbamoil]-	+5.5° (c 0.5, CH_3OH)	485 $(M+H)^+$

		benciltio}-2,3,4,5-tetrahidro-1H-benzo[d]azepina		

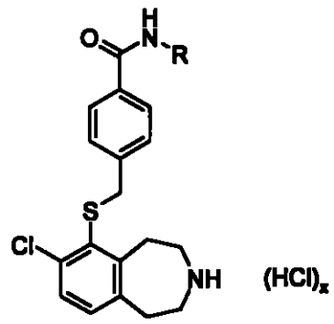
Ejemplo 466

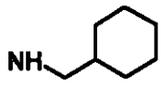
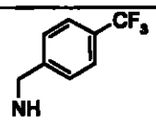
Clorohidrato de 7-Cloro-6-[4-(2,2-dimetil-propilcarbamoil)-benciltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina

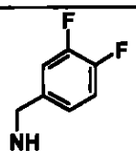
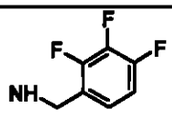


Se usa un método similar al ejemplo 456, usando 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 4-clorometil-N-(2,2-dimetil-propil)-benzamida para dar, después de la desprotección por un método similar al procedimiento general 1-4, el compuesto del título como un sólido blanco. EM (ES+) m/z: 417 $(M+H)^+$.

Los ejemplos 467-471 pueden prepararse esencialmente como se describen en el ejemplo 466 al usar 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y cloruro de bencilo apropiadamente substituido. Los datos EM (ES+) se incluyen en la siguiente tabla.

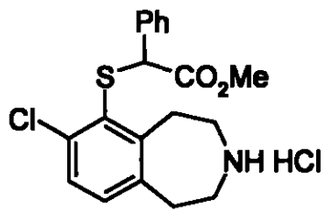


Ej.	NH-R	Compuesto	EM (ES+) m/z
467		Clorohidrato de 6-(4-tert-Butilcarbamoil-benciltio)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina	403 $(M+H)^+$
468		Clorohidrato de 7-Cloro-6-[4-(ciclohexilmetil-carbamoil)-benciltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	443 $(M+H)^+$
469		Clorohidrato de 7-Cloro-6-[4-(4-trifluorometil-bencilcarbamoil)-benciltio]-2,3,4,5-	505 $(M+H)^+$

		tetrahidro-1H-benzo[d]azepina	
470		Clorohidrato de 7-Cloro-6-[4-(3,4-difluoro-bencilcarbamoil)-benciltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	473 $(M+H)^+$
471		Clorohidrato de 7-Cloro-6-[4-(2,3,4-trifluoro-bencilcarbamoil)-benciltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina	491 $(M+H)^+$

Ejemplo 472

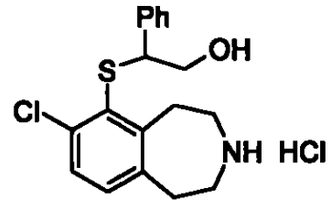
Clorohidrato de (±)-7-Cloro-6-(1-metoxicarbonil-1-fenil-metilltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al procedimiento general 1-4, usando (±)-3-tert-butoxicarbonil-7-cloro-6-(1-metoxicarbonil-1-fenil-metilltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina, para dar el compuesto del título como un sólido blanco. EM (ES+) m/z 362 $(M+H)^+$.

Ejemplo 473

Clorohidrato de (±)-7-Cloro-6-(2-hidroxi-1-fenil-etiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

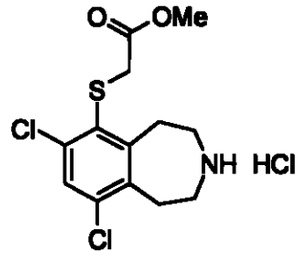


A una solución agitada de (±)-3-tert-butoxicarbonil-6-(1-carboxi-1-fenil-metilltio)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina (220 mg, 0.447 mmol) en THF (10 mL) a 0°C, se agrega una solución 1M de borano en THF (1.4 mL, 1.4 mmol). Se continua agitando durante 2 h a 0°C y luego durante la noche a temperatura ambiente. Se apaga por adición lenta de metanol, se agita 1 h a temperatura ambiente y se concentra in vacuo. Se agrega cloruro de amonio saturado acuoso, se extrae tres veces con EtOAc, se seca sobre $MgSO_4$ anhidro y se concentra in vacuo. Purificación por cromatografía en gel de sílice eluyendo con 19:1 DCM/amonio saturado en metanol. Se usa un método similar al procedimiento general 1-4 para dar

el compuesto del título como un sólido blanco. EM (ES+) m/z: 334 $(M+H)^+$.

Ejemplo 474

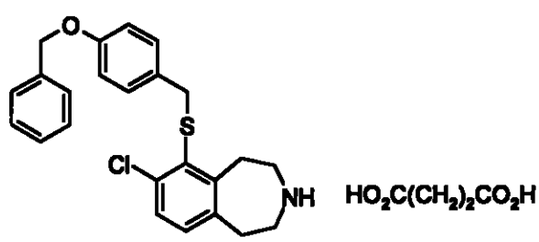
Clorohidrato de 7,9-Dicloro-6-metoxicarbonilmetiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se obtiene como producto menor de la reacción de la mezcla 4:1 de 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 3-tert-butoxicarbonil-7,9-dicloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-benzo[d]azepina con bromoacetato de metilo, se usa un método similar al Ejemplo 347. Se usa un método similar al procedimiento general 1-4 para dar el compuesto del título como un sólido blanco. EM (ES+) m/z: 320 $(M+H)^+$.

Ejemplo 475

Succinato de 6-(4-Benciloxibenciltio)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina



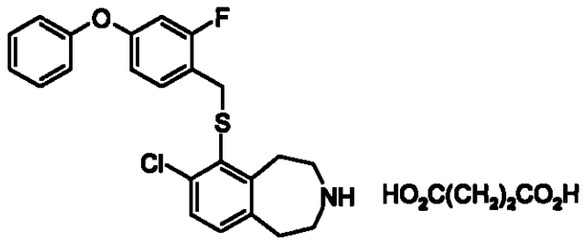
Se disuelve 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina (706 mg, 1.84 mmol) en metanol (20 mL). Se agrega hidróxido de potasio (3.5 g, 55 mmol) y se calienta la mezcla a reflujo durante 3h. Se enfría a temperatura ambiente. Se vacía la reacción en solución de NH_4Cl acuoso saturado. Se extrae tres veces con EtOAc. Los extractos orgánicos se combinan, se secan sobre Na_2SO_4 y se concentran in vacuo para obtener 3-tert-butoxicarbonil-7-cloro-6-mercapto-2,3,4,5-tetrahidro-1H-benzo[d]azepina cruda (602 mg, 100%). Se disuelve 3-tert-butoxicarbonil-7-cloro-6-mercapto-2,3,4,5-tetrahidro-1H-benzo[d]azepina (282 mg, 0.9 mmol) en acetona (30 mL). Se agrega cloruro de 4-benciloxibencilo (251 mg, 1.08 mmol), carbonato de potasio (polvo) (373 mg, 2.7 mmol) y yoduro de potasio (polvo) (15 mg, 0.1 mmol) y se pone a reflujo durante 16 h. Se enfría la reacción a temperatura ambiente, se diluye con acetona, se filtra y se concentra in vacuo. Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (1:0 y 17:3) para dar 6-(4-benciloxibenciltio)-3-tert-butoxicarbonil-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina (309 mg, 67%). EM (ES+) m/z: 510 $(M+H)^+$.

Se usa un método similar al procedimiento general 1-4 y se purifica por cromatografía en gel de sílice eluyendo con

DCM/2M amonio en metanol (95:5) para obtener la base libre del compuesto del título (230 mg, 92%). EM (ES+) m/z: 410 (M+H)+. Se usa un método similar al procedimiento general 2-1 para obtener el compuesto del título.

Ejemplo 476

Succinato de 7-Cloro-6-[(2-fluoro-4-fenoxi)benciltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al ejemplo 475, usando 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 1-bromometil-2-fluoro-4-fenoxibenceno para proporcionar, después de cromatografía en gel de sílice eluyendo con hexano/EtOAc (85:15), 3-tert-butoxicarbonil-7-cloro-6-[(2-fluoro-4-fenoxi)-benciltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina (384 mg, 83%). EM (ES+) m/z: 414 $(M-Boc+2H)^+$.

Se usa un método similar al procedimiento general 1-4 y se purifica por cromatografía en gel de sílice eluyendo con DCM/2M amonio en metanol (95:5) para obtener la base libre del compuesto del título (203 mg, 65%). EM (ES+) m/z: 414

$(M+H)^+$. Se usa un método similar al procedimiento general 2-1 para obtener el compuesto del título.

Ejemplo 477

Clorohidrato de 7-Cloro-6-[2-(4-fluorofenil)-2-oxo-etiltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



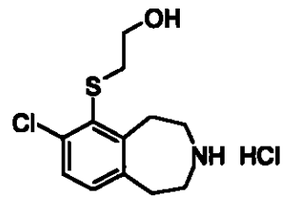
Se usa un método similar al ejemplo 475, usando 3-tert-butoxicarbonil-7-cloro-6-mercapto-2,3,4,5-tetrahidro-1H-benzo[d]azepina cruda y 2-bromo-4'-fluoroacetofenona (239 mg, 1.1 mmol) para proporcionar, después de agitarse a temperatura ambiente durante 16 h y se purifica por cromatografía en gel de sílice eluyendo con hexano/EtOAc (4:1), 3-tert-butoxicarbonil-7-cloro-6-[2-(4-fluorofenil)-2-oxo-etiltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina (38 mg, 9%).

Se usa un método similar al procedimiento general 1-5 y se purifica por cromatografía en gel de sílice eluyendo con DCM/2M amonio en metanol (95:5) para obtener la base libre del compuesto del título (23 mg, 78%). EM (ES+) m/z: 350 $(M+H)^+$. Se usa un método similar al procedimiento general 2-2 para obtener el compuesto del título.

1236

Ejemplo 478

Clorohidrato de 7-Cloro-6-(2-hidroxietiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



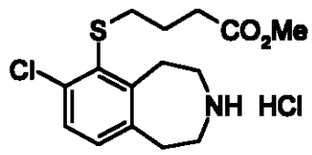
Se usa un método similar al ejemplo 347, usando 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y bromoacetato de metilo para dar 3-tert-butoxicarbonil-7-cloro-6-metoxicarbonilmetiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina.

A una solución de 3-tert-butoxicarbonil-7-cloro-6-metoxicarbonilmetiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina (750 mg, 1.94 mmol) en THF (25 mL) a -78°C bajo nitrógeno, se agrega DIBAL 1M en tolueno (5.0 mL, 5.0 mmol) gota a gota con agitación. Se calienta a -30°C durante 1 h y se apaga cuidadosamente con agua. Se extrae con EtOAc, se seca sobre $MgSO_4$ anhidro y se concentra in vacuo. Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (4:1) para dar 3-tert-butoxicarbonil-7-cloro-6-(2-hidroxi-etiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (651 mg, 94%).

Se usa un método similar al procedimiento general 1-4, usando 3-tert-butoxicarbonil-7-cloro-6-(2-hidroxietiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (190 mg, 0.531 mmol) para dar el compuesto del título como un sólido blanco (105 mg, 67%). EM (ES+) m/z: 258 $(M+H)^+$.

Ejemplo 479

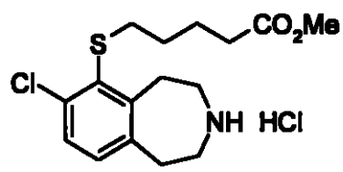
Clorohidrato de 7-Cloro-6-(3-metoxicarbonilpropiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al ejemplo 347, usando 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 4-bromobutirato de metilo para dar, después de la desprotección por el Procedimiento general 1-4, el compuesto del título como un sólido blanco. EM (ES+) m/z: 314 $(M+H)^+$.

Ejemplo 480

Clorohidrato de 7-Cloro-6-(4-metoxicarbonil-butiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

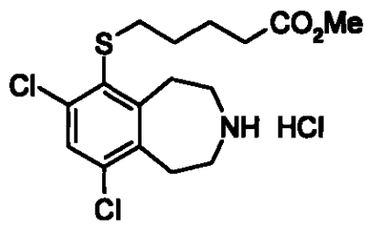


1238

Se usa un método similar al ejemplo 387 para hacer reaccionar 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina con metil-5-bromovalerato. Se purifica por CCD preparativa eluyendo con 19:1 DCM/amonio saturado en metanol. Se usa un método similar al procedimiento general 2-2 para dar el compuesto del título como un sólido blanco. EM (APCI+) m/z: 328 $(M+H)^+$.

Ejemplo 481

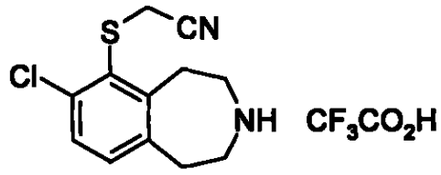
Clorohidrato de 7,9-Dicloro-6-(4-metoxicarbonilbutiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se obtiene la base libre del compuesto del título como un producto menor del ejemplo 480, después de CCD preparativa eluyendo con 19:1 DCM/amonio saturado en metanol. Se usa un método similar al procedimiento general 2-2 para obtener el compuesto del título como un sólido amarillo pálido. EM (APCI+) m/z: 362 $(M+H)^+$.

Ejemplo 482

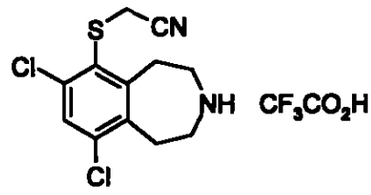
Trifluoroacetato de 7-Cloro-6-cianometiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al ejemplo 387 para hacer reaccionar 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina con bromoacetonitrilo. Se purifica por CLAR preparativa de fase inversa (Columna: Xterra Prep RP18 19x250mm; Solvente A: 10 mM carbonato de amonio acuoso, Solvente B: acetonitrilo; 30-100% B durante 20 minutos; relación de flujo 25 mL/min) para dar el compuesto del título como un sólido blanco. EM (APCI+) m/z: 253 $(M+H)^+$.

Ejemplo 483

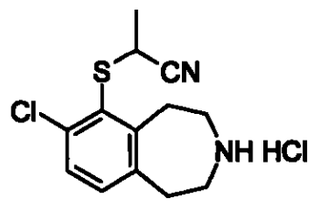
Trifluoroacetato de 6-Cianometiltio-7,9-dicloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se obtiene el compuesto del título como un producto menor del ejemplo 482, después de CLAR preparativa de fase inversa (Columna: Xterra Prep RP18 19x250mm; solvente A: 10 mM carbonato de amonio acuoso, solvente B: acetonitrilo; 30-100% B durante 20 minutos; relación de flujo 25 mL/min). EM (APCI+) m/z: 287 $(M+H)^+$.

Ejemplo 484

Clorohidrato de (±)-7-Cloro-6-(1-cianoetiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar para la preparación 177, usando 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 2-bromopropionitrilo para dar, después de la desprotección usando un método similar al procedimiento general 1-4, el compuesto del título como un sólido blanco. EM (ES+) m/z: 267 $(M+H)^+$.

Ejemplo 485

Clorohidrato de (±)-7-Cloro-6-(1-cianopropiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

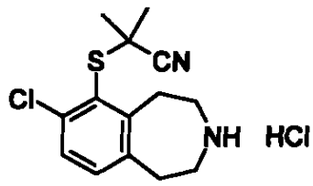


A una solución agitada 1.5M de diisopropilamida de litio en ciclohexano (1.37 mL, 2.05 mmol) en THF seco (5 mL) a -78°C bajo nitrógeno seco, se agrega una solución de 3-tert-butoxicarbonil-7-cloro-6-cianometiltio-2,3,4,5-tetrahidro-1H-benzo[d]-azepina (600 mg, 1.70 mmol) en THF (5 mL) y se continua agitando durante 2 h. Rápidamente se transfiere la solución de arriba por medio de una cánula a una solución de yoduro de etilo (13.2 g, 84.9 mmol) en THF (5 mL) y se continua agitando durante 1 h. Se apaga con una solución de cloruro de amino acuoso saturado, se extrae tres veces con EtOAc, se seca sobre Na_2SO_4 anhidro y se concentra in vacuo. Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (9:1) para dar (±)-3-tert-butoxicarbonil-7-cloro-6-(1-cianopropiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite pálido (350 mg, 68%). Se usa un método similar al procedimiento general 1-4 para dar el

compuesto del título como un sólido blanco opaco. EM (ES+) m/z: 281 $(M+H)^+$.

Ejemplo 486

Clorohidrato de 7-cloro-6-(1-ciano-1-metiletiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

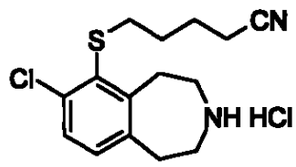


A una solución agitada de 3-tert-butoxicarbonil-7-cloro-6-cianometiltio-2,3,4,5-tetrahidro-1H-benzo[d]-azepina (300 mg, 0.85 mmol) en THF (5 mL) a 0°C, se agrega tert-butóxido de potasio (480 mg, 4.26 mmol) a temperatura ambiente. Después de 15 min, se agrega yoduro de metilo (3.02 g, 21.31 mmol) y se continua agitando durante la noche a temperatura ambiente. Se concentra in vacuo y se purifica por cromatografía en gel de sílice eluyendo con hexano/EtOAc (9:1) para dar 3-tert-butoxicarbonil-7-cloro-6-(1-ciano-1-metil-etiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (177 mg, 55%). EM (ES+) m/z: 282 $(M+H-Boc)^+$. Se usa un método similar al procedimiento general 1-4 para dar el compuesto del título como un sólido blanco opaco. EM (ES+) m/z: 282 $(M+H)^+$.

1243

Ejemplo 487

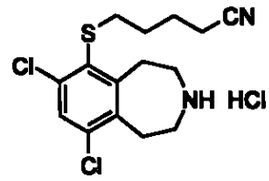
Clorohidrato de 7-Cloro-6-(4-cianobutiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al ejemplo 387 para hacer reaccionar 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina con 5-bromovaleronitrilo. Se purifica por CLAR preparativa de fase inversa (Columna: Xterra Prep RP18 19x250mm; Solvente A: 10 mM carbonato de amonio acuoso, Solvente B: acetonitrilo; 30-100% B durante 20 minutos; relación de flujo 25 mL/min). Se usa un método similar al procedimiento general 2-2 para dar el compuesto del título como un sólido blanco opaco. EM (APCI+) m/z: 295 $(M+H)^+$.

Ejemplo 488

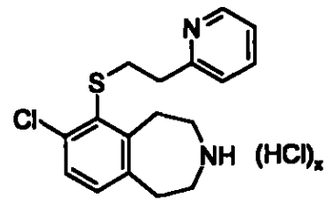
Clorohidrato de 7,9-Dicloro-6-(4-cianobutiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se obtiene la base libre del compuesto del título como un producto menor del ejemplo 487, después de CLAR preparativa de fase inversa (Columna: Xterra Prep RP18 19x250mm; Solvente A: 10 mM carbonato de amonio acuoso, Solvente B: acetonitrilo; 30-100% B durante 20 minutos; relación de flujo 25 mL/min). Se usa un método similar al procedimiento general 2-2 para obtener el compuesto del título como un sólido marrón. EM (ES+) m/z: 329 $(M+H)^+$.

Ejemplo 489

Clorohidrato de 7-Cloro-6-(2-piridin-2-il-etiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

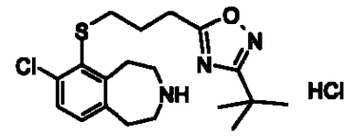


Se usa un método similar para la preparación 177, usando 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y bromohidrato de 2-(2-bromoetil)-piridina para dar, después de la desprotección usando un método similar al Procedimiento general 1-4, el compuesto del título. EM (ES+) m/z 319 $(M+H)^+$.

1245

Ejemplo 490

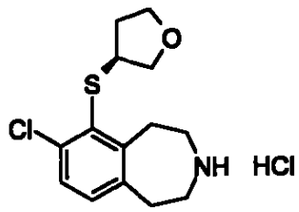
Clorohidrato de 6-[3-(3-tert-Butil-[1,2,4]oxadiazol-5-il)-propiltio]-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al ejemplo 387, usando 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 5-(3-bromopropil)-3-tert-butil-[1,2,4]oxadiazol para dar, después de la desprotección usando un método similar al Procedimiento general 1-4, el compuesto del título como un sólido blanco. EM (APCI+) m/z 380 $(M+H)^+$.

Ejemplo 491

Clorohidrato de (-)-7-Cloro-6-(tetrahidrofuran-3-iltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

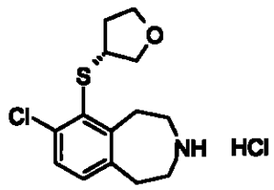


Se usa un método similar al ejemplo 332, usando 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y éster de

tetrahidrofuran-3-ilo del ácido (S)-tolueno-4-sulfónico para dar, después de la desprotección usando un método similar al Procedimiento general 1-4, el compuesto del título como un sólido blanco opaco. EM (APCI+) m/z: 284 $(M+H)^+$; $[\alpha]^{20}_D$ -28.0° (c 0.5, CH_3OH). ee = 97.8% [CLAR quiral: Columna: YMC ODS-AQ 120Å 4.6x50 mm [S-3µm]; eluyente: gradiente desde 95:5 hasta 5:95 A/B; solvente A: agua, 0.01% HFBA, 1% isopropanol; solvente B: acetonitrilo, 0.01% HFBA, 1% isopropanol; relación de flujo 2 mL/min].

Ejemplo 492

Clorohidrato de (+)-7-Cloro-6-(tetrahidrofuran-3-iltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



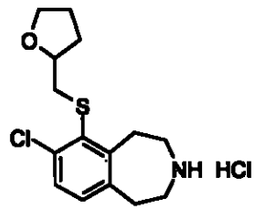
Se usa un método similar al ejemplo 332, usando 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y éster de tetrahidro-furan-3-ilo del ácido (R)-tolueno-4-sulfónico para dar, después de la desprotección usando un método similar al Procedimiento general 1-4, el compuesto del título como un sólido blanco opaco. EM (APCI+) m/z: 284

1242

(M+H); $[\alpha]^{20}_D$ +32.5° (c 0.5, CH_3OH); ee = 95.7% [CLAR quiral: Columna: YMC ODS-AQ 120Å 4.6x50 mm [S-3µm]; eluyente: gradiente desde 95:5 hasta 5:95 A/B; solvente A: agua, 0.01% HFBA, 1% isopropanol; solvente B: acetonitrilo, 0.01% HFBA, 1% isopropanol; relación de flujo 2 mL/min].

Ejemplo 493

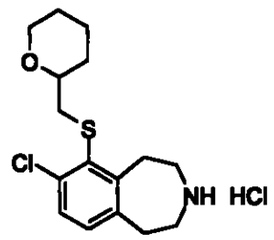
Clorohidrato de (±)-7-Cloro-6-(tetrahidrofuran-2-ilmetiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al ejemplo 330, usando 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 2-(bromometil)tetrahidrofurano para dar, después de la desprotección por el Procedimiento general 1-4, el compuesto del título como cristales blancos. EM (APCI+) m/z: 298 $(M+H)^+$.

Ejemplo 494

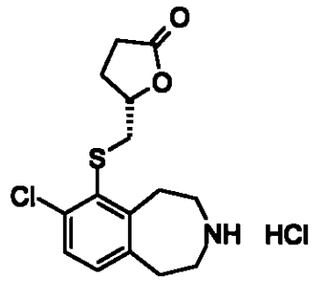
Clorohidrato de (±)-7-Cloro-6-(tetrahidropirano-2-ilmetiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al ejemplo 330, usando 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 2-(bromometil)tetrahidropirano para dar, después de la desprotección por el Procedimiento general 1-4, el compuesto del título como un sólido blanco. EM (APCI+) m/z: 312 $(M+H)^+$.

Ejemplo 495

Clorohidrato de (S)-(+)-7-Cloro-6-(5-oxo-tetrahidrofuran-2-ilmetiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



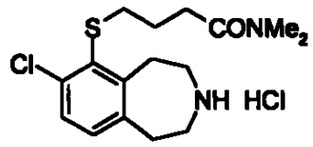
Se usa un método similar al procedimiento general 1-4, usando (S)-3-tert-butoxicarbonil-7-cloro-6-(5-oxo-

1249

tetrahidrofuran-2-ilmetiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina para dar el compuesto del título como un sólido blanco. EM (ES+) m/z: 312 $(M+H)^+$. $[\alpha]^{20}_D$ +78° (c 0.5, CH_3OH).

Ejemplo 496

Clorohidrato de 7-Cloro-6-(3-dimetilcarbamoilpropiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



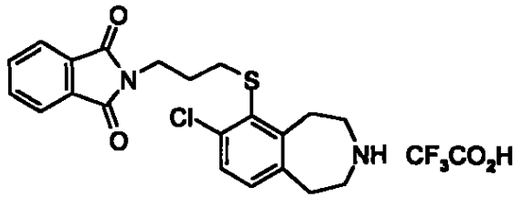
Se trata una solución de 3-tert-butoxicarbonil-7-cloro-6-(3-metoxicarbonil-propiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (385 mg, 0.90 mmol) en dioxano/agua (1:1, 3.5 mL) con hidróxido de litio (43.0 mg, 1.01 mmol) a 80°C durante 1.5 h. Se enfría a temperatura ambiente, se agrega cloruro de amonio saturado acuoso y salmuera, se extrae tres veces con éter etílico, se seca sobre $MgSO_4$ anhidro y se concentra in vacuo. Se disuelve el residuo en DCM (3.5 mL) y se agrega EDC (162 mg, 0.84 mmol), 1-hidroxibenzotriazol (91.0 mg, 0.67 mmol), trietilamina (0.20 mL, 1.35 mmol), y dimetilamina (0.700 mL, 1.35 mmol). Se agita durante la noche a temperatura ambiente. Se diluye con agua, se extrae con éter etílico, se seca sobre $MgSO_4$ anhidro y se concentra in vacuo. Purificación por cromatografía en gel de sílice

eluyendo con hexano/EtOAc/metanol 60:40:1 para dar 3-tert-butoxicarbonil-7-cloro-6-(3-dimetilcarbamoil-propiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina.

Se disuelve 3-tert-butoxicarbonil-7-cloro-6-(3-dimetilcarbamoil-propiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina en DCM (1 mL) a temperatura ambiente y se agrega cloruro de hidrógeno 4M en dioxano (200 µL, 0.8 mmol). Se continua agitando hasta que el CCD muestra el consumo del material de partida. Concentrado in vacuo, se tritura el sólido obtenido con éter dietílico seco y se seca a 50°C bajo alto vacío durante la noche para dar el compuesto del título como un sólido blanco higroscópico (45.0 mg, 57%). EM (ES+) m/z: 327 $(M+H)^+$.

Ejemplo 497

Trifluoroacetato de 7-Cloro-6-[3-(1,3-dioxo-1,3-dihidroisoindol-2-il)-propiltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



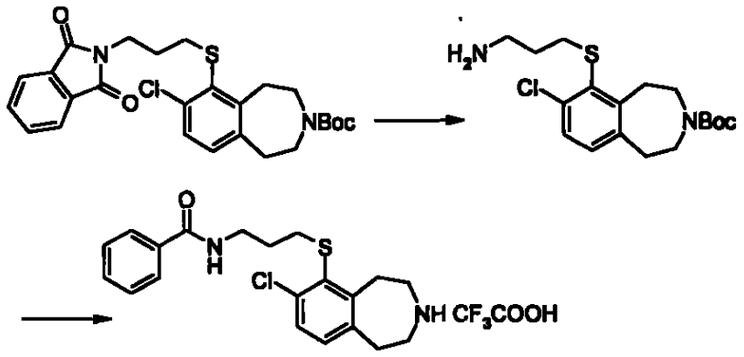
Se disuelve 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-

benzo[d]azepina (2.0 g, 5.20 mmol) en metanol (58 mL) y se agrega hidróxido de potasio (9.36 g, 167 mmol). Se calienta a 50°C durante 2 h. Se enfría a temperatura ambiente, se agrega cloruro de amonio saturado acuoso y agua, se extrae tres veces con EtOAc, se seca sobre Na_2SO_4 anhidro y se concentra in vacuo para dar 3-tert-butoxicarbonil-7-cloro-6-mercapto-2,3,4,5-tetrahidro-1H-benzo[d]azepina (1.62 g, 5.20 mmol). Se disuelve la 3-tert-butoxicarbonil-7-cloro-6-mercapto-2,3,4,5-tetrahidro-1H-benzo[d]azepina cruda (1.40 g, 4.46 mmol) en DMF seco (49.8 mL) y se agrega DBU (0.80 mL, 5.35 mmol) y 3-bromopropil ftalimida (1.55 g, 5.80 mmol). Se agita a temperatura ambiente durante 3 h. Se agrega cloruro de amonio saturado acuoso y agua. Se extrae dos veces con EtOAc, se seca sobre Na_2SO_4 anhidro y se concentra in vacuo. Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (6:1) para dar la base libre del compuesto del título (1.64 g, 74%).

Se usa un método similar al procedimiento general 1-5, para desproteger 3-tert-butoxicarbonil-7-cloro-6-[3-(1,3-dioxo-1,3-dihidro-isoindol-2-il)-propiltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina y se purifica por CLAR preparativa de fase inversa para dar el compuesto del título. EM (APCI+) m/z 401 $(M+H)^+$.

Ejemplo 498

Trifluoroacetato de 6-(3-Benzoilaminopropiltio)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina



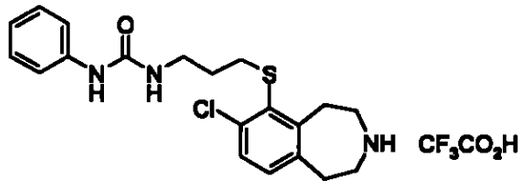
Se suspende 3-tert-butoxicarbonil-7-cloro-6-[3-(1,3-dioxo-1,3-dihidroisoindol-2-il)-propiltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina (1.20 g, 2.39 mmol) en etanol (53.2 mL), se agrega hidrazina (0.150 mL, 4.78 mmol) y se calienta a 65°C durante 2 h. Se enfría a temperatura ambiente, se filtra a partir del precipitado y se concentra in vacuo para proporcionar la 6-(3-aminopropiltio)-3-tert-butoxicarbonil-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina (861 mg, 97%). EM (APCI+) m/z: 371 $(M+H)^+$.

A una solución de 6-(3-aminopropiltio)-3-tert-butoxicarbonil-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina (46.7 mg, 0.126 mmol) en DCM seco (0.5 mL) a temperatura ambiente bajo nitrógeno, se agrega trietilamina (19.3 µL,

0.139 mmol) y cloruro de benzoilo (16.1 µL, 0.139 mmol). Se agita a temperatura ambiente durante 2.5 h. Se agrega cloruro de amonio saturado acuoso y agua, se extrae tres veces con EtOAc, se seca sobre Na_2SO_4 anhidro y se concentra in vacuo. Se disuelve el residuo en DCM (0.16 mL), se agrega ácido trifluoroacético (44.6 µL, 0.58 mmol) y se agita durante 18 h a temperatura ambiente. Se concentra in vacuo y se purifica por CLAR preparativa [Columna: YMC ODS-AQ 120Å 20x250mm [S10-20µm]; eluyente: 95:5 hasta 5:95 A/B; solvente A: agua, 0.1% TFA, 1% isopropanol; solvente B: acetonitrilo, 0.05% TFA, 1% isopropanol; relación de flujo 20 mL/min] para dar el compuesto del título (7.0 mg, 12%). EM (APCI+) m/z 375 $(M+H)^+$.

Ejemplo 499

Trifluoroacetato de 6-[3-(3-Fenilureido)-propiltio]-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina

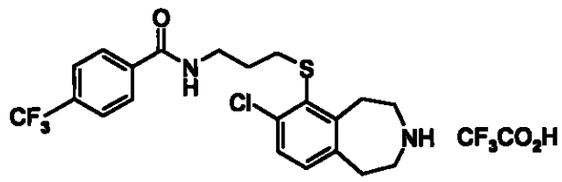


Se usa un método similar al ejemplo 498, usando fenil isocianato, para dar el compuesto del título. EM (APCI+) m/z 390 $(M+H)^+$.

1258

Ejemplo 500

Trifluoroacetato de 7-Cloro-6-[3-(4-trifluorometilbenzoilamino)-propiltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina

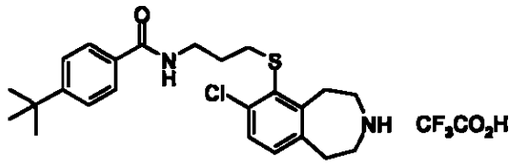


A una solución agitada de ácido 4-trifluorometilbenzoico (60.0 mg, 0.316 mmol) en DMF anhidro (1.2 mL) a temperatura ambiente bajo nitrógeno, se agrega EDC (63.6 mg, 0.332 mmol), 1-hidroxibenzotriazol (44.8 mg, 0.332 mmol), 4-dimetilaminopiridina (40.5 mg, 0.332 mmol) y una solución de 6-(3-aminopropiltio)-3-tert-butoxicarbonil-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina (123 mg, 0.332 mmol) en DCM (2 mL). Se agita durante 18 h a temperatura ambiente. Se agrega agua, se extrae dos veces con EtOAc, se seca sobre Na_2SO_4 anhidro y se concentra in vacuo. Se trata el residuo con ácido trifluoroacético (0.272 mL, 0.640 mmol) en DCM (0.451 mL) a temperatura ambiente durante 18 h. Se concentra in vacuo y se purifica por CLAR preparativa de fase inversa [Columna: YMC ODS-AQ 120Å 20x250mm [S10-20µm]; eluyente: 95:5 hasta 5:95 A/B; solvente A: agua, 0.1% TFA, 1% isopropanol; solvente B: acetonitrilo, 0.05% TFA, 1% isopropanol; relación

de flujo 20 mL/min] para dar el compuesto del título como un sólido blanco (31.0 mg, 18%). EM (APCI+) m/z 443 $(M+H)^+$.

Ejemplo 501

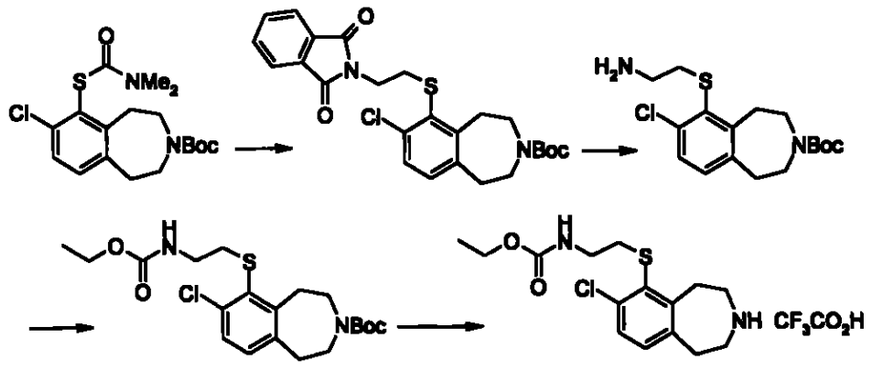
Trifluoroacetato de 7-Cloro-6-[3-(4-tert-butilbenzoilamino)-propiltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al ejemplo 500, usando 6-(3-aminopropiltio)-3-tert-butoxicarbonil-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina y ácido 4-tert-butil benzoico para dar el compuesto del título como un sólido blanco. EM (APCI+) m/z 431 $(M+H)^+$.

Ejemplo 502

Trifluoroacetato de 7-Cloro-6-(2-etoxicarbonilamino-etiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



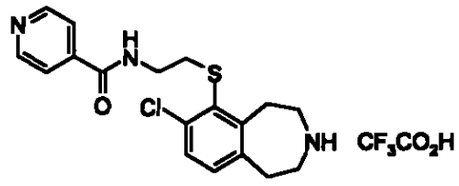
1256.

Se usa un método similar al ejemplo 497, usando 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y 3-bromoetil ftalimida para dar 6-(3-aminoetiltio)-3-tert-butoxicarbonil-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina. EM (ES+) m/z 357 $(M+H)^+$.

Se usa un método similar al ejemplo 498, usando 6-(3-aminoetiltio)-3-tert-butoxicarbonil-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina y etil cloroformiato para dar, después de la desprotección usando un método similar al Procedimiento general 1-5, el compuesto del título como un sólido blanco. EM (APCI+) m/z: 329 $(M+H)^+$.

Ejemplo 503

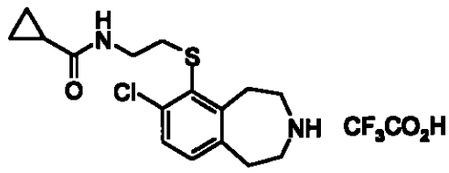
Trifluoroacetato de 7-Cloro-6-{2-[(piridina-4-carbonil)amino]-etiltio}-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al ejemplo 500, usando 6-(3-aminoetiltio)-3-tert-butoxicarbonil-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina y ácido isonicotínico para dar el compuesto del título. EM (ES+) m/z: 362 $(M+H)^+$.

Ejemplo 504

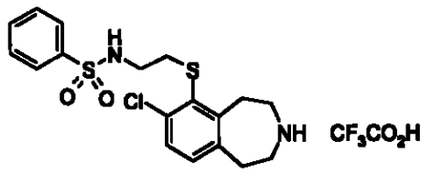
Trifluoroacetato de 7-Cloro-6-[2-(ciclopropanocarbonilamino)-etiltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al ejemplo 498, usando 6-(3-aminoetiltio)-3-tert-butoxicarbonil-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina y cloruro de ciclopropanocarbonilo para dar, después de la desprotección usando un método similar al Procedimiento general 1-5, el compuesto del título. EM (ES+) m/z: 325 $(M+H)^+$.

Ejemplo 505

Trifluoroacetato de 6-(2-Bencenosulfonilamino-etiltio)-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina

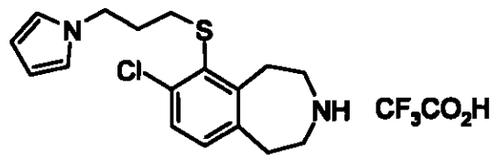


Se usa un método similar al ejemplo 498, usando 6-(3-amino-etiltio)-3-tert-butoxicarbonil-7-cloro-2,3,4,5-tetrahidro-1H-benzo[d]azepina y cloruro de bencenosulfonilo para dar, después de la protección se usa un método similar

al Procedimiento general 1-5, el compuesto del título como un sólido blanco. EM (APCI+) m/z: 397 $(M+H)^+$.

Ejemplo 506

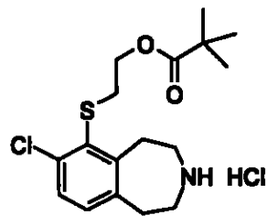
Trifluoroacetato de 7-Cloro-6-(3-pirrol-1-il-propiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al ejemplo 497, usando 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina y N-(3-bromopropil)pirrol para dar, después de la desprotección usando un método similar al Procedimiento general 1-5, el compuesto del título como un sólido blanco. EM (ES+) m/z: 321 $(M+H)^+$.

Ejemplo 507

Clorohidrato de 7-Cloro-6-[2-(2,2-dimetilpropioniloxi)-etiltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina

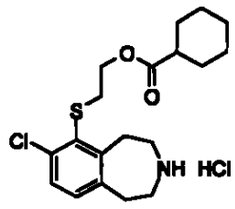


1259

A una solución agitada de 3-tert-butoxicarbonil-7-cloro-6-(2-hidroxietiltio)-2,3,4,5-tetrahidrobenzo[d]azepina (85 mg, 0.238 mmol) en DCM (3 ml) a 0°C, se agrega trietilamina (331 µl, 2.381 mmol) seguido por cloruro de trimetilacetilo (147 µl, 1.190 mmol). Se continua agitando durante 15 min, se diluye con agua, se extrae tres veces con EtOAc, se seca sobre Na_2SO_4 anhidro y se concentra in vacuo. La desprotección por el procedimiento general 1-5, preparación básica, y por el procedimiento general 2-2, da el compuesto del título. EM (ES+) m/z 342 (M+H).

Ejemplo 508

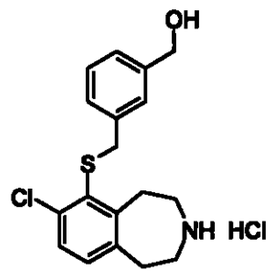
Clorohidrato de 7-Cloro-6-(2-ciclohexanocarboniloxi-etiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al ejemplo 507, usando cloruro de ciclohexanocarbonilo, para dar el compuesto del título. EM (ES+) m/z 368 (M+H).

Ejemplo 509

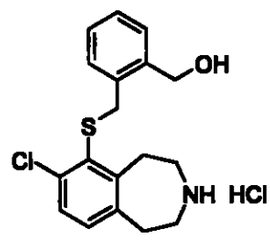
Clorohidrato de 7-Cloro-6-(3-hidroximetilbenciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar para la preparación 242, usando 3-tert-butoxicarbonil-7-cloro-6-(3-hidroximetilbenciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina para dar, después de la desprotección por el Procedimiento general 1-4, el compuesto del título como un sólido blanco. EM (ES+) m/z: 334 $(M+H)^+$.

Ejemplo 510

Clorohidrato de 7-Cloro-6-(2-hidroximetilbenciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

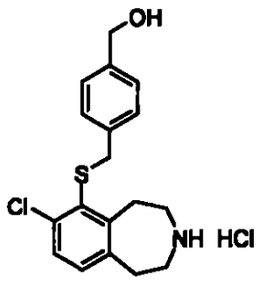


Se usa un método similar para la preparación 242, usando 3-tert-butoxicarbonil-7-cloro-6-(2-hidroximetilbenciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina para dar, después de la

desprotección por el Procedimiento general 1-4, el compuesto del título como un sólido blanco. EM (ES+) m/z: 334 $(M+H)^+$.

Ejemplo 511

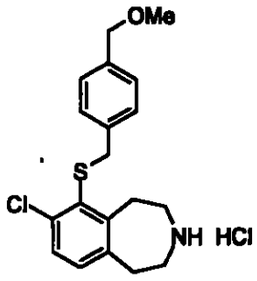
Clorohidrato de 7-Cloro-6-(4-hidroximetilbenciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al procedimiento general 1-4, usando 3-tert-butoxicarbonil-7-cloro-6-(4-hidroximetilbenciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina, para dar el compuesto del título como un sólido blanco. EM (ES+) m/z: 334 $(M+H)^+$.

Ejemplo 512

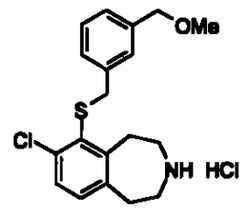
Clorohidrato de 7-Cloro-6-(4-metoximetilbenciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



A una solución agitada de 3-tert-butoxicarbonil-7-cloro-6-(4-hidroximetil-benciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (133 mg, 0.306 mmol) en DMF anhidro (2 mL) bajo nitrógeno, se agrega hidruro de sodio (60% dispersión, 13-15 mg, 0.375 mmol) a temperatura ambiente y se continua agitando durante 30 min. Se agrega yoduro de metilo (80 µL, 1.28 mmol). Después de 15 min, se diluye con agua, se extrae tres veces con EtOAc, se seca sobre $MgSO_4$ anhidro y se concentra *in vacuo*. Purificación por cromatografía en gel de sílice eluyendo con hexano/EtOAc (15:1) para dar 3-tert-butoxicarbonil-7-cloro-6-(4-metoximetil-benciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina como un aceite claro, el cual se cristaliza en reposo hasta un sólido blanco (87 mg, 63%), junto con material de partida recuperado (22 mg, 17%). Se usa un método similar al procedimiento general 1-4 para dar el compuesto del título como un sólido blanco. EM (ES+) m/z: 348 $(M+H-Boc)^+$.

Ejemplo 513

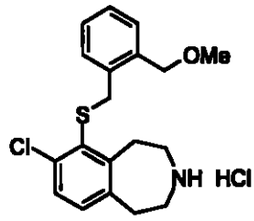
Clorohidrato de 7-Cloro-6-(3-metoximetilbenciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al ejemplo 512, usando 3-tert-butoxicarbonil-7-cloro-6-(3-hidroximetilbenciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina para dar el compuesto del título como un sólido blanco. EM (ES+) m/z: 348 (M+H).

Ejemplo 514

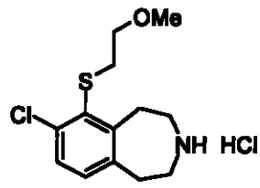
Clorohidrato de 7-Cloro-6-(2-metoximetilbenciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al ejemplo 512, usando 3-tert-butoxicarbonil-7-cloro-6-(2-hidroximetilbenciltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina para dar el compuesto del título como un sólido blanco. EM (ES+) m/z: 348 (M+H).

Ejemplo 515

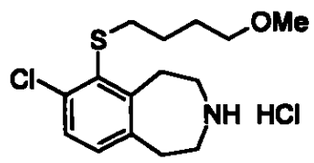
Clorohidrato de 7-Cloro-6-(2-metoxietiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al ejemplo 512, usando 3-tert-butoxicarbonil-7-cloro-6-(2-hidroxi-etiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina, para dar el compuesto del título como un sólido blanco. EM (ES+) m/z: 272 (M+H).

Ejemplo 516

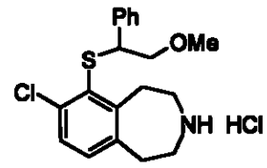
Clorohidrato de 7-Cloro-6-(4-metoxibutiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al ejemplo 478, usando 3-tert-butoxicarbonil-7-cloro-6-(3-metoxicarbonil-propiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina para dar 3-tert-butoxicarbonil-7-cloro-6-(4-hidroxibutiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina. Se usa un método similar al ejemplo 512, usando 3-tert-butoxicarbonil-7-cloro-6-(4-hidroxibutiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina para dar el compuesto del título como un sólido blanco. EM (ES+) m/z: 300 $(M+H)^+$.

Ejemplo 517

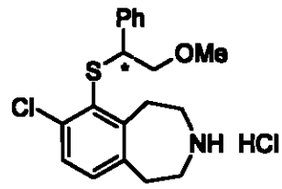
Clorohidrato de (±)-7-cloro-6-(2-metoxi-1-feniletiltio)-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se usa un método similar al Ejemplo 512, usando (±)-3-*tert*-butoxicarbonil-7-cloro-6-(2-hidroxi-1-feniletiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina para dar, después de la desprotección por un método similar al Procedimiento General 1-4, el compuesto del título como un sólido blanco opaco. EM (ER+) *m/z*: 348 $(M+H)^+$.

Ejemplo 518

Clorohidrato de (-)-7-cloro-6-(2-metoxi-1-feniletiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina

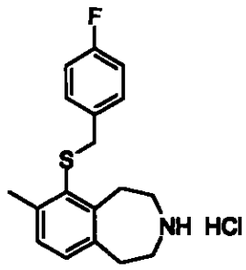


Se separan los enantiómeros de (±)-7-cloro-6-(2-metoxi-1-fenil-etiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina por cromatografía de fase normal quiral (columna Chiralcel OJ 8x33 cm, eluyendo con DMEA 0.2% en etanol/heptano, 40:60). Se

colecta el segundo isómero de elución y se usa el Procedimiento General 2-2 para dar el compuesto del título como un sólido blanco (76 mg, 29%). EM (ER+) *m/z*: 349 $(M+H)^+$. $[\alpha]^{20}_D$ -176° (c 0.5, CH_3OH).

Ejemplo 519

Clorohidrato de 6-(4-Fluorobenciltio)-7-metil-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



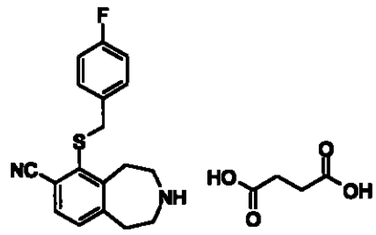
Se usa un método similar al Procedimiento General 7, usando 3-*tert*-butoxicarbonil-6-dimetilcarbamoiltio-7-metil-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (75 mg, 0.206 mmol) y bromuro de 4-fluorobencilo (195 mg, 1.03 mmol) para dar, después de la cromatografía en gel de sílice eluyendo con hexano/EtOAc (1:0, 9:1 y 4:1), 3-*tert*-butoxicarbonil-6-(4-fluorobenciltio)-7-metil-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina como un aceite (59 mg, 71%). EM (ER+) *m/z*: 302 $(M+H-Boc)^+$.

Se usa un método similar al Procedimiento General 1-4, usando 3-*tert*-butoxicarbonil-6-(4-fluoro-benciltio)-7-metil-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (55 mg, 0.137 mmol)

para dar el compuesto del título como un sólido blanco (42 mg, 91%). EM (ER+) *m/z*: 285 $(M+H)^+$.

Ejemplo 520

Succinato de 7-Ciano-6-(4-fluorobenciltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina

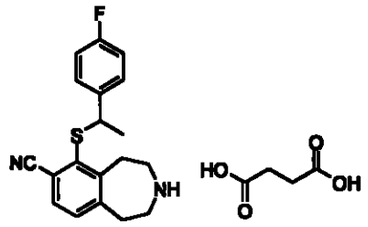


Se usa un método similar al Procedimiento General 7, usando 3-*tert*-butoxicarbonil-7-ciano-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (123 mg, 0.33 mmol) y bromuro de 4-fluorobencilo (204 mg, 1.64 mmol), para dar 3-*tert*-butoxicarbonil-7-ciano-6-(4-fluoro-benciltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina como un aceite incoloro (118 mg, 87%).

Se usa un método similar al Procedimiento General 1-4, usando 3-*tert*-butoxicarbonil-7-ciano-6-(4-fluoro-benciltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (118 mg, 0.286 mmol) para dar, después del trabajo básico, la base libre del compuesto del título (89 mg, 100%). EM (ER+) *m/z* 313 $(M+H)^+$. Se usa un método similar al Procedimiento General 2-1 para dar el compuesto del título (123 mg, 100%). EM (ER+) *m/z* 313 $(M+H)^+$.

Ejemplo 521

Succinato de (±)-7-Ciano-6-[1-(4-fluorofenil)etiltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina

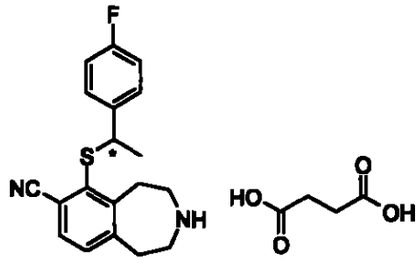


Se usa un método similar al Procedimiento General 7, usando 3-*tert*-butoxicarbonil-7-ciano-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (171 mg, 0.46 mmol) y bromuro (±)-1-(4-fluorofenil)etilo (377 mg, 1.85 mmol) para dar, después de la purificación por cromatografía en gel de sílice, (±)-3-*tert*-butoxicarbonil-7-ciano-6-[1-(4-fluorofenil)-etiltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina como un aceite incoloro (10.3 mg, 5.3%). EM (ER+) *m/z* 449 $(M+Na)^+$, 465 $(M+K)^+$.

Se usa un método similar al Procedimiento General 1-5, usando (±)-3-*tert*-butoxicarbonil-7-ciano-6-[1-(4-fluorofenil)etiltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (10.3 mg, 0.024 mmol) para dar, después del trabajo básico, la base libre del compuesto del título (6.8 mg, 87%). EM (ER+) *m/z* 327 $(M+H)^+$. Se usa un método similar al Procedimiento General 2-1 para dar el compuesto del título como un sólido blanco (9.3 mg, 87%). EM (ER+) *m/z* 327 $(M+H)^+$.

Ejemplo 522

Succinato de 7-Ciano-6-[1-(4-fluorofenil)etiltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina, Isómero 1

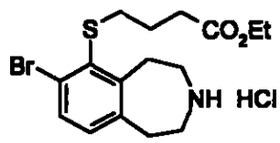


Se separan los dos enantiómeros de (±)-7-ciano-6-[1-(4-fluorofenil)etiltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina por CLAR quiral (columna Chiralpak AD-H 15cm x 4.6mm con un tamaño de empaque de 5 µm. Eluyendo con heptano/etanol (95:5) que contiene DEA 0.2% a 0.5 mL/min con un volumen de inyección de 10.00 µL).

Se somete el primer isómero de elución (t_R = 17.2 min, ee > 99%) al Procedimiento General 2-1 para proporcionar el compuesto del título como un sólido blanco. EM (ER+) *m/z* 327 $(M+H)^+$.

Ejemplo 523

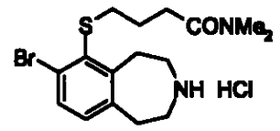
Clorohidrato de 7-Bromo-6-(3-etoxicarbonilpropiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



Se usa un método similar a la Preparación 177, usando 3-*tert*-butoxicarbonil-7-bromo-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina y 4-bromobutirato de etilo para dar, después de la desprotección por un método similar al Procedimiento General 1-4, el compuesto del título. EM (ER+) *m/z*: 374 $(M+H)^+$.

Ejemplo 524

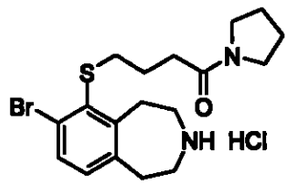
Clorohidrato de 7-Bromo-6-(3-dimetilcarbamoilpropiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



Se usa un método similar al Ejemplo 523, usando 7-bromo-3-*tert*-butoxicarbonil-6-(3-etoxicarbonilpropiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina, para dar el compuesto del título como un sólido blanco. EM (ER+) *m/z*: 373 $(M+H)^+$.

Ejemplo 525

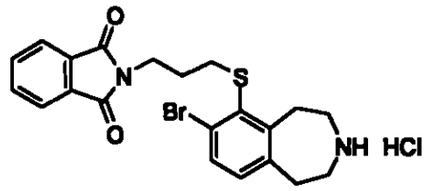
Clorohidrato de 7-Bromo-6-(4-oxo-4-pirrolidin-1-il-butiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



Se usa un método similar al Ejemplo 523, usando 7-bromo-3-*tert*-butoxicarbonil-6-(3-etoxicarbonilpropiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina y pirrolidina para dar el compuesto del título. EM (ER+) *m/z*: 397 $(M+H)^+$.

Ejemplo 526

Clorohidrato de 7-Bromo-6-[3-(1,3-dioxo-1,3-dihidroisoindol-2-il)-propiltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina

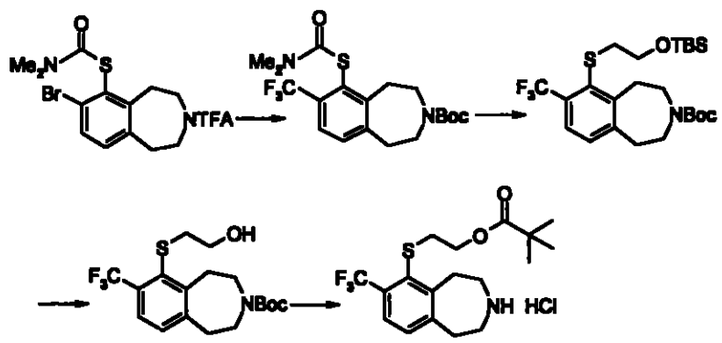


Se usa un método similar al Ejemplo 497 para reaccionar 7-bromo-3-*tert*-butoxicarbonil-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina con ftalimida de 3-bromopropilo. Se usa un método similar al Procedimiento

General 1-4 para dar el compuesto del título como un sólido blanco. EM (ER+) *m/z* 445 $(M+H)^+$.

Ejemplo 527

Clorohidrato de 6-[2-(2,2-Dimetilpropioniloxi)-etiltio]-7-trifluorometil-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



3-tert-Butoxicarbonil-6-dimetilcarbamoiltio-7-trifluorometil-2,3,4,5-tetrahidro-benzo[d]azepina: A una solución agitada de 7-bromo-6-dimetilcarbamoiltio-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (1.383 g, 3.254 mmol), en NMP (40 ml) se agrega acetato de trifluorometil sodio (3.54 g, 26.03 mmol), yoduro de cobre(I) (2.47 g, 13.0 mmol) y se calienta la mezcla a 180°C durante 4 h. Se enfría a temperatura ambiente. Se diluye con EtOAc, agua y se remueve el residuo sólido de cobre por filtración. Se separan las capas del filtrado y se extrae la capa acuosa tres veces con EtOAc. Se seca sobre Na_2SO_4 anhidro, y se concentra *in vacuo*. Se purifica por cromatografía en gel de sílice eluyendo con

hexano/EtOAc (6:1) para dar el intermediario deseado como un aceite amarillo (882 mg, 74%).

3-*tert*-Butoxicarbonil-6-[2-(*tert*-butil-dimetilsilaniloxi)etiltio]-7-trifluorometil-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina: Se usa un método similar a la Preparación 177, usando 3-*tert*-butoxicarbonil-6-dimetilcarbamoiltio-7-trifluorometil-2,3,4,5-tetrahidro-benzo[*d*]azepina y (2-bromoetoxi)-*tert*-butildimetilsilano para dar el intermediario deseado.

3-*tert*-Butoxicarbonil-6-(2-hidroxietiltio)-7-trifluorometil-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina: Se disolvió 6-[2-(*tert*-butil-dimetil-silaniloxi)-etiltio]-7-trifluorometil-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (153 mg, 0.303 mmol) en THF (3 mL). se agrega fluoruro de tetrabutilamonio 1.0 M en THF (600 µL, 0.606 mmol,) y se agita durante la noche. Se diluye con agua, se extrae tres veces con EtOAc, se seca sobre Na_2SO_4 anhidro, y se concentra *in vacuo*. Se purifica por cromatografía en gel de sílice eluyendo con hexano/EtOAc (85:15) para dar el intermediario deseado.

Clorohidrato de 6-[2-(2,2-Dimetilpropioniloxi)-etiltio]-7-trifluorometil-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina: Se usa un método similar al Ejemplo 507, usando 3-*tert*-

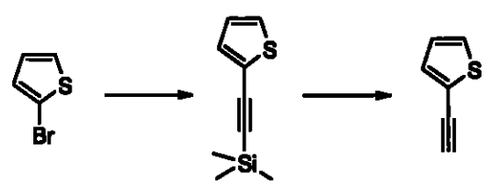
butoxicarbonil-6-(2-hidroxietiltio)-7-trifluorometil-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina para dar, después de la desprotección usando un método similar al Procedimiento General 1-4, el compuesto del título como un sólido blanco. EM (ER+) *m/z*: 376 $(M+H)^+$.

Procedimiento General 8

Se disuelve el bromuro apropiado (2 equiv.) en isopropilamina (300-400 equiv.) a temperatura ambiente, bajo nitrógeno, luego se agrega paladio(II) bis(benzonitrilo) dicloruro (0.2 equiv.), trifenilfosfina (0.4 equiv.) y yoduro de cobre(I) (0.2 equiv.). Se desgasifica la solución y se purga con nitrógeno, luego se agrega el alquino apropiado (1.0 equiv.). Se sella el recipiente de reacción, se agita a temperatura ambiente durante 30 min, luego a 75°C durante 3-4 h. Se remueve la mayoría del solvente *in vacuo*, se agrega éter de dietilo y HCl acuoso 2M. Se seca la capa orgánica sobre $MgSO_4$, se filtra y se concentra *in vacuo*. Se purifica por cromatografía en gel de sílice eluyendo con isohexano/EtOAc o mezclas hexano/EtOAc.

Preparación 249

2-Etinil-tiofeno

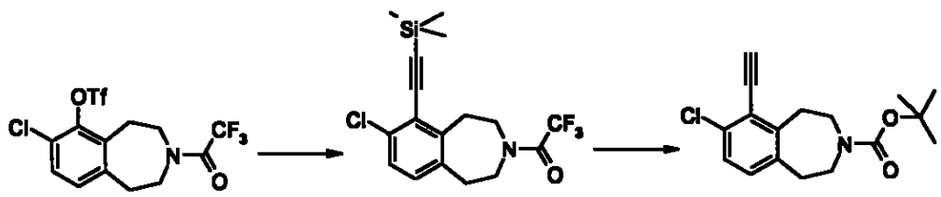


Trimetil-tiofen-2-iletinil-silano: Se usa un método similar al Procedimiento General 8 para acoplar 2-bromo-tiofeno (0.97 mL, 10 mmol) con etinil-trimetilsilano (2.82 mL, 20 mmol). Se purifica por cromatografía en gel de sílice eluyendo con isohexano para dar el intermediario deseado (1.46 g, 81%). CG-EM *m/z* 180 (M^+).

2-Etinil-tiofeno: Se agrega una solución saturada de carbonato de potasio en metanol (7.5 mL) a trimetil-tiofen-2-iletinil-silano (540 mg, 3 mmol) en metanol desoxigenado (100 mL) a temperatura ambiente bajo nitrógeno. Se agota la reacción durante 3.5 h, luego se diluye con diclorometano (100 mL) y se lava con agua (3 x 100 mL). Se remuve la capa orgánica, se seca usando un separadaor de fase ISCO® y luego se concentra *in vacuo* para dar el compuesto del título (302 mg, 93%).

Preparación 250

3-*tert*-Butoxicarbonil-7-cloro-6-etinil-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



7-cloro-3-(2,2,2-trifluoroacetil)-6-trimetilsilaniletinil-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina: Se usa un método similar al Procedimiento General 3 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (425 mg, 1 mmol) con 2-trimetilsililacetileno (0.28 mL, 2 mmol). Se purifica por cromatografía en gel de sílice eluyendo con isohexano/EtOAc (100:0 hasta 85:15 gradiente durante 40 min) para dar el intermediario deseado (247 mg, 81%). EM (ER+) *m/z*: 306 $(M+H)^+$.

3-*tert*-Butoxicarbonil-7-cloro-6-etinil-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina: Se agrega una solución de carbonato de potasio (999 mg, 7.2 mmol) en agua (5 mL) a 7-cloro-3-(2,2,2-trifluoroacetil)-6-trimetilsilaniletinil-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (180 mg, 0.48 mmol) en metanol (10 mL) y se agita a temperatura ambiente, bajo nitrógeno durante 1.5 h. Se agrega di-*tert*-butil-dicarbonato (115 mg, 0.53 mmol) en diclorometano (8 mL) y se agita durante 3 días. Se agrega otra solución de di-*tert*-butil-dicarbonato (115 mg, 0.53 mmol) en diclorometano (5 mL) y se agita durante 2 h. Se agrega agua (10 mL) y diclorometano (10 mL) y se separa la capa orgánica. Se extrae la capa acuosa con diclorometano (3 x 10 mL) y se combinan las capas orgánicas. Se seca usando un separador de fase ISCO® y se concentra. Se purifica por

cromatografía en gel de sílice eluyendo con isohexano/EtOAc (gradiente 1:0 hasta 4:1 durante 30 min) para dar el compuesto del título como un sólido (150 mg, 100%). EM (ER+) *m/z*: 328 $(M+Na)^+$.

Preparación 251

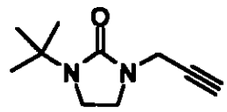
2-cloro-piridazina



Se agrega 3(2*H*)-piridazinona (2 g, 22 mmol) a oxicloruro de fosforo puro (4 mL) en un tubo sellado y se calienta la mezcla a 80°C con agitación durante 2 h. Se agrega cuidadosamente agua (10 mL), $NaHCO_3$ acuoso saturado (50 mL) y Na_2CO_3 sólido hasta pH = 9. Se extrae la mezcla con diclorometano (4 x 50 mL). Se seca la capa orgánica sobre Na_2SO_4, se filtra y se concentra *in vacuo* para dar el compuesto del título como aceite café (2 g, 84%).

Preparación 252

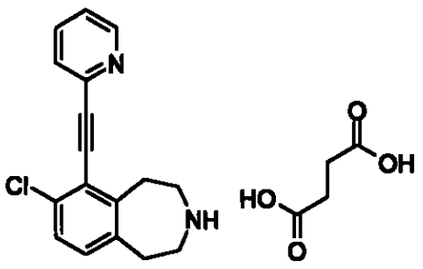
1-*tert*-Butil-3-prop-2-inil-imidazolidin-2-ona



Se disuelve 1-*tert*-butil-imidazolidin-2-ona (2 g, 14 mmol) en THF anhidro (60 mL) y se enfría a -78°C. Se agrega lentamente *n*-butilitio (6.8 mL, 17 mmol, solución 2.5 M en hexanos). Se agita la solución durante 30 min. Se agrega rapidamente bromuro de propargilo (3.2 mL, 28.2 mmol, 80% solución en tolueno). Se entibia la solución a temperatura ambiente mientras se agita durante la noche. Se concentra la mezcla de reacción *in vacuo* y se filtra el residuo en una almohadilla de gel de sílice eluyendo con diclorometano/éter de dietilo (1:1) para dar el compuesto del título como un aceite amarillo que se solidifica en reposo (1.77 g, 70%). CG-EM *m/z* (%) 180 (M^+, 7), 165 (100), 123 (12), 84 (17).

Ejemplo 528

Succinato de 7-cloro-6-piridin-2-iletinil-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



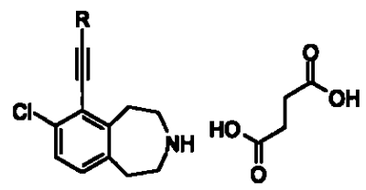
Se usa un método similar al Procedimiento General 3 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (425 mg, 1 mmol) con 2-etinil-piridina (0.20

mL, 2 mmol). Se purifica por cromatografía en gel de sílice eluyendo con isohexano/EtOAc (gradiente 1:0 hasta 1:1 durante 40 min) para dar 7-cloro-6-piridin-2-iletinil-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (342 mg, 90%). EM (ER+) *m/z*: 379 $(M+H)^+$.

Se usa un método similar al Procedimiento General 1-2 para desproteger 7-cloro-6-piridin-2-iletinil-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (60 mg, 0.159 mmol). Se purifica por cromatografía SCX para dar la base libre del compuesto del título (33 mg, 73%). EM (ER+) *m/z*: 283 $(M+H)^+$. Se usa un método similar al Procedimiento General 2-1 para dar el compuesto del título como un sólido café ligero (45 mg, 95%). EM (ER+) *m/z*: 283 $(M+H)^+$.

Ejemplos 529-531

Los Ejemplos 529-531 se pueden preparar esencialmente como se describe en el Ejemplo 528 al usar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina y el alquino apropiado. Los rendimientos generales y datos EM (ER+) se muestran en la Tabla a continuación.

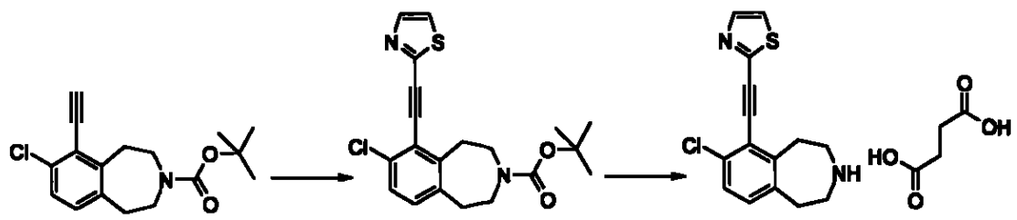


Ej.	R	Compuesto	Rendimiento (%)	EM (ER+) m/z	
529	3-Piridilo	Succinato de 7-cloro-6-piridin-3-iletinil-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	78	283 (M+H)+	
530	4-Piridilo	Succinato de 7-cloro-6-piridin-4-iletinil-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	84	283 (M+H)+	
531	2-Tiofenilo	Succinato de 7-cloro-6-tiofen-2-iletinil-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	95	288 (M+H)+	

1781

Ejemplo 532

Succinato de 7-cloro-6-tiazol-2-iletinil-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



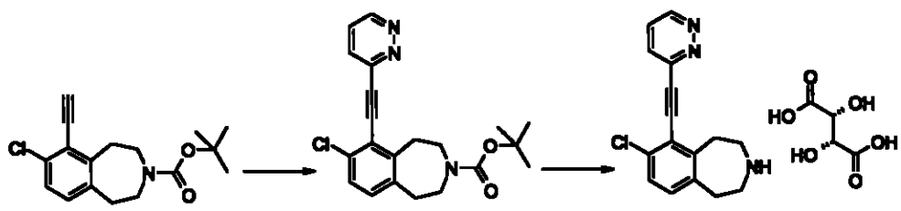
3-*tert*-Butoxicarbonil-7-cloro-6-(tiazol-2-iletinil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina: Se usa un método similar al Procedimiento General 8 para acoplar 2-bromo-tiazol (0.09 mL, 0.96 mmol) con 3-*tert*-butoxicarbonil-7-cloro-6-etinil-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (148 mg, 0.48 mmol). Se purifica por cromatografía en gel de sílice eluyendo con isohexano/EtOAc (gradiente 1:0 hasta 4:1 durante 30 min) para dar el intermediario deseado (165 mg, 89%).. EM (ER+) *m/z*: 389 $(M+H)^+$.

Succinato de 7-cloro-6-(tiazol-2-iletinil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina: Se usa un método similar al Procedimiento General 1-5 para desproteger 3-*tert*-butoxicarbonil-7-cloro-6-(tiazol-2-iletinil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (140 mg, 0.36 mmol). Se eluye a través de columna SCX para dar la base libre del compuesto del título (89 mg, 86%). EM (ER+) *m/z*: 289 $(M+H)^+$. Se usa un

método similar al Procedimiento General 2-1 para dar el compuesto del título como un sólido amarillo ligero (125 mg, 86%). EM (ER+) *m/z*: 289 $(M+H)^+$.

Ejemplo 533

(*L*)-Tartrato de 7-cloro-6-piridazin-3-iletinil-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



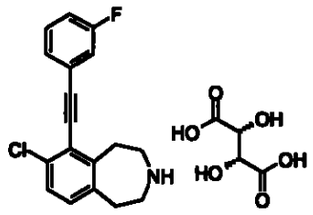
3-*tert*-Butoxicarbonil-7-cloro-6-piridazin-3-iletinil-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina: Se usa un método similar al Procedimiento General 8 para acoplar 2-cloro-piridazina (98 mg, 0.86 mmol) con 3-*tert*-butoxicarbonil-7-cloro-6-etinil-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (104 mg, 0.34 mmol). Se purifica por cromatografía en gel de sílice eluyendo con isohexano/EtOAc (gradiente 1:0 hasta 4:1 durante 30 min) para dar 3-*tert*-butoxicarbonil-7-cloro-6-piridazin-2-iletinil-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (26 mg, 10%). EM (ER+) *m/z*: 384 $(M+H)^+$.

(*L*)-tartrato de 7-cloro-6-piridazin-3-iletinil-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina: Se usa un método similar al

Procedimiento General 1-5 para desproteger 3-*tert*-butoxicarbonil-7-cloro-6-piridazin-2-iletinil-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina. Se usa un método similar al Procedimiento General 2-6 para dar el compuesto del título como un sólido (15 mg, 51%). EM (ER+) *m/z*: 284 $(M+H)^+$.

Ejemplo 534

(*L*)-Tartrato de 7-cloro-6-(3-fluoro-feniletinil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



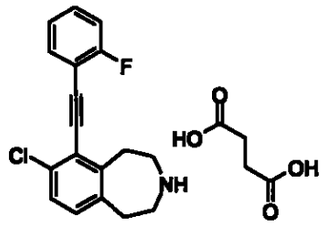
Se usa un método similar al Procedimiento General 3 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (425 mg, 1 mmol) con (3-fluorofenil)-etinilo (241 mg, 2 mmol). Se purifica por cromatografía en gel de sílice eluyendo con isohexano/EtOAc (gradiente 1:0 hasta 1:1 durante 40 min) para dar 7-cloro-6-(3-fluoro-feniletinil)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (247 mg, 64%). EM (ER+) *m/z*: 396 $(M+H)^+$.

Se usa un método similar al Procedimiento General 1-1 para desproteger 7-cloro-6-(3-fluoro-feniletinil)-3-(2,2,2-

trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (68 mg, 0.18 mmol). Se purifica por cromatografía SCX para dar la base libre del compuesto del título (46 mg, 85%). EM (ER+) *m/z*: 300 $(M+H)^+$. Se usa un método similar al Procedimiento General 2-6 para dar el compuesto del título como un sólido blanco (61 mg, 94%). EM (ER+) *m/z*: 300 $(M+H)^+$.

Ejemplo 535

Succinato de 7-cloro-6-(2-fluoro-feniletinil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



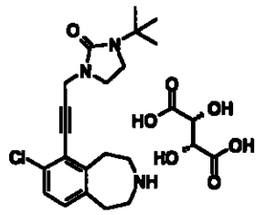
Se usa un método similar al Procedimiento General 3 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (425 mg, 1 mmol) con (2-fluorofenil)-etinilo (241 mg, 2 mmol). Se purifica por cromatografía en gel de sílice eluyendo con isohexano/EtOAc (gradiente 1:0 hasta 1:1 durante 40 min) para dar 7-cloro-6-(2-fluoro-feniletinil)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (262 mg, 68%). EM (ER+) *m/z*: 396 $(M+H)^+$.

1285

Se usan métodos similares a los Procedimientos Generales 1-1 y 2-1 para dar el compuesto del título como un sólido blanco (93%). EM (ER+) *m/z*: 300 $(M+H)^+$.

Ejemplo 536

(*L*)-Tartrato de 6-[3-(3-*tert*-Butil-2-oxo-imidazolidin-1-il)-prop-1-inil]-7-cloro-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



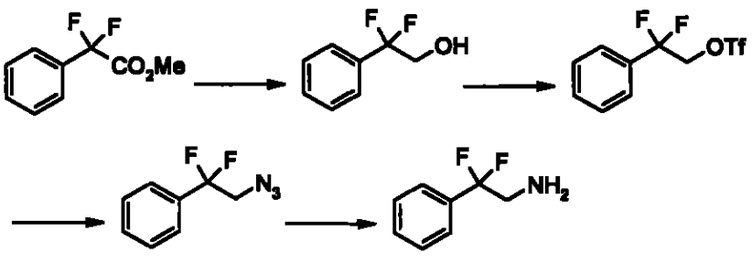
Se usa un método similar al Procedimiento General 3 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (425 mg, 1 mmol) con 1-*tert*-butil-3-prop-2-inil-imidazolidin-2-ona (360 mg, 2 mmol). Se purifica por cromatografía en gel de sílice eluyendo con isohexano/EtOAc (19:1 hasta 3:2 gradiente) para dar 6-[3-(3-*tert*-butil-2-oxo-imidazolidin-1-il)-prop-1-inil]-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (380 mg, 83%) como un aceite amarillo. CL-EM (ER+) *m/z*: 478 $(M+Na)^+$, 456 $(M+H)^+$, t_R = 4.43 min.

Se usa un método similar al Procedimiento General 1-1, pero agregando agua (10 mL) a la solución de amoniaco/metanol

(20 mL, solución 7N), para desproteger 6-[3-(3-*tert*-butil-2-oxo-imidazolidin-1-il)-prop-1-inil]-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (329 mg, 0.72 mmol) y dar la base libre del compuesto del título (217 mg, 84%). Se usa un método similar al Procedimiento General 2-6 para dar el compuesto del título como un sólido (211 mg, 58% rendimiento general). CL-EM (ER+) *m/z*: 360 $(M+H)^+$, t_R = 4.54 min.

Preparación 253

2,2-Difluoro-2-fenil-etilamina



2,2-Difluoro-2-fenil-etanol: Se agrega hidruro de aluminio litio (5.18 mL, 5.18 mmol, solución 1M en THF) a una solución de difluorofeniletanoato de metilo (0.964 g, 5.18 mmol, preparado al seguir el procedimiento descrito en *J. Org. Chem.* 1995, *60*, 5174-5179) en THF anhidro (10 mL) a 0°C. Se agita la mezcla a temperatura ambiente durante 45 min. Se enfría a 0°C y se apaga con EtOAc y luego agua. Se separa la fase orgánica y se extrae dos veces la fase acuosa con EtOAc. Se secan los extractos orgánicos combinados sobre Na_2SO_4, se

filtran y se concentran *in vacuo* para proporcionar el intermediario deseado (0.8 g, 98%) que se usó sin ninguna purificación adicional.

Trifluorometansulfonato de 2,2-Difluoro-2-fenil-etilo: Se agrega anhídrido tríflico (1.28 mL, 2.14 g) gota a gota a una solución agitada de 2,2-difluoro-2-fenil-etanol (0.8 g, 5.06 mmol) y 2,6-di-*tert*-butil-4-metilpiridina (1.556 g, 7.59 mmol) en diclorometano anhidro (25 mL) a -78°C. Se agita la reacción durante la noche mientras la temperatura se entibia. Se diluye la mezcla con pentano y se filtra el precipitado sobre Celite®. Se concentra el filtrado *in vacuo* y se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con hexano y hexano/EtOAc (95:5) para proporcionar el compuesto del título (946 mg, 64%).

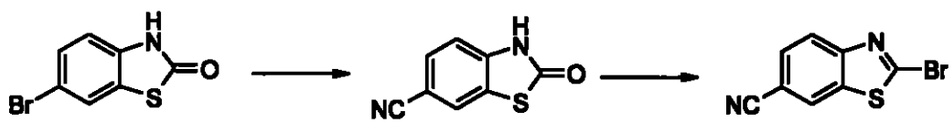
(2-Azido-1,1-difluoro-etil)-benceno: Se calienta a 60°C una solución de trifluorometansulfonato de 2,2-difluoro-2-fenil-etilo (759 mg, 2.617 mmol) y azida de sodio (357 mg, 5.496 mmol) en DMF anhidro (10 mL) bajo nitrógeno durante 3 h. Se enfría la mezcla de reacción a temperatura ambiente. Se diluye con agua y se extrae la fase acuosa dos veces con éter de dietilo. Se lavan los extractos orgánicos combinados dos veces con agua enfriada en hielo, se seca sobre Na_2SO_4, se filtra y se concentra *in vacuo* para proporcionar el

intermediario deseado como un aceite (475 mg, 99%) que se usó sin ninguna purificación adicional.

2,2-Difluoro-2-fenil-etilamina: Se disuelve (2-azido-1,1-difluoro-etil)-benceno (475 mg, 2.59 mmol) en EtOAc (30 mL). Se agrega Pd/C 10% y se expone la mezcla a hidrogenación bajo presión atmosférica (globo) durante 1 h. Se filtra el catalizador a través de Celite® y se concentra el filtrado *in vacuo* para proporcionar el compuesto del título como un aceite (400 mg, 98%) que se usó sin ninguna purificación adicional.

Preparación 254

2-Bromo-benzotiazol-6-carbonitrilo



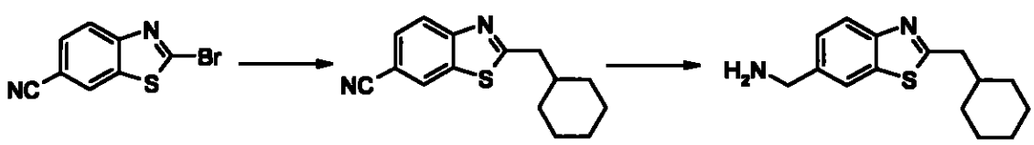
2-Oxo-2,3-dihidro-benzotiazol-6-carbonitrilo: Se combina 6-bromobenzotiazolinona (2 g, 8.69 mmol), cianuro de cobre (1.3 g, 1.48 mmol), DMF anhidro (5 mL) y se calienta a reflujo durante 15 h. Se agrega agua (20 mL) y cianuro de sodio (1.4 g, 27.7 mmol) a 100°C. Se enfría la mezcla de reacción a temperatura ambiente y se agita durante 2 h. Se extrae la mezcla de reacción con EtOAc (5 x 30 mL) a 70°C. Se combinan las capas orgánicas, se lavan con agua (3 x 40 mL) y se secan

sobre Na_2SO_4 anhidro. Se concentra *in vacuo* para obtener el intermediario deseado como un sólido amarillo (2 g, 87%). CG-EM *m/z*: 176 (M^+).

2-Bromo-benzotiazol-6-carbonitrilo: Se combina 2-oxo-2,3-dihidro-benzotiazol-6-carbonitrilo (1.1 g, 6.24 mmol), bromuro de tetrabutilamonio (3 g, 9.36 mmol), pentóxido de fosforo (2.7 g, 18.7 mmol), tolueno anhidro (40 mL) y se calienta a reflujo durante 2.5 h. Se enfría la mezcla de reacción a temperatura ambiente. Se decanta la capa de tolueno y se lava con $NaHCO_3$ acuoso saturado (3 x 10 mL). Se concentra la fase orgánica *in vacuo* y se purifica el residuo por cromatografía en gel de sílice eluyendo con hexano/EtOAc (gradiente 1:0 hasta 4:1) para obtener el compuesto del título como un aceite incoloro (0.9 g, 61%). CG-EM *m/z*: 239 (M^+).

Preparación 255

6-Aminometil-2-ciclohexilmetil-benzotiazol



2-Ciclohexilmetil-benzotiazol-6-carbonitrilo: Se coloca 2-bromo-benzotiazol-6-carbonitrilo (0.2 g, 0.96 mmol), THF anhidro (3 mL), 1-metil-2-pirrolidinona (3 mL), yoduro de

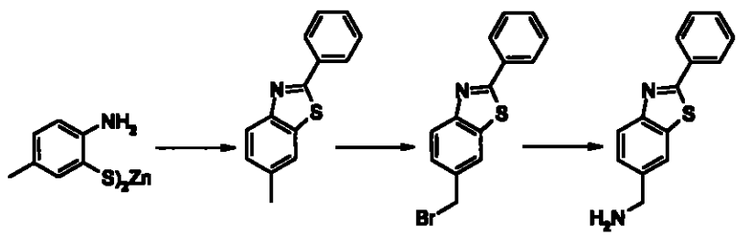
tetrabutilamonio (1.1 g, 2.89 mmol), tris(dibencilidenoacetona)dipaladio (0) (18 mg, 0.09 mmol) y [1,1'-bis(difenilfosfina)ferrocino]dicloropaladio (II) (11 mg, 0.09 mmol) en un matraz. Se agrega bromuro de ciclohexilmetilzinc 0.5M en THF (3.8 mL, 1.92 mmol) a la mezcla, se desgasifica 3 veces al evacuar parcialmente la atmósfera y se limpia con nitrógeno y se agita la mezcla de reacción a 80°C durante 2 h. Se enfría la mezcla de reacción a temperatura ambiente, se diluye con EtOAc (10 mL) y se lava con salmuera (10 mL). Se seca la capa orgánica sobre Na_2SO_4 anhidro, se filtra y se concentra *in vacuo*. Se purifica el residuo por cromatografía en gel de sílice eluyendo secuencialmente con hexano/EtOAc (gradiente 1:0 hasta 4:1) para obtener el intermediario deseado como un sólido amarillo (140 mg, 57%). CG-EM *m/z*: 256 (M^+).

6-Aminometil-2-ciclohexilmetil-benzotiazol: Se disuelve 2-ciclohexilmetil-benzotiazol-6-carbonitrilo (0.2 g, 0.55 mmol) en THF anhidro (2 mL) y se agrega lentamente hidruro de aluminio litio 1M en THF (0.82 mL, 0.82 mmol) a temperatura ambiente. Se agita la mezcla de reacción a temperatura ambiente durante 0.5 h. Se apaga la mezcla de reacción con agua hasta que un precipitado granular comienza a formarse y se filtra a través de una almohadilla de Celite®. Se evapora el solvente y se purifica el residuo por cromatografía SCX

para obtener el compuesto del título como un aceite amarillo (0.1 g, 92%). EM (ER+) *m/z*: 260 $(M+H)^+$.

Preparación 256

6-Aminometil-2-fenil-benzotiazol



6-Metil-2-fenil-benzotiazol: Se calienta a reflujo una mezcla de sal de 2-amino-5-metil-bencenotiol zinc (13.5 g, 24.9 mmol, preparada al seguir el procedimiento descrito en *Helv. Chim. Acta* 1974, *57*, 2664) y clorohidrato de etil benzimidato (9.23 g, 49.7 mmol) en metanol (240 mL) durante 9 h. Se filtra la mezcla, se evapora el filtrado y se purifica el residuo por cromatografía en gel de sílice eluyendo con hexano/EtOAc (100:0 hasta 85:15 gradiente) para obtener el intermediario deseado (5.7 g, 51%). EM (EI) *m/z*: 225 (M^+).

6-Bromometil-2-fenil-benzotiazol: Se calienta 5-metil-2-fenil-benzotiazol (5.7 g, 25.3 mmol) y NBS (4.73 g, 26.6 mmol) en tetracloruro de carbono (140 mL) a 80°C durante 3 h. Se enfría la mezcla, el volumen doble con diclorometano, se filtra y se concentra *in vacuo*. Se purifica la mezcla cruda

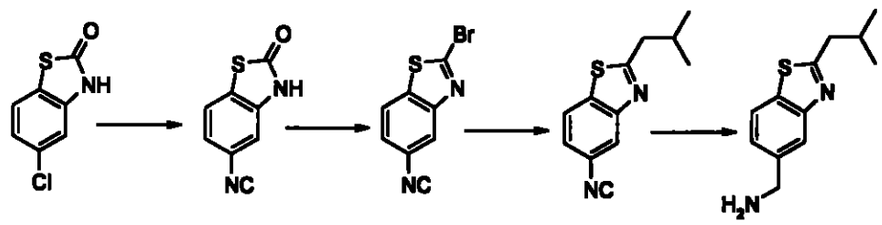
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por cromatografía en gel de sílice eluyendo con hexano/EtOAc (1:0 hasta 7:3 gradiente) para obtener el intermediario deseado (3.1 g, 40%). EM (EI) *m/z*: 303, 305 (M^+).

6-Aminometil-2-fenil-benzotiazol: Se agrega 6-bromometil-2-fenil-benzotiazol (2 g, 6.57 mmol) como una suspensión en metanol (100 mL) a amoniaco 7M en metanol (400 mL) a 0°C durante 10 min y luego se agita durante 3 h a temperatura ambiente. Se concentra *in vacuo* y se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con diclorometano/metanol (1:0 hasta 3:1) para obtener el compuesto del título (1.2 g, 76%). EM (ER+) *m/z*: 241 ($M+H^+$).

Preparación 257

5-Aminometil-2-isobutil-benzotiazol



2-Oxo-2,3-dihidro-benzotiazol-5-carbonitrilo: Se calienta una mezcla de 5-cloro-3*H*-benzotiazol-2-ona (9.3 g, 50 mmol), bromuro de niquel(II) (10.9 g, 50 mmol) y cianuro de sodio (4.91 g, 100 mmol) en 1-metil-pirrolidinona (100 mL) en un reactor de microondas a 200°C durante 15 min y se mantiene 1 h. Se filtra la mezcla enfriada a través de un vidrio

fritado, se agrega éter de dietilo y salmuera y se filtra nuevamente. Se lava la fase orgánica con salmuera tres veces y se concentra *in vacuo*. Se pasó el residuo a través de un tapón de gel de sílice eluyendo con hexano/EtOAc (2:1) y luego diclorometano/metanol (9:1) para obtener el intermediario deseado (3.2 g, 36%). EM (ER+) *m/z*: 177 $(M+H)^+$.

2-Bromo-benzotiazol-5-carbonitrilo: Se calienta 2-oxo-2,3-dihidro-benzotiazol-5-carbonitrilo (3.2 g, 18.2 mmol) en tolueno (120 mL) con bromuro de tetrabutilamonio (8.78 g, 27.2 mmol) y pentóxido de fosforo (7.73 g, 54.5 mmol) durante 3 h a reflujo. Se enfría la mezcla, se decanta la solución del residuo de reacción y se divide entre éter de dietilo y salmuera. Se agrega agua y diclorometano al residuo de reacción y se pone a reflujo durante 20 min. Se lava la capa de diclorometano con $NaHCO_3$ acuoso saturado y salmuera, y se combina con el éter lavado. Se seca la mezcla orgánica sobre Na_2SO_4 y se concentra *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con hexano/EtOAc (1:0 hasta 3:7 gradiente) para dar el intermediario deseado (0.85 g, 20%). EM (EI) *m/z*: 238, 240 (M^+).

2-Isobutil-benzotiazol-5-carbonitrilo: Se calienta 2-bromo-benzotiazol-5-carbonitrilo (0.3 g, 1.26 mmol) en 1-metil-pirrolidinona (4.2 mL) con bromuro de 2-metilpropilzinc (5

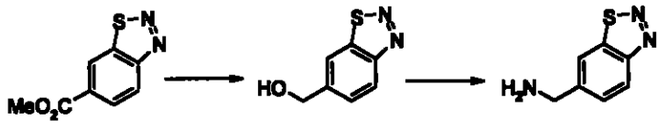
mL, 2.5 mmol, solución 0.5M en THF), N-metilimidazol (0.15 g, 1.88 mmol) y complejo de [1,1'-bis(difenilfosfina)ferroceno]dicloropaladio(II) con diclorometano (1:1) (20.5 mg, 0.025 mmol) a 80°C durante 3 h. Se enfría la mezcla y se divide entre éter de dietilo y salmuera. Se seca la capa orgánica sobre Na_2SO_4 y se concentra *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con hexano/EtOAc (gradiente 1:0 hasta 1:1) para dar el intermediario deseado (113 mg, 42%). EM (EI) *m/z*: 216 (M^+).

5-Aminometil-2-isobutil-benzotiazol: Se agrega hidruro de aluminio litio (0.78 mL, 0.78 mmol, solución 1M en THF) a 2-isobuti-benzotiazol-5-carbonitrilo (113 mg, 0.52 mmol) en THF (5 mL) y se agita durante 4 h a temperatura ambiente. Se agrega agua (0.27 mL), hidróxido de sodio 2N (0.27 mL) y agua (0.37 mL). Se filtra el precipitado y se lava el filtrado con salmuera. Se seca sobre Na_2SO_4 y se concentra *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con hexano/EtOAc (1:1) y luego amoniaco 1M en metanol/diclorometano (1:9). Se purifica la fracción polar por cromatografía SCX para dar el compuesto del título (63 mg, 55%). EM (ER+) *m/z*: 221 ($M+H^+$).

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Preparación 258

6-Aminometil-benzo[1,2,3]tiadiazol



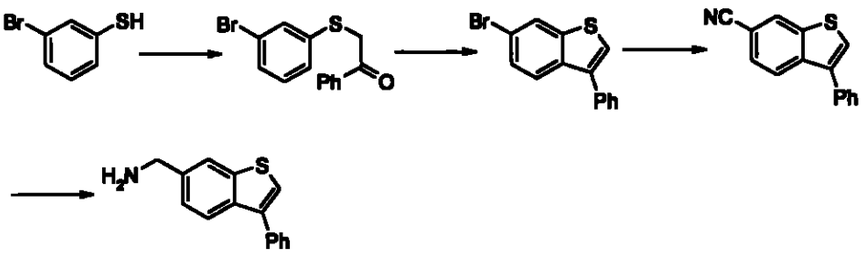
6-Hidroximetil-benzo[1,2,3]tiadiazol: Se agrega borohidruro de sodio (1.35 g, 36 mmol) en cinco porciones durante 4 h a una solución de éster de metilo del ácido benzo[1,2,3]tiadiazol-6-carboxílico (0.35 g, 1.8 mmol, preparado al seguir el procedimiento descrito en *J. Heterocyclic Chem.* 1972, 1149) en metanol (18 mL) a 0°C. Se agrega acetona para apagar y evaporar la mezcla sobre gel de sílice. Se purifica el residuo por cromatografía en gel de sílice eluyendo con hexano/EtOAc (1:0 hasta 2:3 gradiente) para dar el intermediario deseado (133 mg, 45%). EM (GCEM) *m/z*: 166 M^+.

6-Aminometil-benzo[1,2,3]tiadiazol: Se agita 6-hidroximetil-benzo[1,2,3]tiadiazol (133 mg, 0.8 mmol) en cloruro de tionilo (5 mL) durante 3 h a temperatura ambiente. Se evapora la mezcla luego se agrega amoniaco 7M en metanol (10 mL) y se agita a temperatura ambiente en un tubo sellado durante 48 h. Se evapora la mezcla y se purifica el residuo por cromatografía SCX para dar el compuesto del título (115 mg, 87%). EM (ER+) *m/z*: 166 $(M+H)^+$.

1298

Preparación 259

6-Aminometil-3-fenil-benzotiofeno



2-(3-Bromo-feniltio)-1-fenil-etanona: Se agrega hidróxido de potasio (4.89 g, 87.3 mmol) y 2-bromoacetofenona (15.8 g, 79.3 mmol) a una solución de 3-bromobencenotiol (15 g, 79.3 mmol) en etanol (200 mL, 70% en agua) a 0°C. Después de agitar 16 h, se agrega agua para precipitar un sólido amarillo. Se filtra para obtener el intermediario deseado (24.6 g, 100%).

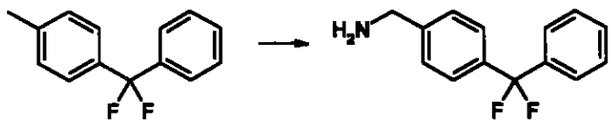
6-Bromo-3-fenilbenzotiofeno: Se calienta 2-(3-bromo-feniltio)-1-fenil-etanona (4 g, 13 mmol) en ácido polifosfórico (4 g) a 80°C durante 4 h. Se agrega EtOAc y agua a la mezcla y se lava con $NaHCO_3$ acuoso saturado y salmuera. Se seca la capa orgánica sobre Na_2SO_4, se filtra y se concentra *in vacuo*. Se hace mezcla espesa del residuo en hexano y se purifica por cromatografía en gel de sílice eluyendo con hexano para dar el intermediario deseado que se usa sin purificación adicional (2.7 g, 72%). EM (GCEM) *m/z*: 289 M^+.

6-Ciano-3-fenilbenzotiofeno: Se combina 6-bromo-3-fenilbenzotiofeno (0.5 g, 1.73 mmol) y cianuro de cobre (0.56 g, 6.23 mmol) y se pone a reflujo 3 h en 1-metil-2-pirrolidinona (1.73 mL). Se agrega cloruro férrico (2.11 g, 7.79 mmol) en HCl concentrado (1.73 mL) y se agita 1.5 h. Se enfría la mezcla y se divide entre éter de dietilo y salmuera. Se seca la capa orgánica sobre Na_2SO_4, se filtra y evapora sobre gel de sílice. Se purifica el residuo por cromatografía en gel de sílice eluyendo con hexano/EtOAc (1:0 hasta 3:2 gradiente) para dar el intermediario deseado que se usa sin purificación adicional (0.27 g, 67%). EM (GCEM) *m/z*: 235 M^+.

6-Aminometil-3-fenil-benzotiofeno: Se disuelve 6-ciano-3-fenilbenzotiofeno (0.27 g, 1.16 mmol) en THF anhidro (6 mL) y se agrega hidruro de aluminio litio (3.45 mL, solución 1M en THF) a 0°C. Después de 2 h, se agrega agua (0.86 mL), NaOH acuoso 2N (0.86 mL) y agua (1.24 mL). Se filtran completamente los sólidos y se evapora el residuo. Se purifica por CLAR preparativa (columna Zorbax SB-Fenil 21.2 x 250 mm, 5% hasta 50% acetonitrilo en solución TFA-agua 0.1%) y se obtiene la base libre por cromatografía SCX para dar el compuesto del título que se usa sin purificación adicional (187 mg, 68%). EM (ER+) *m/z*: 223 $(M-NH_2)^+$.

Preparación 260

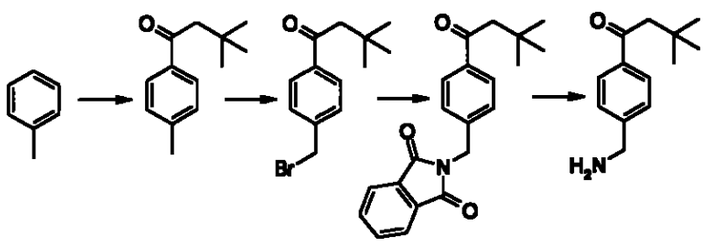
4-(Difluoro-fenil-metil)-bencilamina



Se combina 4-(difluoro-fenil-metil)-tolueno (0.29 g, 1.35 mmol, preparado al seguir el procedimiento descrito en *Tetrahedron* 1996, *52*, 9), NBS (0.26 g, 1.48 mmol), y AIBN (6 mg, 0.03 mmol) en tetracloruro de carbono (8 mL) y se calienta a 80°C durante 16 h. Se evapora la mezcla y se pasa el residuo a través de una almohadilla de gel de sílice lavado con hexano y se evapora el filtrado. Se disuelve el residuo en metanol y se agrega gota a gota a amoniaco 7M en metanol (100 mL) a 0°C. Después de 4.5 h, se evapora la mezcla y se aisla la amina por cromatografía SCX (0.1 g, 32%). EM (ER+) *m/z*: 234 $(M+H)^+$.

Preparación 261

4-(3,3-Dimetil-butiril)-bencilamina



3,3,4'-Trimetilbutirofenona: Se agrega lentamente cloruro de *tert*-butilacetilo (2 g, 14.858 mmol) a una solución agitada enfriada en hielo de tricloruro de aluminio (2.972 g, 22.28 mmol) en tolueno anhidro (40 mL). Se agita la mezcla de reacción a temperatura ambiente durante la noche. Se agrega lentamente agua enfriada en hielo y se extrae la mezcla dos veces con EtOAc. Se secan los extractos orgánicos combinados sobre Na_2SO_4, se filtran y se concentran *in vacuo* para dar el intermediario deseado (2.82 g, 100%) que se usó sin ninguna purificación adicional. CG-EM *m/z*: 190 (M^+).

Bromuro de 4-(3,3-Dimetil-butiril)-bencilo: Se calienta una mezcla de 3,3,4'-trimetilbutirofenona (2 g, 10.52 mmol), NBS (2.061 g, 11.57 mmol), y AIBN (43 mg, 0.263 mmol) en tetracloruro de carbono (60 mL) durante 14 h a reflujo. Se enfría la mezcla de reacción a temperatura ambiente y se lava secuencialmente con agua, HCl acuoso 1M, $NaHCO_3$ acuoso 5% y salmuera. Se concentra la capa orgánica *in vacuo* para proporcionar el intermediario deseado como aceite (2.54 g, 90%) que se usó sin ninguna purificación adicional.

2-[4-(3,3-Dimetil-butiril)-bencil]-isoindol-1,3-diona: Se agrega bromuro de 4-(3,3-dimetil-butiril)-bencilo (1 g, 3.731 mmol) a una suspensión agitada de ftalimida de potasio (0.705 g, 3.805 mmol) en DMF anhidro (20 mL). Se agita la mezcla

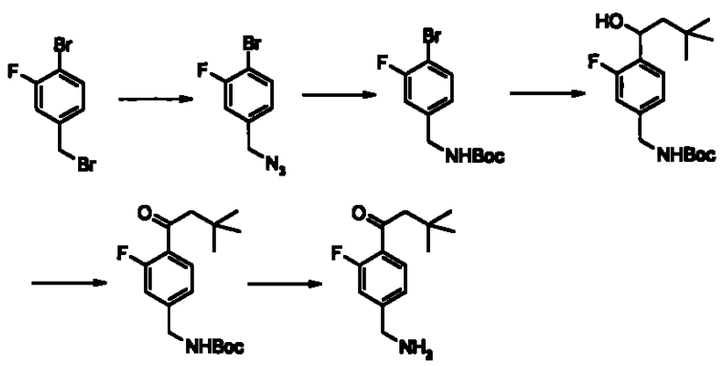
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durante la noche a temperatura ambiente. Se diluye con EtOAc y se lava dos veces con agua enfriada en hielo. Se seca la capa orgánica sobre Na_2SO_4, se filtra y se concentra *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo secuencialmente con hexano y hexano/EtOAc (19:1, 4:1) para proporcionar el intermediario deseado como aceite (1.24 g, 100%).

4-(3,3-Dimetil-butiril)-bencilamina: Se agrega hidrato de hidrazina (0.189 mL, 3.913 mmol) a una suspensión agitada de 2-[4-(3,3-dmetil-butiril)-bencil]-isoindol-1,3-diona (875 mg, 2.609 mmol) en metanol (15 mL). Se calienta la mezcla a reflujo durante la noche. Se enfría la mezcla a temperatura ambiente y se concentra *in vacuo*. Se divide el residuo entre EtOAc y HCl acuoso 5N y se lava la fase acuosa ácida nuevamente con HCl acuoso 5N. Se basifica con NaOH acuoso 5N a un pH 12. Se extrae la solución acuosa básica tres veces con cloroformo. Se secan los extractos orgánicos combinados sobre Na_2SO_4, se filtran y se concentran *in vacuo* para dar el compuesto del título como un aceite amarillo (411 mg, 77%) que se usó sin ninguna purificación adicional.

Preparación 262

4-(3,3-Dimetil-butiril)-3-fluoro-bencilamina



4-Azidometil-1-bromo-2-fluoro-benceno: Se agrega azida de sodio (2.912 g, 44.8 mmol) a una solución de bromuro de 4-bromo-3-fluorobencilo (6 g, 22.4 mmol) en DMF anhidro (127 mL) a temperatura ambiente bajo nitrógeno. Se calienta la mezcla a 90°C durante 1 h. Se concentra *in vacuo* y se divide el residuo entre agua y EtOAc. Se extrae la fase acuosa dos veces con EtOAc. Se lavan los extractos orgánicos combinados con agua y hielo. Se seca la capa orgánica sobre Na_2SO_4, se filtra y se concentra *in vacuo* para obtener el intermediario deseado como un sólido (4.92 g, 96%).

4-Bromo-*N*-(*tert*-butoxicarbonil)-3-fluoro-bencilamina: Se agrega Pd/C 10% (492 mg) y di-*tert*-butil-dicarbonato (4.668 g, 21.4 mmol) a una solución de 4-azidometil-1-bromo-2-fluoro-benceno (4.92 g, 21.4 mmol) en etanol (90 mL) y se expone la mezcla a hidrogenación a presión atmosférica durante la noche. Se filtra la mezcla de reacción sobre Celite® y se concentra *in vacuo*. Se purifica por cromatografía en gel de sílice eluyendo con hexano/EtOAc

(85:15) para obtener el intermediario deseado como un sólido (1.55 g, 25%).

***N*-(*tert*-Butoxicarbonil)-3-fluoro-4-(1-hidroxi-3,3-dimetil-butil)-bencilamina**: Se agrega butil litio (7.3 mL, 11.7 mmol) a una solución de 4-bromo-*N*-(*tert*-butoxicarbonil)-3-fluoro-bencilamina (1.55 g, 5.1 mmol) en éter de dietilo (54 mL) a -78°C bajo nitrógeno y se agita durante 30 min. Se agrega 3,3-dimetilbutiraldehído (562 mg, 0.7 mL, 5.6 mmol), se agita durante 30 min a -78°C y luego se entibia a temperatura ambiente. Se agrega agua y se extrae dos veces la fase acuosa con EtOAc. Se secan los extractos orgánicos combinados sobre Na_2SO_4, se filtran y se concentran *in vacuo*. Se purifican por cromatografía en gel de sílice eluyendo con hexano/EtOAc (85:15) para obtener el intermediario deseado como un aceite amarillo (394 mg, 24%).

***N*-(*tert*-Butoxicarbonil)-4-(3,3-dimetil-butiril)-3-fluoro-bencilamina**: Se agrega dióxido de manganeso (1.132 g, 13 mmol) a una solución de *N*-(*tert*-butoxicarbonil)-3-fluoro-4-(1-hidroxi-3,3-dimetil-butil)-bencilamina (283 mg, 0.87 mmol) en 1,4-dioxano anhidro (11.5 mL) a temperatura ambiente. Se calienta la mezcla de reacción a 70°C durante la noche. Se filtra la mezcla de reacción sobre Celite® y se concentra *in vacuo*. Se purifica por cromatografía en gel de sílice

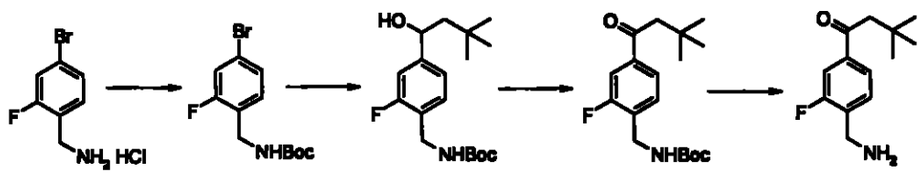
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eluyendo con hexano/EtOAc (4:1) para obtener el intermediario deseado como un aceite (216 mg, 77%).

4-(3,3-Dimetil-butiril)-3-fluoro-bencilamina: Se agrega cloruro de hidrógeno 4N en dioxano (2.7 mL, 10.8 mmol) a una solución de *N*-(*tert*-butoxicarbonil)-4-(3,3-dimetil-butiril)-3-fluoro-bencilamina (296 mg, 0.92 mmol) en diclorometano (11 mL) y se agita durante 4 h. Se concentra *in vacuo* y se lava el sólido obtenido con éter de dietilo. Se suspende el sólido en $NaHCO_3$ acuoso saturado y se agita durante 30 min. Se extrae dos veces con diclorometano. Se secan los extractos orgánicos combinados sobre Na_2SO_4, se filtran y se concentran *in vacuo* para obtener el compuesto del título como un aceite (175 mg, 82%).

Preparación 263

4-(3,3-Dimetil-butiril)-2-fluoro-bencilamina



4-Bromo-*N*-(*tert*-butoxicarbonil)-2-fluoro-bencilamina: Se agrega trietilamina (6.334 g, 8.8 mL, 52.6 mmol) y di-*tert*-butil-dicarbonato (4.54 g, 20.8 mmol) a una solución de clorohidrato de 4-bromo-2-fluoro-bencilamina (5 g, 20.8 mmol)

en diclorometano (254 mL) y se agita durante la noche. Se lava la capa orgánica con agua y entonces se extrae nuevamente la fase acuosa con diclorometano. Se secan los extractos orgánicos combinados sobre Na_2SO_4, se filtran y se concentran *in vacuo* para obtener el intermediario deseado como un sólido blanco (6.11 g, 97%).

N-(tert-Butoxicarbonil)-2-fluoro-4-(1-hidroxi-3,3-dimetil-butil)-bencilamina: Se agrega butil litio (14.2 mL, 22.7 mmol) a una solución de 4-bromo-*N*-(*tert*-butoxicarbonil)-2-fluoro-bencilamina (3 g, 9.9 mmol) en éter de dietilo (105 mL) a -78°C bajo nitrógeno y se agita durante 30 min. Se agrega 3,3-dimetilbutiraldehído (1.086 g, 1.4 mL, 10.8 mmol), se agita durante 30 min a -78°C y luego se entibia a temperatura ambiente. Se agrega agua y se extrae dos veces la fase acuosa con EtOAc. Se secan los extractos orgánicos combinados sobre Na_2SO_4, se filtran y se concentran *in vacuo*. Se purifican por cromatografía en gel de sílice eluyendo con hexano/EtOAc (85:15) para obtener el intermediario deseado como un aceite amarillo (1.179 g, 37%).

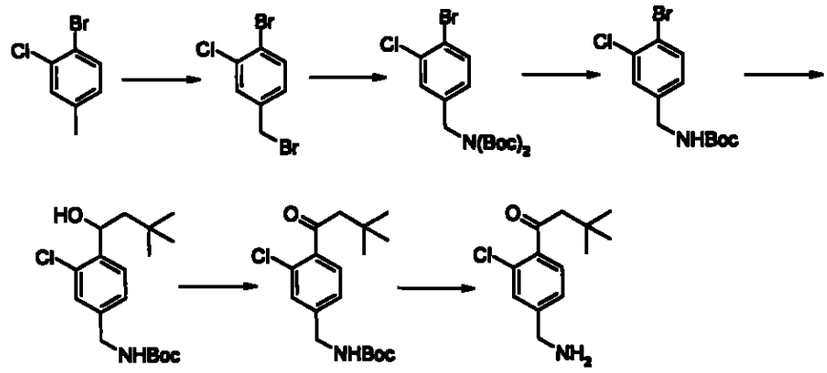
N-(tert-Butoxicarbonil)-4-(3,3-dimetil-butiril)-2-fluoro-bencilamina: Se agrega dióxido de manganeso (4.4 g, 50.6 mmol) a una solución de *N*-(*tert*-butoxicarbonil)-2-fluoro-4-(1-hidroxi-3,3-dimetil-butil)-bencilamina (1.1 g, 3.38 mmol)

en 1,4-dioxano anhidro (45 mL) a temperatura ambiente. Se calienta la mezcla de reacción a 70°C durante la noche. Se filtra la mezcla de reacción sobre Celite® y se concentra *in vacuo*. Se purifica por cromatografía en gel de sílice eluyendo con hexano/EtOAc (9:1) para obtener el intermediario deseado como un aceite (980 mg, 90%).

4-(3,3-Dimetil-butiril)-2-fluoro-bencilamina: Se agrega cloruro de hidrógeno 4N en dioxano (5.5 mL, 22 mmol) a una solución de *N*-(*tert*-butoxicarbonil)-4-(3,3-dimetil-butiril)-2-fluoro-bencilamina (600 mg, 1.85 mmol) en diclorometano (22 mL) y se agita durante 6.5 h. Se concentra *in vacuo* y se lava el sólido obtenido con éter de dietilo. Se suspende el sólido en $NaHCO_3$ acuoso saturado y se agita durante 30 min. Se extrae la fase acuosa dos veces con EtOAc. Se secan los extractos orgánicos combinados sobre Na_2SO_4, se filtran y se concentran *in vacuo* para obtener el compuesto del título como un aceite (420 mg, 99%).

Preparación 264

3-cloro-4-(3,3-dimetil-butiril)-bencilamina



Bromuro de 4-Bromo-3-cloro-bencilo: Se agrega NBS (5.266 g, 23.9 mmol) y peróxido de benzoilo (49 mg, 0.2 mmol) a una solución de 4-bromo-3-clorotolueno (4.925 g, 23.9 mmol) en tetracloruro de carbono (49 mL) y se calienta durante la noche a 90°C. Se enfría a 0°C y se filtra la mezcla. Se concentra el filtrado *in vacuo* para obtener el intermediario deseado como un aceite amarillo (5.807 g, 85%).

4-Bromo-3-cloro-N-(di-tert-butoxicarbonil)-bencilamina: Se agrega hidruro de sodio (382 mg, 15.9 mmol) a una solución de di-*tert*-butil-iminodicarboxilato (2.533 g, 11.7 mmol) en DMF anhidro (15 mL) a temperatura ambiente bajo nitrógeno y se agita durante 15 min. Entonces se agrega una solución de bromuro de 4-bromo-3-cloro-bencilo (3 g, 10.6 mmol) en DMF anhidro (5 mL) y se agita durante 1 h. Se agrega agua y extrae la fase acuosa dos veces con EtOAc. Se lavan los extractos orgánicos combinados con agua con hielo. Se seca la capa orgánica sobre Na_2SO_4, se filtra y se concentra *in vacuo*.

Se purifica por cromatografía en gel de sílice eluyendo con hexano/EtOAc (4:1) para obtener el intermediario deseado (2.783 g, 62%).

4-Bromo-3-cloro-*N*-(*tert*-butoxicarbonil)-bencilamina: Se agrega una solución de hidróxido de sodio (264 mg, 6.6 mmol) en metanol (23.5 mL) a una solución de 4-bromo-3-cloro-*N*-(di-*tert*-butoxicarbonil)-bencilamina (2.783 g, 6.6 mmol) en THF (11.7 mL) y se agita durante la noche. Se concentra *in vacuo*. Se agrega agua y se filtra el precipitado formado para obtener el intermediario deseado como un sólido blanco (1.823 g, 86%).

***N*-(*tert*-Butoxicarbonil)-3-cloro-4-(1-hidroxi-3,3-dimetil-butil)-bencilamina**: Se agrega butil litio (8.2 mL, 13.1 mmol) a una solución de 4-bromo-3-cloro-*N*-(*tert*-butoxicarbonil)-bencilamina (1.823 g, 5.7 mmol) en éter de dietilo (46 mL) a -78°C bajo nitrógeno y se agita durante 30 min. Se agrega 3,3-dimetilbutiraldehído (1.427 g, 1.7 mL, 14.3 mmol), se agita durante 30 min a -78°C y luego se entibia a temperatura ambiente. Se agrega agua y se extrae dos veces la fase acuosa con EtOAc. Se secan los extractos orgánicos combinados sobre Na_2SO_4, se filtran y se concentran *in vacuo*. Se purifica por cromatografía en gel de sílice eluyendo con hexano/EtOAc

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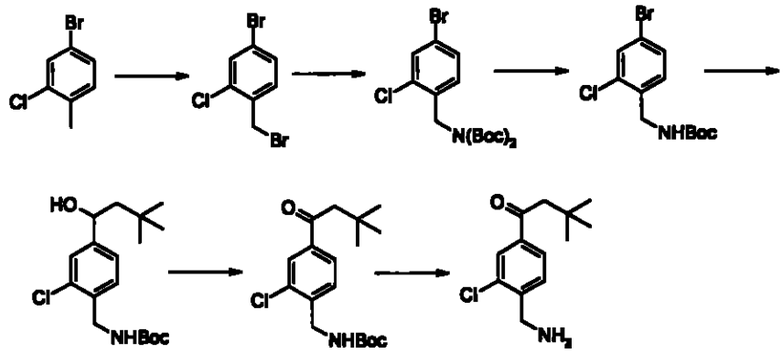
(4:1) para obtener el intermediario deseado como un aceite amarillo (274 mg, 14%).

N-(*tert*-Butoxicarbonil)-3-cloro-4-(3,3-dimetil-butiril)-bencilamina: Se agrega dióxido de manganeso (1.096 g, 12.6 mmol) a una solución de *N*-(*tert*-butoxicarbonil)-3-cloro-4-(1-hidroxi-3,3-dimetil-butil)-bencilamina (274 mg, 0.8 mmol) en 1,4-dioxano anhidro (11.5 mL) a temperatura ambiente. Se calienta la mezcla a 70°C durante la noche. Se filtra la mezcla de reacción sobre Celite® y se concentra *in vacuo*. Se purifica por cromatografía en gel de sílice eluyendo con hexano/EtOAc (4:1) para obtener el intermediario deseado como un aceite amarillo (175 mg, 64%).

3-cloro-4-(3,3-dimetil-butiril)-bencilamina: Se agrega cloruro de hidrógeno 4N en dioxano (0.9 mL, 3.6 mmol) a una solución de *N*-(*tert*-butoxicarbonil)-3-cloro-4-(3,3-dimetil-butiril)-bencilamina (100 mg, 0.3 mmol) en diclorometano (6 mL) y se agita durante la noche. Se concentra *in vacuo* y se lava el sólido obtenido con éter de dietilo. Se suspende el sólido en $NaHCO_3$ acuoso saturado y se agita durante 30 min. Se extrae dos veces con dichorometano. Se secan los extractos orgánicos combinados sobre Na_2SO_4, se filtran y se concentran *in vacuo* para obtener el compuesto del título como un aceite amarillo (66 mg, 92%).

Preparación 265

2-cloro-4-(3,3-dimetil-butiril)-bencilamina



Bromuro de 4-Bromo-2-cloro-bencilo: Se agrega NBS (13.171 g, 74 mmol) y peróxido de benzoilo (152 mg, 0.63 mmol) a una solución de 4-bromo-2-clorotolueno (15.2 g, 74 mmol) en tetracloruro de carbono (152 mL) y se agita durante 6 días a 90°C. Se enfría a 0°C, se filtra la mezcla y se concentra el filtrado *in vacuo*. Se purifica por cromatografía en gel de sílice eluyendo con hexano/EtOAc (99:1) para obtener el intermediario deseado como un aceite amarillo (12.7 g, 61%).

4-Bromo-2-cloro-*N*-di-(*tert*-butoxicarbonil)-bencilamina: Se agrega hidruro de sodio (382 mg, 15.9 mmol) a una solución de di-*tert*-butil-iminodicarboxilato (2.533 g, 11.7 mmol) en DMF anhidro (15 mL) a temperatura ambiente bajo nitrógeno y se agita durante 15 min. Entonces se agrega una solución de bromuro de 4-bromo-2-cloro-bencilo (3 g, 10.6 mmol) en DMF anhidro (5 mL) y se agita durante 1 h. Se agrega agua y se

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extrae la fase acuosa dos veces con EtOAc. Se lavan los extractos orgánicos combinados con agua con hielo. Se seca la capa orgánica sobre Na_2SO_4, se filtra y se concentra *in vacuo*. Se purifica por cromatografía en gel de sílice eluyendo secuencialmente con hexano y hexano/EtOAc (4:1) para obtener el intermediario deseado (4.2 g, 94%).

4-Bromo-*N*-(*tert*-butoxicarbonil)-2-cloro-bencilamina: Se agrega una solución de hidróxido de sodio (399 mg, 9.98 mmol) en metanol (35.5 mL) a una solución de 4-bromo-2-cloro-*N*-di-(*tert*-butoxicarbonil)-bencilamina (4.2 g, 9.98 mmol) en THF (17.7 mL) y se agita durante la noche. Se concentra *in vacuo* y se divide el residuo entre agua y EtOAc. Se extrae la fase acuosa dos veces con EtOAc. Se secan los extractos orgánicos combinados sobre Na_2SO_4, se filtran y se concentran *in* vacuo. Se purifican por cromatografía en gel de sílice eluyendo con hexano/EtOAc (4:1) para obtener el intermediario deseado (2.625 g, 82%).

***N*-(*tert*-Butoxicarbonil)-2-cloro-4-(1-hidroxi-3,3-dimetil-butil)-bencilamina**: Se agrega butil litio (11.7 mL, 18.65 mmol) a una solución de 4-bromo-*N*-(*tert*-butoxicarbonil)-2-cloro-bencilamina (2.601 g, 8.11 mmol) en éter de dietilo (86 mL) a -78°C bajo nitrógeno y se agita durante 2 h. Se agrega 3,3-dimetilbutiraldehído (1.868 g, 2.3 mL, 18.65 mmol), se agita durante 30 min a -78°C y luego se entibia a temperatura

ambiente. Se agrega agua y se extrae dos veces la fase acuosa con EtOAc. Se secan los extractos orgánicos combinados sobre Na_2SO_4, se filtran y se concentran *in vacuo*. Se purifica por cromatografía en gel de sílice eluyendo hexano/EtOAc (85:15) para obtener el intermediario deseado como un aceite amarillo (1.825 mg, 66%).

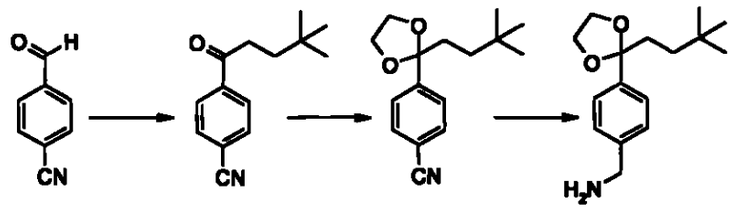
N-(tert-Butoxicarbonil)-2-cloro-4-(3,3-dimetil-butiril)-bencilamina: Se agrega dióxido de manganeso (7.276 g, 83.7 mmol) a una solución de *N*-(*tert*-butoxicarbonil)-2-cloro-4-(1-hidroxi-3,3-dimetil-butil)-bencilamina (1.819 g, 5.3 mmol) en 1,4-dioxano anhidro (75 mL) a temperatura ambiente. Se calienta la mezcla a 70°C durante la noche. Se filtra la mezcla de reacción sobre Celite® y se concentra *in vacuo*. Se purifica por cromatografía en gel de sílice eluyendo con hexano/EtOAc (85:15) para obtener el intermediario deseado como un aceite amarillo (1.362 g, 76%).

2-cloro-4-(3,3-dimetil-butiril)-bencilamina: Se agrega cloruro de hidrógeno 4N en dioxano (6 mL, 24 mmol) a una solución de *N*-(*tert*-butoxicarbonil)-2-cloro-4-(3,3-dimetil-butiril)-bencilamina (700 mg, 2.06 mmol) en diclorometano (25 mL) y se agita durante la noche. Se concentra *in vacuo* y se lava el sólido obtenido con éter de dietilo. Se suspende el sólido en $NaHCO_3$ acuoso saturado y se agita durante 30 min.

Se extrae dos veces con diclorometano. Se secan los extractos orgánicos combinados sobre Na_2SO_4, se filtran y se concentran *in vacuo* para obtener el compuesto del título como un aceite amarillo (477 mg, 97%).

Preparación 266

4-[2-(3,3-Dimetil-butil)-[1,3]dioxolan-2-il]-bencilamina



4-(4,4-Dimetil-pentanoil)-benzonitrilo: Se mantienen molduras de Mg (402 mg, 15.251 mmol) *in vacuo* en un matraz de fondo redondo de dos cuellos durante 2 h. Se purga el matraz con nitrógeno/vacío varias veces. Se agregan algunos cristales de yodo, THF anhidro (60 mL) y 3,3-dimetil-bromobutano (0.8 mL, 5.59 mmol) lentamente (se observa reacción exotérmica). Se agrega gota a gota el 3,3-dimetil-bromobutano restante (1.6 mL, 11.18 mmol) y se pone a reflujo la mezcla durante la noche. Se agrega algo de 3,3-dimetil-bromobutano adicional (0.24 mL, 1.67 mmol) y se pone a reflujo durante 30 min. Se enfría la mezcla a -10°C y se agrega una solución de 4-cianobenzaldehído (4 g, 30.502 mmol) en THF anhidro (40 mL). Se entibia el matraz gradualmente a temperatura ambiente durante la noche. Se apaga la mezcla con HCl acuoso 0.1M (100

mL) y se extrae dos veces con EtOAc. Se secan los extractos orgánicos combinados sobre Na_2SO_4, se filtran y se concentran *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con hexano/EtOAc (19:1) para dar el intermediario deseado como un aceite (0.752 g, 23%).

4-[2-(3,3-Dimetil-butil)-[1,3]dioxolan-2-il]-benzonitrilo: Se disuelve 4-(4,4-dimetil-pentanoil)-benzonitrilo (275 mg, 1.28 mmol) en tolueno (10 mL). Se agrega etilen glicol (0.35 mL, 6.4 mmol) y monohidrato del ácido p-toluensulfónico (24 mg, 0.128 mmol). Se calienta la mezcla a 135°C en una Dean-Stark durante 2 h y luego a 120°C durante la noche. Se enfría la mezcla a temperatura ambiente, se diluye con EtOAc y se lava con $NaHCO_3$ acuoso saturado. Se seca la fase orgánica sobre $MgSO_4$, se filtra y se concentra *in vacuo*. Se purifica la mezcla cruda por cromatografía en alúmina básica eluyendo con hexano y hexano/EtOAc (19:1) para dar el intermediario deseado como un aceite (0.272 g, 82%).

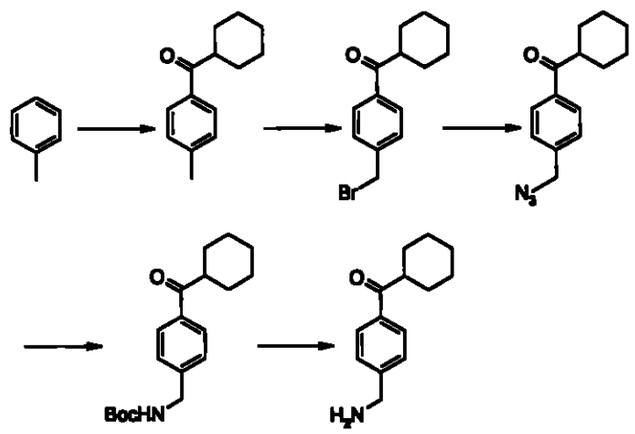
4-[2-(3,3-Dimetil-butil)-[1,3]dioxolan-2-il]-bencilamina: Se disuelve 4-[2-(3,3-dimetil-butil)-[1,3]dioxolan-2-il]-benzonitrilo (271 mg, 1.046 mmol) en THF anhidro (10 mL). Se agrega bajo nitrógeno hidruro de aluminio litio 1M en THF (2.1 mL, 2.1 mmol) a 0°C y se agita la mezcla a temperatura ambiente durante 2 h. Se enfría a 0°C, se agrega agua y se extrae la fase acuosa dos veces con EtOAc. Se secan los

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extractos orgánicos combinados sobre $MgSO_4$, se filtran y se concentran *in vacuo* para obtener el intermediario deseado como un aceite (0.263 mg) que se usó sin ninguna purificación adicional.

Preparación 267

4-Ciclohexanocarbonil-bencilamina



Ciclohexil-p-toluil-metanona: Se disuelve cloruro de ciclohexanocarbonilo (2 g, 13.6 mmol) en tolueno anhidro (30 mL). Se enfría la solución a 0°C, se agrega tricloruro de aluminio (2.72 g, 20.46 mmol) en tres porciones y se agita la mezcla de reacción a temperatura ambiente durante la noche. Se enfría a 0°C, se agrega lentamente agua y se extrae la mezcla con EtOAc. Se seca la capa orgánica sobre Na_2SO_4, se filtra y se concentra *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con hexano y

hexano/EtOAc (19:1) para dar el intermediario deseado (2.75 g, 100%).

Bromuro de 4-(Ciclohexanocarbonil)-bencilo: Se calienta una mezcla de ciclohexil-*p*-toluil-metanona (1 g, 4.943 mmol), NBS (1.232 g, 6.92 mmol), y AIBN (41 mg, 0.247 mmol) en tetracloruro de carbono (80 mL) durante 14 h a reflujo. Se agrega NBS adicional (264 mg) y AIBN (19 mg) y se pone a reflujo la mezcla durante 4 h. Se enfría la mezcla de reacción a temperatura ambiente y se filtra. Se concentra el filtrado *in vacuo* para proporcionar el intermediario deseado como aceite (1.132 g, 81%) que se usó sin ninguna purificación adicional.

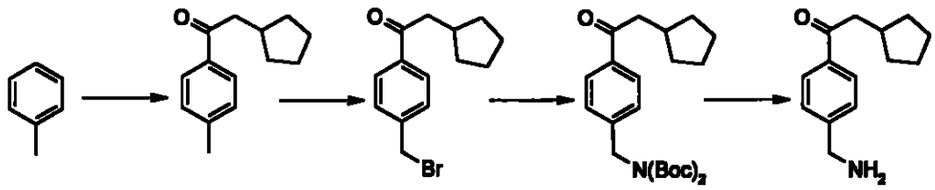
(4-Azidometil-fenil)-ciclohexil-metanona: Se agrega azida de sodio (441 mg, 6.785 mmol) a una solución agitada de bromuro de 4-(ciclohexanocarbonil)-bencilo (954 mg, 3.393 mmol) en DMF anhidro (20 mL) y se calienta la mezcla a 90°C durante 2 h. Se enfría la mezcla a temperatura ambiente, se agrega agua y se extrae la solución acuosa con éter de dietilo. Se secan los extractos orgánicos combinados sobre Na_2SO_4, se filtran y se concentran *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con hexano y hexano/EtOAc (19:1) para dar el intermediario deseado como aceite (310 mg, 38%).

***N*-(*tert*-Butoxicarbonil)-4-ciclohexanocarbonil-bencilamina**: Se agrega Pd/C 10% (100 mg) a una solución de (4-azidometil-fenil)-ciclohexil-metanona (310 mg, 1,274 mmol) y di-*tert*-butil-dicarbonato (278 mg, 1274 mmol) en etanol (5 mL). Se somete la mezcla a hidrogenación bajo presión atmosférica (globo) durante 1 h. Se filtra el catalizador a través de Celite® y se concentra el filtrado *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con hexano y hexano/EtOAc (92:8) para proporcionar el intermediario deseado como un sólido blanco (197 mg, 49%).

4-Ciclohexanocarbonil-bencilamina: Se agrega cloruro de hidrógeno 4N en dioxano (1 mL) a una solución agitada de *N*-(*tert*-butoxicarbonil)-4-ciclohexanocarbonil-bencilamina (197 mg, 0.621 mmol) en diclorometano anhidro (4 mL) y se agita la mezcla a temperatura ambiente durante 16 h. Se concentra *in vacuo* y se divide el residuo entre diclorometano y $NaHCO_3$ acuoso saturado. Se extrae la fase acuosa dos veces con diclorometano. Se secan los extractos orgánicos combinados sobre Na_2SO_4, se filtran y se concentran *in vacuo* para dar el compuesto del título (125 mg, 93%) que se usó sin ninguna purificación adicional. EM (ER+) *m/z*: 218 $(M+H)^+$.

Preparación 268

4-(2-Ciclopentil-acetil)-bencilamina



2-Ciclopentil-1-*p*-toluil-etanona: Se agrega tricloruro de aluminio (2.719 g, 20.4 mmol) en tres porciones a una solución de cloruro de ciclopentilacetilo (2 g, 13.6 mmol) en tolueno anhidro (30 mL) a 0°C. Se agita la solución a temperatura ambiente durante la noche. Se enfría a 0°C, se agrega agua y se extrae la fase acuosa con EtOAc. Se seca la fase orgánica sobre $MgSO_4$, se filtra y se concentra *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con hexano y hexano/EtOAc (19:1) para dar el intermediario deseado como un aceite (2.5 g, 91%).

1-(4-Bromometil-fenil)-2-ciclopentil-etanona: Se agrega NBS (523 mg, 2.94 mmol) y AIBN (44 mg, 0.267 mmol) a una solución de 2-ciclopentil-1-*p*-toluil-etanona (540 mg, 2.67 mmol) en tetracloruro de carbono (80 mL) y se calienta durante la noche a 85°C. Se agrega agua y se extrae la fase acuosa con diclorometano. Se seca la fase orgánica sobre $MgSO_4$, se filtra y se concentra *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con hexano y hexano/EtOAc (98:2, 95:5) para obtener el intermediario deseado como un aceite (479 mg, 64%).

N-Di-(*tert*-butoxicarbonil)-4-(2-ciclopentil-acetil)-bencilamina: Se agrega hidruro de sodio (42 mg, 1.65 mmol) a una solución de di-*tert*-butil-iminodicarboxilato (262 mg, 1.21 mmol) en DMF anhidro (5 mL) a temperatura ambiente bajo nitrógeno y se agita durante 5 min. Entonces se agrega una solución de 1-(4-bromometil-fenil)-2-ciclopentil-etanona (310 mg, 1.1 mmol) en DMF anhidro (15 mL) y se agita durante 1 h. Se agrega agua y se extrae la fase acuosa dos veces con EtOAc. Se lavan los extractos orgánicos combinados con agua con hielo. Se seca la capa orgánica sobre $MgSO_4$, se filtra y se concentra *in vacuo*. Se purifica por cromatografía en gel de sílice eluyendo con hexano/EtOAc (19:1) para obtener el intermediario deseado (360 mg, 78%).

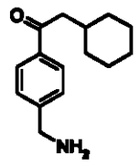
4-(2-Ciclopentil-acetil)-bencilamina: Se agrega cloruro de hidrógeno 4N en dioxano (15 mL) a una solución de *N*-di-(*tert*-butoxicarbonil)-4-(2-ciclopentil-acetil)-bencilamina (300 mg, 0.72 mmol) en EtOAc (20 mL) y se agita durante la noche. Se concentra *in vacuo*, se suspende el sólido obtenido en éter de dietilo y se agrega hexano. Se filtra y se lava el sólido con hexano. Se suspende el sólido en diclorometano, se agrega $NaHCO_3$ acuoso saturado y se agita hasta que ambas fases se limpian (15 min). Se extrae la fase acuosa con diclorometano y EtOAc. Se secan los extractos orgánicos combinados sobre $MgSO_4$, se filtran y se concentran *in vacuo* para obtener el

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compuesto del título como un aceite que se usó sin ninguna purificación adicional.

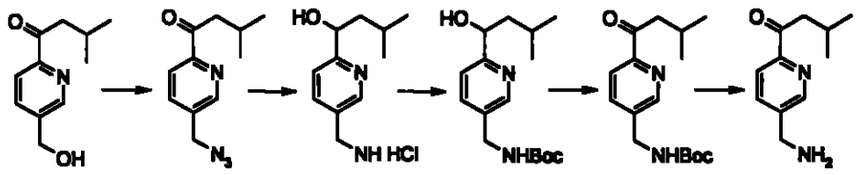
Preparación 268

El compuesto de la Preparación 269 se pueden preparar esencialmente como se describe en la Preparación 268 al usar cloruro de ciclohexilacetilo. Rendimiento general y datos EM (ER+) se muestran en la Tabla a continuación.

Prep.	NH-R	**Compuesto**	**Rendimiento (%)**	**EM (ER+) m/z**
269		4-(2-Ciclohexil-acetil)-bencilamina	40	232 $(M+H)^+$

Preparación 270

5-Aminometil-2-(3-metil-butiril)-piridina



5-Azidometil-2-(3-metil-butiril)-piridina: Se agrega DBU (240 mg, 1.55 mmol) a una solución de 5-hidroximetil-2-(3-metil-butiril)-piridina (250 mg, 1.29 mmol) y difenilfosforilazida (430 mg, 1.55 mmol) en tolueno anhidro (10 mL) a 0°C. Se agita a 0°C durante 30 min, se entibia a temperatura ambiente y se agita durante 4 h. se diluye con EtOAc y agua. Se extrae la fase acuosa dos veces con EtOAc. Se secan los extractos orgánicos combinados sobre Na_2SO_4, se filtran y se concentran *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con hexano y hexano/EtOAc (9:1) para proporcionar el intermediario deseado (300 mg, 99%). EM (ER+) *m/z*: 219 $(M+H)^+$.

Clorohidrato de 5-Aminometil-2-(1-hidroxi-3-metil-butil)-piridina: Se agrega Pd/C 10% (20 mg) a una solución de 5-azidometil-2-(3-metil-butiril)-piridina (80 mg, 0.367 mmol) en etanol (10 mL) que contiene HCl concentrado (1 mL). Se somete la mezcla a hidrogenación a presión atmosférica durante 2 h. Se filtra la mezcla de reacción sobre Celite y se concentra *in vacuo* para proporcionar el intermediario deseado (95 mg, 98%). EM (ER+) *m/z*: 195 $(M+H)^+$.

5-*tert*-Butoxicarbonilaminometil-2-(1-hidroxi-3-metil-butil)-piridina: Se agrega di-*tert*-butil-dicarbonato (78 mg, 0.356 mmol) y trietilamina (0.149 mL, 1.068 mmol) a una solución de

clorohidrato de 5-aminometil-2-(1-hidroxi-3-metil-butil)-piridina (95 mg, 0.356 mmol) en diclorometano anhidro (5 mL). Se agita la solución a temperatura ambiente durante 3 h., se diluye la mezcla de reacción con diclorometano y se lava con agua. Se extrae la fase acuosa con diclorometano. Se secan los extractos orgánicos combinados sobre Na_2SO_4, se filtran y se concentran *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con hexano/EtOAc (4:1) para proporcionar el intermediario deseado (60 mg, 59%).

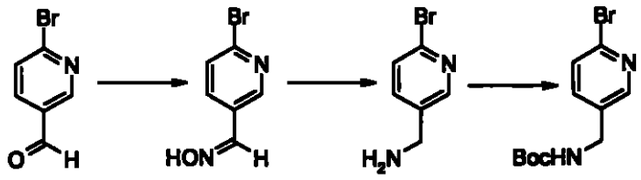
5-*tert*-Butoxicarbonilaminometil-2-(3-metil-butiril)-piridina: Se agrega dióxido de manganeso (240 mg) a una solución de 5-*tert*-butoxicarbonilaminometil-2-(1-hidroxi-3-metil-butil)-piridina (60 mg, 0.2 mmol) en 1,4-dioxano anhidro (1 mL) a temperatura ambiente. Se calienta la mezcla de reacción a 70°C durante 2 h. Se filtra la mezcla de reacción sobre Celite® y se concentra *in vacuo* para proporcionar el intermediario deseado (60 mg, 99%).

5-Aminometil-2-(3-metil-butiril)-piridina: Se agrega cloruro de hidrógeno 4N en dioxano (0.5 mL) a una solución de 5-*tert*-butoxicarbonilaminometil-2-(3-metil-butiril)-piridina (60 mg, 0.2 mmol) en diclorometano anhidro (2 mL) y se agita la solución durante la noche. Se concentra *in vacuo* y se divide el residuo entre $NaHCO_3$ acuoso saturado y diclorometano. Se

extrae la fase acuosa con diclorometano (2 x 15 mL) y EtOAc (2 x 15 mL). Se secan los extractos orgánicos combinados sobre Na_2SO_4, se filtran y se concentran *in vacuo* para obtener el compuesto del título (37 mg, 95%) que se usó sin ninguna purificación adicional.

Preparación 271

2-Bromo-5-*tert*-butoxicarbonilaminometil-piridina



Oxima de 2-Bromo-piridina-5-carbaldehído: Se agrega clorohidrato de hidroxilamina (1.494 g, 21.504 mmol) y una solución de $NaHCO_3$ (2.71 g, 32.256 mmol) en agua (15 mL) a una solución de 2-bromo-5-formil-piridina (2 g, 10.752 mmol, preparado al seguir el procedimiento descrito en *J. Org. Chem.* 2004, *69*, 250-262) en etanol absoluto (100 mL). Se agita la mezcla a temperatura ambiente durante 2 h. Se concentra *in vacuo* y se divide el residuo entre EtOAc y agua. Se extrae la fase acuosa con EtOAc. Se secan los extractos orgánicos combinados sobre Na_2SO_4, se filtran y se concentran *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con hexano y hexano/EtOAc (9:1, 4:1)

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para proporcionar el intermediario deseado como un sólido (1.362 g, 63%).

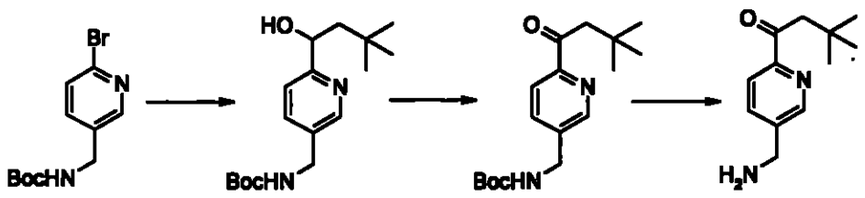
5-Aminometil-2-bromo-piridina: Se agrega gota a gota una solución de oxima de 2-bromo-piridina-5-carbaldehído (0.5 g, 2.487 mmol) en DME (10 mL) a una solución de cloruro de titanio(IV) (0.573 mL, 5.223 mmol) y borohidruro de sodio (395 mg, 10.445 mmol) en DME (20 mL) a 0°C. Se permite la mezcla entibiar hasta temperatura ambiente y se agita durante 3 h. Se agrega agua y se remueve el solvente *in vacuo*. Se basifica la mezcla a un pH 12 con NaOH acuoso 1N y se extrae con diclorometano. Se secan los extractos orgánicos combinados sobre Na_2SO_4, se filtran y se concentran *in vacuo* para proporcionar el intermediario deseado (340 mg, 73%) que se usó sin purificación adicional.

2-Bromo-5-*tert*-butoxicarbonilaminometil-piridina: Se agrega di-*tert*-butil-dicarbonato (397 mg, 1.818 mmol) y trietilamina (0.507 mL, 3.636 mmol) a una solución de 5-aminometil-2-bromo-piridina (340 mg, 1.818 mmol) en diclorometano anhidro (15 mL). Se agita la solución durante la noche a temperatura ambiente. Se diluye la mezcla de reacción con diclorometano y se lava con agua. Se extrae la fase acuosa con diclorometano. Se secan los extractos orgánicos combinados sobre Na_2SO_4, se filtran y se concentran *in vacuo*. Se purifica la mezcla cruda

por cromatografía en gel de sílice eluyendo con hexano y hexano/EtOAc (4:1) para proporcionar el compuesto del título como un sólido (322 mg, 62%).

Preparación 272

5-Aminometil-2-(3,3-dimetil-butiril)-piridina



5-*tert*-Butoxicarbonilaminometil-2-(1-hidroxi-3,3-dimetil-butil)-piridina: Se agrega lentamente butil litio (1.088 mL, 1.741 mmol, solución 1.6M en hexano) a una solución de 2-bromo-5-*tert*-butoxicarbonilaminometil-piridina (200 mg, 0.696 mmol) en THF anhidro (10 mL) a -78°C. Se agita la mezcla a esta temperatura durante 35 min. Se agrega 3,3-dimetilbutiraldehído (0.219 mL, 1.741 mmol) y se agita la mezcla a -78°C durante 3 h. Se apaga la mezcla de reacción a -78°C con salmuera. Se extrae la fase acuosa con EtOAc (3 x 15 mL). Se secan los extractos orgánicos combinados sobre Na_2SO_4, se filtran y se concentran *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con hexano y hexano/EtOAc (3:2) para proporcionar el intermediario deseado como un aceite incoloro (118 mg, 55%). EM (ER+) *m/z*: 309 $(M+H)^+$.

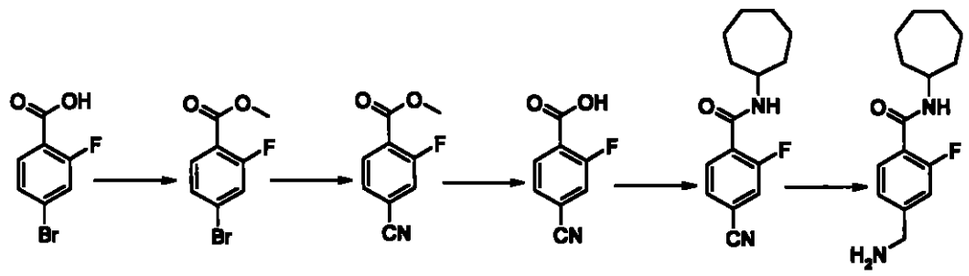
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5-*tert*-Butoxicarbonilaminometil-2-(3,3-dimetil-butiril)-piridina: Se agrega dióxido de manganeso (472 mg, 5.429 mmol) a una solución de 5-*tert*-butoxicarbonilaminometil-2-(1-hidroxi-3,3-dimetil-butil)-piridina (118 mg, 0.383 mmol) en 1,4-dioxano anhidro (5 mL) a temperatura ambiente. Se calienta la mezcla de reacción a 70°C durante la noche. Se filtra la mezcla de reacción sobre Celite® y se concentra *in vacuo* para obtener el intermediario deseado (104 mg, 89%).

5-Aminometil-2-(3,3-dimetil-butiril)-piridina: Se agrega cloruro de hidrógeno 4N en dioxano (1 mL) a una solución de 5-*tert*-butoxicarbonilaminometil-2-(3,3-dimetil-butiril)-piridina (104 mg, 0.339 mmol) en diclorometano anhidro (4 mL) y se agita la solución durante la noche. Se concentra *in vacuo* y se divide el residuo entre $NaHCO_3$ acuoso saturado y diclorometano. Se extrae la fase acuosa con diclorometano (2 x 15 mL) y EtOAc (2 x 15 mL). Se secan los extractos orgánicos combinados sobre Na_2SO_4, se filtran y se concentran *in vacuo* para obtener el compuesto del título como un aceite (62 mg, 88%) que se usó sin ninguna purificación adicional. EM (ER+) *m/z*: 207 $(M+H)^+$.

Preparación 273

4-Aminometil-*N*-cicloheptil-2-fluoro-benzamida



4-Bromo-2-fluoro-benzoato de metilo: Se disuelve ácido 4-bromo-2-fluoro-benzoico (15 g, 68.5 mmol) en metanol (70 mL). Se agrega ácido sulfúrico concentrado (500 µl) a la solución y se calienta la mezclá a reflujo durante 20 h bajo una atmósfera de nitrógeno. Se enfría la mezcla a temperatura ambiente y se concentra *in vacuo*. Se disuelve el residuo en EtOAc (200 mL) y se lava sucesivamente con $NaHCO_3$ acuoso saturado (50 mL) y agua (2 x 50 mL). Se seca la capa orgánica sobre Na_2SO_4, se filtra y se concentra *in vacuo* para obtener el intermediario deseado (15.4 g, 96%). CG-EM *m/z*: 232 (M^+).

4-Ciano-2-fluoro-benzoato de metilo: Se hace en mezcla espesa 4-bromo-2-fluoro-benzoato de metilo (5 g, 21.5 mmol) y cianuro de cobre (I) (3.8 g, 42.9 mmol) en DMF anhidro (90 mL). Se calienta la mezcla a reflujo durante 20 h bajo una atmósfera de nitrógeno. Se enfría la mezcla a temperatura ambiente, se diluye con hexano/EtOAc (1:1, 300 mL) y agua (150 mL). Se filtra la mezcla a través de Celite® lavando con hexano/EtOAc (1:1) para reducir la capa de emulsión. Se

separa la capa orgánica y se extrae la capa acuosa con hexano/EtOAc (1:1, 2 x 200 mL). Se secan los extractos orgánicos combinados sobre Na_2SO_4, se filtran y se concentran *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con hexano/EtOAc (9:1 hasta 1:1 gradiente) para obtener el intermediario deseado (2.9 g, 76%). CG-EM *m/z*: 179 (M^+).

Ácido 4-Ciano-2-fluoro-benzoico: Se disuelve 4-ciano-2-fluoro-benzoato de metilo (2.9 g, 16.2 mmol) en etanol absoluto (100 mL). Se agrega hidróxido de potasio (4.5 g, 80.2 mmol) y se agita la mezcla blanca lechosa durante 1.5 h. se diluye la mezcla con agua (125 mL) y se lava con éter de dietilo (50 mL). Se colecta la capa acuosa y se concentra *in vacuo* hasta que los sólidos comienzan a aparecer en el matraz, luego se ajusta la mezcla a un pH 1 con HCl concentrado. Se extrae la mezcla acuosa con éter de dietilo (3 x 500 mL). Se combinan los extractos orgánicos y se concentran *in vacuo* para obtener el intermediario deseado como un sólido blanco (2.2 g, 83%).

4-Ciano-*N*-cicloheptil-2-fluoro-benzamida: Se disuelve ácido 4-ciano-2-fluoro-benzoico (1 g, 6.1 mmol) en tolueno anhidro (25 mL) y cloruro de tionilo (15 mL). Se agita la mezcla durante 1 h a 90°C bajo una atmósfera de nitrógeno (se apagan

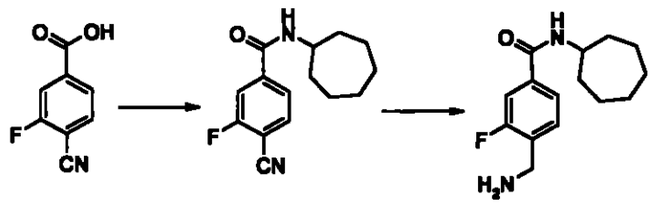
las alícuotas con metanol y se evalua por CLAR para determinar si el material de partida se ha consumido). Se enfría la reacción a temperatura ambiente y se concentra *in vacuo* para obtener el cloruro ácido como un aceite amarillo (1.25 g). Se disuelve el cloruro ácido (1.25 g) en éter de dietilo (75 mL), se agrega trietilamina (0.85 mL, 6.1 mmol) y cicloheptilamina (0.78 mL, 6.1 mmol). Se agita la mezcla a temperatura ambiente durante 16 h bajo una atmósfera de nitrógeno. Se apaga la reacción con Na_2CO_3 acuoso saturado (20 mL). Se extrae la mezcla con EtOAc (30 mL). Se seca la capa orgánica sobre Na_2SO_4, se filtra y se concentra *in vacuo* para obtener el intermediario deseado (1.45 g, 91%). CG-EM *m/z*: 260 (M^+).

4-Aminometil-*N*-cicloheptil-2-fluoro-benzamida: Se agrega 4-ciano-*N*-cicloheptil-2-fluoro-benzamida (1.4 g, 5.4 mmol), Pd/C 10% (tipo Degussa E101, 415 mg), etanol (40 mL), agua (15 mL) y ácido acético (1.8 mL) a un recipiente de presión. Se presuriza el recipiente a 55 psi (3.8665 kg/cm^2) con hidrógeno, y se agita la mezcla durante 0.5 h (se monitorea la reacción por CCD). Se filtra la mezcla a través de Celite y se lava la torta con etanol caliente seguido por diclorometano bajo una atmósfera de nitrógeno. Se concentra el filtrado *in vacuo* para obtener el producto como la sal de

ácido acético. Se usa cromatografía SCX para obtener el compuesto del título (1.36 g, 95%). CG-EM *m/z*: 264 (M^+).

Preparación 274

4-Aminometil-*N*-cicloheptil-3-fluoro-benzamida



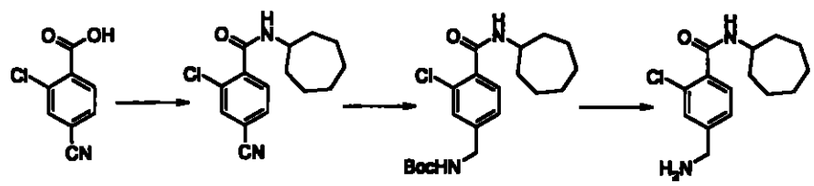
4-Ciano-*N*-cicloheptil-3-fluoro-benzamida: Se disuelve ácido 4-ciano-3-fluoro-benzoico (1 g, 6.1 mmol) en tolueno anhidro (20 mL) y cloruro de tionilo (10 mL). Se agita la mezcla durante 1.5 h a 90°C bajo una atmósfera de nitrógeno (se apagan las alícuotas con metanol y se evaluan por CLAR para determinar si el material de partida se ha consumido). Se enfría la reacción a temperatura ambiente y se concentra *in vacuo* para obtener el cloruro ácido como un aceite amarillo. Se disuelve el aceite amarillo en éter de dietilo (50 mL), se agrega trietilamina (0.86 mL, 6.1 mmol) y cicloheptilamina (0.79 mL, 6.1 mmol). Se agita la mezcla a temperatura ambiente durante 16 h bajo una atmósfera de nitrógeno. Se apaga la reacción con Na_2CO_3 acuoso saturado (20 mL). Se extrae la mezcla con EtOAc (2 x 50 mL). Se secan los extractos orgánicos combinados sobre Na_2SO_4, se filtran y se

concentran *in vacuo* para obtener el intermediario deseado (1.24 g, 77%). EM (ES-) *m/z*: 259.2 $(M-H)^+$.

4-Aminometil-*N*-cicloheptil-3-fluoro-benzamida: Se agrega 4-ciano-*N*-cicloheptil-3-fluoro-benzamida (0.86 g, 3.3 mmol), Pd/C 10% (tipo Degussa E101, 250 mg), etanol (25 mL), agua (9 mL) y ácido acético (1 mL) a un recipiente de presión bajo una atmósfera de nitrógeno. Se presuriza el recipiente a 50 psi (3.515 kg/cm^2) con hidrógeno, y se agita la mezcla durante 0.5 h. Se filtra la mezcla a través de Celite® y se lava la torta con etanol caliente seguido por diclorometano bajo una atmósfera de nitrógeno. Se concentra el filtrado *in vacuo* para obtener el compuesto del título como la sal de ácido acético. Se usa cromatografía SCX para obtener el compuesto del título (805 mg, 92%). EM (ER+) *m/z*: 265.3 $(M+H)^+$.

Preparación 275

4-Aminometil-2-cloro-*N*-cicloheptil-benzamida



2-cloro-4-ciano-*N*-cicloheptil-benzamida: Se disuelve ácido 2-cloro-4-ciano-benzoico (1.1 g, 6 mmol) en tolueno anhidro (20

mL) y cloruro de tionilo (15 mL). Se agita la mezcla durante 1 h a 90°C bajo una atmósfera de nitrógeno (se apagan las alícuotas con metanol y se evaluan por CLAR para determinar si el material de partida se ha consumido). Se enfría la reacción a temperatura ambiente y se concentra *in vacuo* para obtener el cloruro ácido como un aceite. Se disuelve el aceite en éter de dietilo (40 mL), se agrega trietilamina (0.84 mL, 6 mmol) y cicloheptilamina (0.77 mL, 6 mmol). Se agita la mezcla a temperatura ambiente durante 1 h bajo una atmósfera de nitrógeno. Se apaga la reacción con Na_2CO_3 acuoso saturado (20 mL). Se extrae la mezcla con EtOAc (100 mL). Se seca la capa orgánica sobre Na_2SO_4, se filtra y se concentra *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con diclorometano para obtener el intermediario deseado (1.1 g, 66%). EM (ER+) *m/z*: 277.2 $(M+H)^+$.

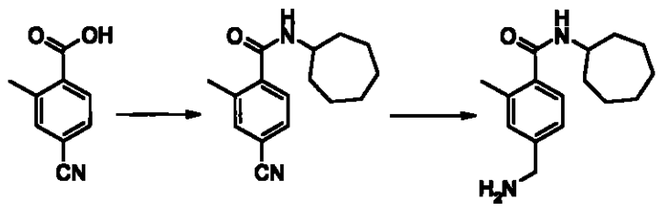
4-*tert*-Butoxicarbonilaminometil-2-cloro-*N*-cicloheptil-benzamida: Se disuelve 2-cloro-4-ciano-*N*-cicloheptil-benzamida (460 mg, 1.7 mmol) en metanol (15 mL). Se enfría la solución a 0°C bajo una atmósfera de nitrógeno y se agrega dicarbonato di-*tert*-butilo (726 mg, 3.3 mmol) y hexahidrato de cloruro niquel(II) (40 mg, 0.17 mmol). Se agrega entonces borohidruro de sodio (360 mg, 9.5 mmol) en porciones sobre 30 min. Se agita a 0°C durante 1 h luego se concentra la mezcla

in vacuo. Se diluye el residuo con EtOAc (100 mL), se lava con $NaHCO_3$ acuoso saturado (40 mL). Se extrae la capa acuosa con EtOAc (3 x 40 mL). Se secan los extractos orgánicos combinados sobre Na_2SO_4, se filtran y se concentran *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con EtOAc para obtener el intermediario deseado (627 mg, 99%). EM (ER+) *m/z*: 381.3 $(M+H)^+$.

4-Aminometil-2-cloro-*N*-cicloheptil-benzamida: Se disuelve 4-*tert*-butoxicarbonilaminometil-2-cloro-*N*-cicloheptil-benzamida (624 mg, 1.6 mmol) en diclorometano (30 mL) luego se agrega ácido trifluoroacético (2 mL). Se agita la solución a temperatura ambiente bajo una atmósfera de nitrógeno durante 1 h. Se concentra la mezcla *in vacuo*. Se purifica la mezcla cruda por cromatografía SCX para obtener el intermediario deseado (395 mg, 85%). EM (ER+) *m/z*: 281.2 $(M+H)^+$.

Preparación 276

4-Aminometil-*N*-cicloheptil-2-metil-benzamida



4-Ciano-*N*-cicloheptil-2-metil-benzamida: Se agrega cicloheptilamina (0.83 mL, 6.5 mmol), HOBT (838 mg, 6.2

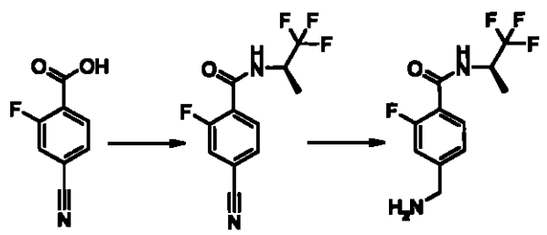
mmol), EDC (1.2 g, 6.2 mmol) y diisopropiletilamina (3.2 mL, 18.6 mmol) a una solución de ácido 4-ciano-2-metil-benzoico (1 g, 6.2 mmol) en diclorometano (20 mL) a temperatura ambiente bajo una atmósfera de nitrógeno. Se agita la mezcla durante 16 h a temperatura ambiente. Se lava la mezcla con agua (20 mL), se separa y se concentra la capa orgánica *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con hexano/EtOAc (19:1 hasta 3:2 gradiente) para obtener el intermediario deseado (830 mg, 52%). EM (ER+) *m/z*: 257.3 $(M+H)^+$.

4-Aminometil-*N*-cicloheptil-2-metil-benzamida: Se agrega 4-ciano-*N*-cicloheptil-2-metil-benzamida (0.82 g, 3.2 mmol), etanol (23 mL), agua (8 mL) y ácido acético (1 mL) a un recipiente de presión. Se calienta el recipiente a 50°C hasta disolver todos los sólidos. Se agrega Pd/C 10% (tipo Degussa E101, 250 mg) bajo una atmósfera de nitrógeno, luego se presuriza el recipiente a 55 psi (3.8665 kg/cm^2) con hidrógeno a temperatura ambiente. Se agita la mezcla durante 40 min. Se filtra la mezcla a través de Celite® y se lava la torta con etanol caliente (50 mL) seguido por diclorometano (100 mL) bajo una atmósfera de nitrógeno. Se concentra el filtrado *in vacuo* para obtener el compuesto del título como la sal de ácido acético. Se usa cromatografía SCX para

obtener el compuesto del título (820 mg, 98%). EM (ER+) *m/z*: 261.3 $(M+H)^+$.

Preparación 277

(*R*)-4-Aminometil-2-fluoro-*N*-(2,2,2-trifluoro-1-metil-etil)-benzamida

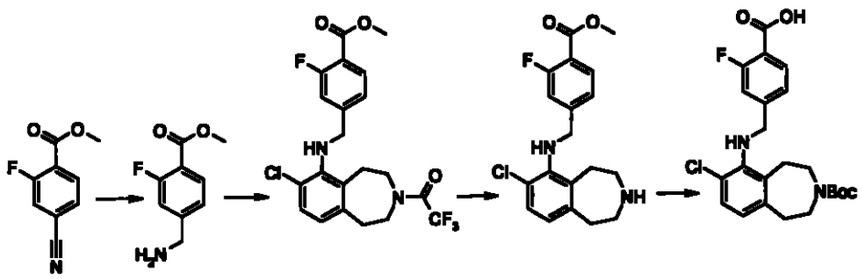


(*R*)-4-Ciano-2-fluoro-*N*-(2,2,2-trifluoro-1-metil-etil)-benzamida: Se agrega (*R*)-(2,2,2-trifluoro-1-metil)-etilamina (0.909 g, 6.08 mmol), HOBT (0.82 g, 6.1 mmol), diisopropiletilamina (2.1 mL, 12 mmol) y EDC (1.17 g, 6.08 mmol) a una mezcla de ácido 4-ciano-2-fluorobenzoico (1.004 g, 6.08 mmol) en THF anhidro (40 mL) a temperatura ambiente. Se agita durante la noche y se divide la mezcla entre EtOAc (250 mL) y $NaHCO_3$ acuoso saturado (100 mL). Se seca el extracto orgánico sobre Na_2SO_4, se filtra y se concentra *in vacuo*. Se purifica por cromatografía en gel de sílice eluyendo con diclorometano/hexano (1:1 hasta 1:0 gradiente durante 71 min; 50 mL/min) para proporcionar el intermediario deseado como un sólido blanco (0.985 g, 62%).

(*R*)-4-Aminometil-2-fluoro-*N*-(2,2,2-trifluor -1-metil-etil)-benzamida: Se combina una solución de (*R*)-4-ciano-2-fluoro-*N*-(2,2,2-trifluoro-1-metil-etil)-benzamida (0.904 g, 3.475 mmol) en etanol absoluto (26 mL), agua (9.7 mL) y ácido acético glacial (1.2 mL) con Pd/C 10% (tipo Degussa E101, 0.27 g, 0.13 mmol) bajo nitrógeno. Se purga la mezcla con nitrógeno y luego con hidrógeno. Se agita la mezcla espesa a temperatura ambiente bajo hidrógeno a 55 psi (3.8665 kg/cm^2) durante 30 min. Se purga la mezcla de reacción con nitrógeno y luego se filtra la mezcla espesa sobre Celite®. Se lava la torta filtro con etanol (100 mL) y THF (100 mL). Se concentra el filtrado y se purifica por cromatografía SCX eluyendo con diclorometano/metanol (1:1) para remover impurezas y luego con diclorometano/amoniaco 2M en metanol (1:1) para eluir el producto. Se concentra para proporcionar el compuesto del título como un aceite incoloro (0.86 g, 94%).

Preparación 278

3-*tert*-Butoxicarbonil-6-(4-carboxi-3-fluoro-bencilamino)-7-cloro-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



4-Aminometil-2-fluoro-benzoato de metilo: Se combina una solución de 4-ciano-2-fluoro-benzoato de metilo (1 g, 5.58 mmol) en etanol absoluto (42 mL) y ácido acético (1.9 mL) con una mezcla de Pd/C 10% (tipo Degussa E101, 0.17 g, 0.078 mmol) en agua (15.6 mL) a temperatura ambiente bajo nitrógeno. Se purga con nitrógeno y luego con hidrógeno a 55 psi (3.8665 kg/cm^2) y se agita durante 1 h. Se purga la reacción con nitrógeno, se filtra a través de Celite® y se lava la torta filtro con etanol (100 mL), THF (100 mL) e isopropanol (100 mL). Se concentra *in vacuo* y se purifica por cromatografía SCX y luego cromatografía en gel de sílice (columna 40 g RediSep®) eluyendo con diclorometano/amoniaco 2M en metanol (99:1 hasta 9:1 gradiente durante 30 min; 35 mL/min) para proporcionar el intermediario deseado como un sólido blanco (0.602 g, 59%).

7-cloro-6-(3-fluoro-4-metoxicarbonil-bencilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina: Se usa un método similar al Procedimiento General 5-2 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (1.24 g, 2.91 mmol) con 4-aminometil-2-fluoro-benzoato de metilo (1.065 g, 5.821 mmol) al usar tris(dibencilidenoacetona)dipaladio(0) (0.533 g, 0.582 mmol), BINAP (0.725 g, 1.16 mmol) y carbonato de cesio (3.32 g, 10.2

mmol) bajo nitrógeno en tolueno anhidro (20 mL). Se purifica por cromatografía en gel de sílice eluyendo con hexano/EtOAc (gradiente 19:1 hasta 1:1 durante 71 min; 50 mL/min) para proporcionar el intermediario deseado cómo un aceite amarillo (1.3 g, 100%).

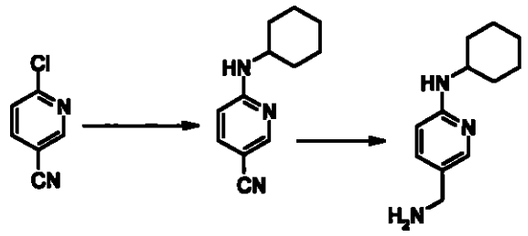
7-cloro-6-(3-fluoro-4-metoxicarbonil-bencilamino)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina: Se agrega NaOH acuoso 1M (2.8 mL, 2.8 mmol) a una solución de 7-cloro-6-(3-fluoro-4-metoxicarbonil-bencilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (1.31 g, 2.86 mmol) en 1,4-dioxano (13.3 mL) y agua (2.6 mL) a 11°C. Se permite la mezcla entibiar hasta temperatura ambiente y se agita durante 1 h. Se concentra *in vacuo* y se divide el residuo entre diclorometano (250 mL) y $NaHCO_3$ acuoso saturado (100 mL). Se seca la fase orgánica sobre Na_2SO_4, se filtra y se concentra *in vacuo* para proporcionar el intermediario deseado que se usó sin purificación adicional.

3-*tert*-Butoxicarbonil-6-(4-carboxi-3-fluoro-bencilamino)-7-cloro-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina: Se agrega NaOH acuoso 1M (5.7 mL, 5.7 mmol) a una mezcla de 7-cloro-6-(3-fluoro-4-metoxicarbonil-bencilamino)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (1.04 g, 2.86 mmol) en 1,4-dioxano (13.3 mL) y agua (2.6 mL) a temperatura ambiente. Se calienta la mezcla

a 50°C durante 2 h. Se enfría la mezcla a 0°C, se agrega una solución de di-*tert*-butil-dicarbonato (0.62 g, 2.9 mmol) en 1,4-dioxano (2 mL) y se agita a 0°C durante 2 h. Se concentra *in vacuo*, se agrega EtOAc (50 mL), $KHSO_4$ acuoso 1N (5.7 mL, 5.7 mmol) y agua (20 mL) a un pH = 1. Se seca la fase orgánica sobre Na_2SO_4, se filtra y se concentra *in vacuo* para proporcionar el compuesto del título como un aceite amarillo (1.25 g, 98%) que se usó sin purificación adicional. EM (ER+) *m/z*: 449.1 $(M+H)^+$.

Preparación 279

5-Aminometil-2-ciclohexilamino-piridina

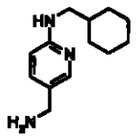


6-Ciclohexilamino-nicotinonitrilo: Se agrega ciclohexilamina (7.1 g, 72 mmol) a una mezcla de 6-cloronicotinitrilo (1 g, 7.2 mmol), carbonato de potasio (3 g, 21.7 mmol) y DMF anhidro (10 mL). Se calienta la mezcla en un matraz sellado a 120°C durante 1.5 h. Se enfría la reacción a temperatura ambiente, se diluye con hexano/EtOAc (1:1, 100 mL) y se lava la mezcla con cloruro de sodio 5% acuoso (3 x 30 mL). Se colecta la capa orgánica y se concentra *in vacuo* para obtener el intermediario deseado (1.4 g, 97%). CG-EM *m/z*: 201 (M^+).

5-Aminometil-2-ciclohexilamino-piridina: Se carga una solución de 6-ciclohexilamino-nicotinonitrilo (1.4 g, 7.1 mmol) en metanol (70 mL) y ácido trifluoroacético (5 mL) a un recipiente de presión que contiene Pd/C 10% (tipo Degussa E101, 600 mg). Se presuriza el recipiente a 40 psi (2.812 kg/cm^2) con hidrógeno y se agita durante 2 h. Se filtra la mezcla a través de Celite®, se lava con etanol caliente, y diclorometano. Se concentra el filtrado *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con diclorometano/amoniaco .2M en metanol (99:1 hasta 90:10 gradiente) para obtener el compuesto del título (920 mg, 54%). EM (ER+) *m/z*: 206.1 $(M+H)^+$.

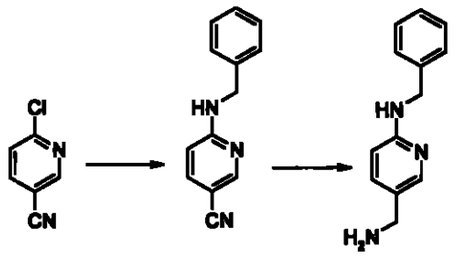
Preparación 280

El compuesto de la Preparación 280 se pueden preparar esencialmente como se describe en la Preparación 279 usando 6-cloronicotinonitrilo y ciclohexilmetilamina. Rendimiento general y datos EM (ER+) se muestran en la Tabla a continuación.

Prep.	Estructura	Compuesto	Rendimiento (%)	EM (ER+) m/z
280		5-Aminometil-2-ciclohexilmetil amino-piridina	95	220.3 $(M+H)^+$

Preparación 281

6-Bencilamino-piridin-3-ilmetilamina

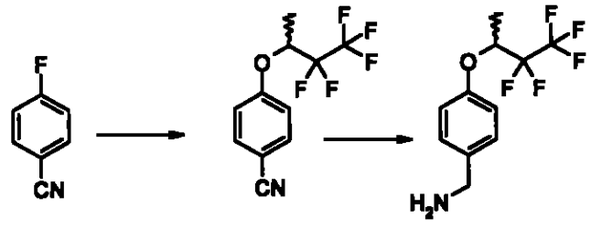


6-Bencilamino-nicotinonitrilo: Se calienta 6-cloroniconitrilo (0.58 g, 4.2 mmol) y bencilamina (4.6 mL, 42 mmol) en DMF anhidro (3 mL) a 120°C durante 4.5 h. Se enfría a temperatura ambiente. Se diluye con agua y se extrae con EtOAc. Se lava la fase orgánica con salmuera, se seca sobre $MgSO_4$, se filtra, y se concentra *in vacuo*. Se purifica por cromatografía en gel de sílice eluyendo secuencialmente con hexano/EtOAc (4:1, 2:1, 1:2) para dar el intermediario deseado como un sólido blanco (840 mg, 96%). EM (ER+) *m/z*: 210 $(M+H)^+$.

6-Bencilamino-piridin-3-ilmetilamina: Se agita 6-bencilamino-nicotinonitrilo (680 mg, 3.3 mmol) y Pd/C 10% (tipo Degussa E101) vigorosamente en etanol absoluto (80 mL) bajo hidrógeno a 25 psi (1.7575 kg/cm^2) durante 1 h. Se filtra la solución a través de Celite® y se concentra *in vacuo*. Se purifica por cromatografía en gel de sílice eluyendo secuencialmente con amoniaco 2M en metanol/diclorometano (4:96, 9:91) para dar el compuesto del título como un sólido blanco (320 mg, 45%). EM (ER+) *m/z*: 214 $(M+H)^+$.

Preparación 282

(±)-4-[1-(1,1,2,2,2-Pentafluoroetil)-etoxi]-bencilamina



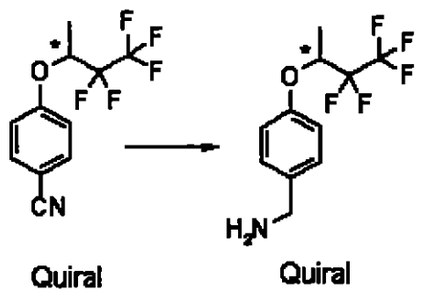
(±)-4-[1-(1,1,2,2,2-Pentafluoroetil)-etoxi]-benzonitrilo: Se agrega carbonato de potasio (27.4 g, 198 mmol) a una mezcla de 4-fluorobenzonitrilo (8 g, 66 mmol) y (±)-3,3,4,4,4-pentafluoro-2-butanol (17.2 g, 105 mmol) en DMF anhidro (60 mL). Se calienta la mezcla en un matraz sellado durante 4 h a 130°C. Se enfría la reacción a temperatura ambiente, se diluye con hexano/EtOAc (1:1, 350 mL) y se lava con cloruro de sodio 5% acuoso (3 x 100 mL). Se colecta la capa orgánica, se seca sobre Na_2SO_4, se filtra y se concentra *in vacuo* para

obtener el intermediario deseado (17.1 g, 98%). CG-EM *m/z*: 432 (M^+).

(±)-4-[1-(1,1,2,2,2-Pentafluoroetil)-etoxi]-bencilamina: Se agrega (±)-4-[1-(1,1,2,2,2-pentafluoroetil)-etoxi]-benzonitrilo (1 g, 3.8 mmol) a una mezcla espesa de hidruro de aluminio litio (400 mg, 10 mmol) en éter de dietilo (30 mL) a 0°C bajo una atmósfera de nitrógeno. Se agita la mezcla a temperatura ambiente durante 2 h, y luego se apaga la reacción secuencialmente con agua (1 mL) e hidróxido de sodio 5N (1 mL). Se filtra la mezcla espesa a través de Celite®, se seca el filtrado sobre Na_2SO_4, se filtra y se concentra *in vacuo* para obtener el compuesto del título (990 mg, 98%). CG-EM *m/z*: 268 (M^+).

Preparación 283

4-[1-(1,1,2,2,2-Pentafluoroetil)-etoxi]-bencilamina Isómero 2



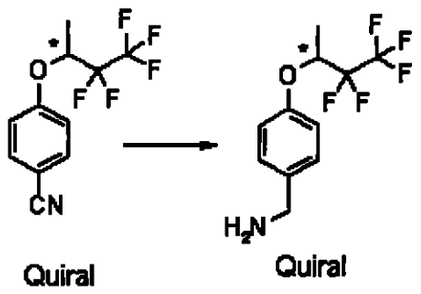
4-[1-(1,1,2,2,2-Pentafluoroetil)-etoxi]-benzonitrilo Isómero 2: Se separa (±)-4-[1-(1,1,2,2,2-pentafluoroetil)-etoxi]-

benzonitrilo por cromatografía quiral de fase normal (Chiralcel OJ, 8 x 33 cm, eluyendo con heptano/etanol 3A 97:3, relación de flujo 375 mL/min). Se colecta el 2do isómero de elución como el intermediario deseado (11.3 g, 40% recuperado, 98.6% ee (Chiralcel OJ, 4.6 x 250 mm, eluyendo con heptano/etanol 3A 97:3, 1 mL/min). CG-EM *m/z*: 265 (M^+).

4-[1-(1,1,2,2,2-Pentafluoroetil)-etoxi]-bencilamina Isómero 2: Se reduce 4-[1-(1,1,2,2,2-pentafluoroetil)-etoxi]-benzonitrilo isómero 2 (11.4 g, 43 mmol) usando Procedimiento General 6-4 para obtener el compuesto del título (11.38 g, 98%). CG-EM *m/z*: 268 (M^+).

Preparación 284

4-[1-(1,1,2,2,2-Pentafluoroetil)-etoxi]-bencilamina Isómero 1



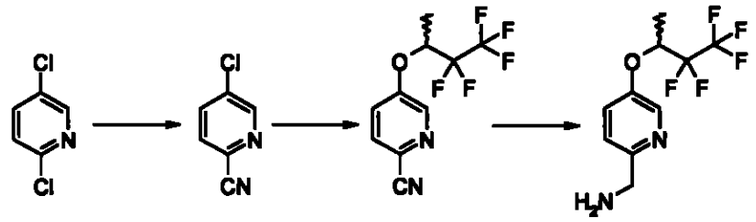
4-[1-(1,1,2,2,2-Pentafluoroetil)-etoxi]-benzonitrilo Isómero 1: Se separa (±)-4-[1-(1,1,2,2,2-pentafluoroetil)-etoxi]-benzonitrilo por cromatografía quiral de fase normal (Chiralcel OJ, 8 x 33 cm, eluyendo con heptano/3A etanol

97:3, relación de flujo 375 mL/min). Se colecta el 1er isómero de elución como el intermediario deseado (4.5 g, 33% recuperado, 99.3% ee (Chiralcel OJ, 4.6 x 250 mm, eluyendo con heptano/3A etanol 97:3, 1 mL/min). CG-EM *m/z*: 265 (M^+).

4-[1-(1,1,2,2,2-Pentafluoroetil)-etoxi]-bencilamina Isómero 1: Se reduce 4-[1-(1,1,2,2,2-pentafluoroetil)-etoxi]-benzonitrilo isómero 1 (4.5 g, 17 mmol) usando Procedimiento General 6-4 para obtener el compuesto del título (4.3 g, 94%). CG-EM *m/z*: 268 (M^+).

Preparación 285

(±)-2-Aminometil-5-[1-(1,1,2,2,2-pentafluoroetil)-etoxi]-piridina



5-cloro-piridina-2-carbonitrilo: Se hace mezcla espesa 2,5-dicloropiridina (6 g, 40.5 mmol), cianuro de zinc (2.9 g, 24.7 mmol), zinc (polvo) (116 mg, 1.8 mmol) y complejo de [1,1'-bis(difenilfosfina)ferroceno]dicloropaladio(II) con diclorometano (720 mg, 0.98 mmol) en DMF anhidro (40 mL). Se calienta la mezcla a reflujo bajo una atmósfera de nitrógeno

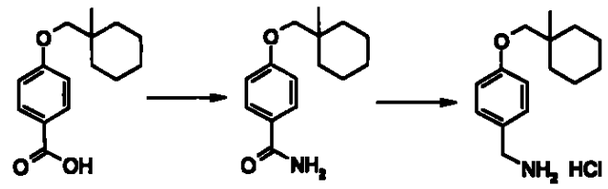
durante 4.5 h. Se enfría la mezcla a temperatura ambiente, se diluye con EtOAc (300 mL), se lava con cloruro de sodio 10% acuoso (3 x 75 mL). Se colecta capa orgánica, se seca sobre Na_2SO_4, se filtra y se concentra *in vacuo*. Se purifica por cromatografía en gel de sílice eluyendo con hexano/EtOAc (9:1 hasta 1:1 gradiente) para obtener el intermediario deseado (2.6 g, 46%). CG-EM *m/z*: 138 (M^+).

(±)-4-[1-(1,1,2,2,2-Pentafluoroetil)-etoxi]-piridina-2-carbonitrilo: Se agrega (±)-3,3,4,4,4-pentafluoro-2-butanol (710 mg, 4.3 mmol) lentamente a una mezcla espesa de hidruro de sodio (104 mg, 1.2 equiv, 60% aceite mineral, se lava con hexano) en hexametilfosforamida (2 mL) bajo nitrógeno a 0 °C. Se permite la mezcla espesa entibiar hasta temperatura ambiente y se agita durante 5 min. Se agrega 5-cloro-piridina-2-carbonitrilo (300 mg, 2.2 mmol), luego se calienta la mezcla en un matraz sellado a 130°C durante 4 h (reacción monitoreada por CG/EM). Se enfría la reacción a temperatura ambiente, se ajusta la mezcla a un pH 9 con Na_2CO_3 acuoso saturado, luego se extrae con éter de dietilo (2 x 50 mL). Se secan los extractos orgánicos combinados sobre Na_2SO_4, se filtran y se concentran *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con hexano/EtOAc (19:1 hasta 7:3 gradiente) para obtener el intermediario deseado (380 mg, 66%). CG-EM *m/z*: 266 (M^+).

(±)-2-Aminometil-5-[1-(1,1,2,2,2-pentafluoroetil)-etoxi]-piridina: Se agrega (±)-4-[1-(1,1,2,2,2-pentafluoroetil)-etoxi]-piridina-2-carbonitrilo (280 mg, 1 mmol), Pd/C 10% (tipo Degussa E101, 100 mg), metanol (20 mL) y ácido trifluoroacético (3 mL) a un recipiente de presión. Se presuriza el recipiente a 40 psi (2.812 kg/cm^2) con hidrógeno, y se agita la mezcla durante 1 h (se monitorea la reacción por CCD). Se filtra la mezcla a través de Celite y se lava la torta con etanol caliente seguido por diclorometano bajo una atmósfera de nitrógeno. Se concentra el filtrado *in vacuo* para obtener el producto crudo como una sal de ácido trifluoroacético. Se prepara la base libre usando cromatografía SCX, luego se purifica por cromatografía en gel de sílice eluyendo con diclorometano/amoniaco 2M en metanol (20:1) para obtener el compuesto del título (172 mg, 61%). CG-EM *m/z*: 270 (M^+).

Preparación 286

Clorohidrato de 4-(1-Metil-ciclohexilmetoxi)-bencilamina



4-(1-Metil-ciclohexilmetoxi)-benzamida: Se agrega una gota de DMF anhidro a una mezcla de ácido 4-(1-metil-

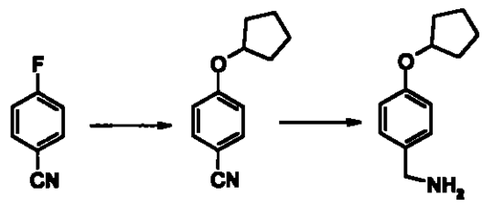
ciclohexilmetoxi)-benzoico (preparado al seguir el procedimiento described en *Chem. Pharm. Bull.* 1982, *30*, 3601-3616) (1 g, 4.03 mmol) y cloruro de tionilo (3.5 mL) a temperatura ambiente. Se agita la mezcla durante 1.5 h y luego se remueve el exceso de cloruro de tionilo *in vacuo*. Se toma el cloruro ácido crudo en THF anhidro (10 mL) y se agrega la solución resultante para enfriar NH_4OH concentrado (50 mL). Se agita durante 2.5 h a temperatura ambiente y se concentra *in vacuo*. Se colecta el sólido formado por medio de filtración y se seca *in vacuo* para obtener el intermediario deseado (0.94 g, 94%). EM (ER+) *m/z*: 248 $(M+H)^+$.

Clorohidrato de 4-(1-Metil-ciclohexilmetoxi)-bencilamina: Se agrega una solución de 4-(1-metil-ciclohexilmetoxi)-benzamida (6.82 g, 27.6 mmol) en THF anhidro (75 mL) gota a gota durante 45 min a una mezcla espesa de hidruro de aluminio litio (1.57 g, 41.3 mmol) en éter de dietilo (100 mL) a temperatura ambiente. Después de que la adición se completa, se calienta la mezcla a reflujo durante 5.5 h. Se enfría la mezcla de reacción con un baño de hielo y se apaga secuencialmente con agua (1.6 mL), NaOH acuoso 5N (1.6 mL) y agua (4.8 mL). Se agita la suspensión resultante durante 1 h y se remueven los sólidos formados por medio de filtración a través de Celite® eluyendo con THF. Se seca el filtrado sobre Na_2SO_4 y se trata la solución con un exceso de cloruro de

hidrógeno en éter de dietilo. Se concentra la mezcla *in vacuo* para obtener el compuesto del título (6.68 g, 90%). EM (ER+) *m/z*: 233 $(M+H)^+$.

Preparación 287

4-Ciclopentiloxi-bencilamina



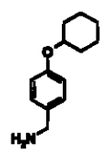
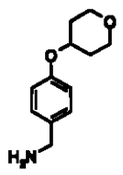
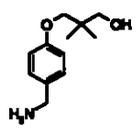
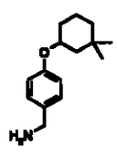
4-Ciclopentiloxi-benzonitrilo: Se suspende hidruro de sodio (336 mg, 2.8 mmol, 60% de suspensión en aceite mineral) en 1,4-dioxano anhidro (10 mL) bajo atmósfera de nitrógeno. Se agrega ciclopentanol (620 mg, 7.2 mmol) y se agita la solución resultante durante 30 min. Se agrega la solución preformada (3.35 mL, 2.4 mmol) a 4-fluorobenzonitrilo puro (240 mg, 2 mmol) en un tubo de microondas y se calienta la mezcla sellada a 100°C durante 30 min. Se enfría a temperatura ambiente y se concentra *in vacuo*. Se purifica por cromatografía en gel de sílice eluyendo con isohexano/EtOAc (95:5 hasta 1:1 gradiente) para obtener el intermediario deseado (300 mg, 80%). CG-EM *m/z*: 187 (M^+).

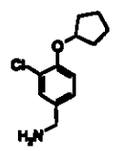
4-Ciclopentiloxi-bencilamina: Se agrega una solución de complejo BH_3-THF 1M en THF (4.8 mL, 4.8 mmol) a 4-ciclopentiloxi-benzonitrilo puro (300 mg, 1.6 mmol) y se agita la mezcla durante 3 h a temperatura ambiente y luego durante 3 h a reflujo. Se enfría a temperatura ambiente, se vacía la reacción en HCl acuoso 2N (10 mL) y se agita la mezcla durante 1 h a temperatura ambiente luego se concentra *in vacuo*. Se disuelve la mezcla cruda en metanol y se filtra a través de columna SCX eluyendo con metanol seguido por amoniaco 3M en metanol para obtener el compuesto del título (223 mg, 73%).

Preparaciones 288-292

Los compuestos de Preparaciones 288-292 se pueden preparar esencialmente como se describe en la Preparación 287 usando los alcoholes apropiados. Para Preparaciones 288, 290 y 291, bis(trimetilsilil)amida de sodio (1.2 equiv., solución 2M en THF) se usó como base en la primera etapa. Los rendimientos totales y datos EM (EI) se muestran en la Tabla a continuación.

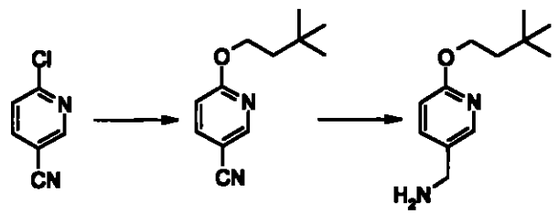
1350

Prep.	Estructura	Compuesto	Rendimiento (%)	EM (EI) m/z
288		4-Ciclohexiloxi-bencilamina	52	205 (M^+)
289		4-(Tetrahidro-piran-4-iloxi)-bencilamina	42	207 (M^+)
290		3-(4-Aminometil-fenoxi)-2,2-dimetil-propan-1-ol	38	209 (M^+)
291		(±)-4-(3,3-Dimetil-ciclohexiloxi)-bencilamina	37	233 (M^+)

292		3-cloro-4-ciclopentil oxi-bencilamina	42	225 (M^+)

Preparación 293

5-Aminometil-2-(3,3-dimetil-butoxi)-piridina



6-(3,3-Dimetil-butoxi)-nicotinonitrilo: Se agrega bis(trimetilsilil)amida de sodio (3.95 mL, 7.9 mmol, solución 2M en THF) a una solución de 3,3-dimetil-butan-1-ol (960 □L, 7.9 mmol) en THF anhidro (10 mL). Se agita durante 30 min a temperatura ambiente y luego se agrega una solución de 6-cloro-nicotinonitrilo (1 g, 7.2 mmol) en THF anhidro (5 mL). Se agita a temperatura ambiente durante la noche y luego se apaga la mezcla de reacción con $NaHCO_3$ acuoso saturado (100 mL). Se extrae la capa acuosa con diclorometano (3 x 100 mL) y se lava la capa orgánica con salmuera (100 mL). Se secan los extractos orgánicos combinados sobre $MgSO_4$ y se concentran *in vacuo* para dar el intermediario deseado como un sólido amarillo (1.4 g, 94%). CG-EM *m/z*: 204 (M^+).

5-Aminometil-2-(3,3-dimetil-butoxi)-piridina: Se disuelve 6-(3,3-dimetil-butoxi)-nicotinonitrilo (1.4 g, 6.86 mmol) en THF anhidro (10 mL) bajo nitrógeno y se agrega complejo BH_3-THF 1M en THF (20.6 mL, 20.6 mmol). Se agita la mezcla durante la noche bajo nitrógeno y luego Se vacía la reacción cuidadosamente en HCl acuoso 5N (20 mL). Se agita la suspensión resultante durante 6 h a temperatura ambiente. Luego se basifica al agregar NaOH acuoso 2N (50 mL) y se extrae con diclorometano (3 x 100 mL). Se secan los extractos orgánicos combinados sobre $MgSO_4$, se filtran y se concentran *in vacuo*. Se toma el aceite resultante en metanol y se filtra esto a través de una columna SCX eluyendo con metanol seguido por amoniaco 3M en metanol. Se concentra *in vacuo* para obtener el compuesto del título (754 g, 50%). CG-EM *m/z*: 208 (M^+).

Preparación 294

3,3-Dimetilbutanotiol

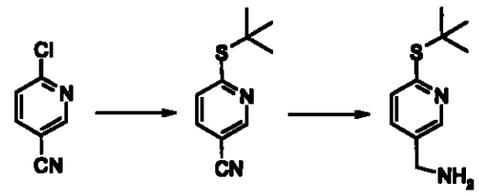


En cuatro tubos de microondas separados se agrega tiourea (630 mg, 8.3 mmol) a una solución de 1-cloro-3,3-dimetilbutano (0.5 g, 4.4 mmol) en etanol (5 mL) y se calienta en un tubo sellado en un reactor de microondas a 150 W a 100°C durante 4 h. Se enfría a temperatura ambiente luego

se deja durante tres días. Se combinan las reacciones y se concentran *in vacuo* para proporcionar un sólido blanco. Se agrega NaOH acuoso 2M (50 mL) y se calienta a reflujo durante la noche. Se enfría a temperatura ambiente luego se acidifica a un pH 2 con HCl acuoso 5M (20 mL). Se extrae en éter de dietilo (50 mL), se lava con salmuera (30 mL) luego se seca sobre $MgSO_4$ y se concentra *in vacuo* para dar el compuesto del título como un aceite claro (2 g, 100%).

Preparación 295

5-Aminometil-2-*tert*-butiltio-piridina



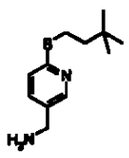
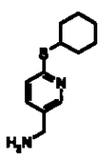
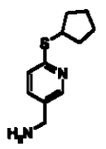
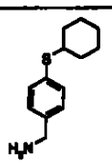
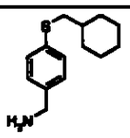
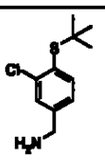
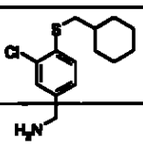
6-(*tert*-Butiltio)nicotinonitrilo: Se agrega etóxido de sodio (12 mL de 21% p/v en etanol, 36 mmol) a una solución de 2-metil-2-propanotiol (4.06 mL, 36 mmol) en etanol anhidro (90 mL) a 0°C bajo atmósfera de nitrógeno. Se agita la solución y se permite entibiar hasta temperatura ambiente durante 30 min. Se agrega 6-cloronicotinonitrilo (5 g, 36 mmol) y luego se calienta la reacción a reflujo durante la noche. Se enfría a temperatura ambiente, se agrega $NaHCO_3$ acuoso saturado y se concentra *in vacuo*. Se extrae en EtOAc o diclorometano y se lava con salmuera. Se seca sobre $MgSO_4$ y se concentra *in*

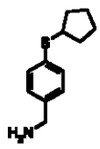
vacuo para dar el intermediario deseado como cristales anaranjados (6.31 g, 91%). EM (ER+) *m/z*: 193 $(M+H)^+$.

5-Aminometil-2-*tert*-butiltio-piridina: Se usa un método similar al Procedimiento General 6-5 para reaccionar 6-(*tert*-butiltio)nicotinonitrilo (4.4 g, 22.7 mmol) en THF anhidro (25 mL) con complejo BH3-THF 1M en THF (25 mL, 25 mmol). Se agrega HCl acuoso 5M (10 mL) cuidadosamente y se agita la mezcla durante la noche a temperatura ambiente. Se extrae into EtOAc, se lava con salmuera, se seca sobre $MgSO_4$ y se concentra *in vacuo* para dar an orange solid. Se disuelve la mezcla cruda en metanol y se filtra a través de an columna SCX eluyendo con metanol seguido por amoniaco 3M en metanol para obtener el compuesto del título (2.74 g, 61%). EM (ER+) *m/z*: 197 $(M+H)^+$.

Preparaciones 296-303

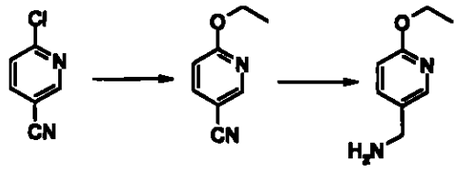
Los compuestos de las Preparaciones 296-303 se pueden preparar esencialmente como se describe en la Preparación 295 usando el tiol apropriado y 6-cloronicotinonitrilo (Preparaciones 296-298) o el fluoruro de arilo apropiado (Preparaciones 299-303). Los rendimientos totales y datos EM (ER+) se muestran en la Tabla a continuación.

Prep.	Estructura	Compuesto	Rendimiento (%)	EM (ER+) m/z
296		5-Aminometil-2-(3,3-dimetil-butiltio)-piridina	5	225 $(M+H)^+$
297		5-Aminometil-2-ciclohexiltio-piridina	47	223 $(M+H)^+$
298		5-Aminometil-2-ciclopentiltio-piridina	63	209 $(M+H)^+$
299		4-Ciclohexiltio-bencilamina	30	205 $(M+H-NH_3)^+$
300		4-Ciclohexilmetiltio-bencilamina	30	219 $(M+H-NH_3)^+$
301		4-*tert*-Butiltio-3-cloro-bencilamina	52	213 $(M+H-NH_3)^+$
302		4-Ciclohexilmetil	31	253 $(M+H-NH_3)^+$

		tio-3-cloro-bencilamina		
303		4-Ciclopentiltio-bencilamina	61	208 $(M+H)^+$

Preparación 304

5-Aminometil-2-etoxi-piridina



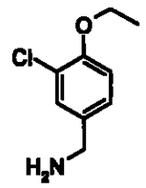
6-(Etoxi)nicotinonitrilo: Se agrega etóxido de sodio (1.6 mL de 21% p/v en etanol, 4.8 mmol) a una solución de 6-cloronicotinonitrilo (612 mg, 4.41 mmol) en etanol anhidro (15 mL) y se calienta la reacción a reflujo durante 3 h. Se enfría a temperatura ambiente y se agita durante la noche bajo atmósfera de nitrógeno. Se concentra *in vacuo* y se disuelve el residuo en diclorometano. Se lava con $NaHCO_3$ acuoso saturado, se seca sobre $MgSO_4$ y se concentra *in vacuo* para dar el intermediario deseado como un sólido blanco opaco (545 mg, 83%).

5-Aminometil-2-etoxi-piridina: Se agrega una solución de complejo BH_3-THF 1M en THF (7 mL, 7 mmol) a una

solución de 6-(etoxi)nicotinonitrilo (911 mg, 4.41 mmol) en THF anhidro (7 mL) y se agita la mezcla durante la noche a reflujo. Se agrega una segunda alícuota del complejo BH_3-THF 1M en THF (7 mL, 7 mmol) y se agita la mezcla durante la noche a reflujo. Se agrega HCl acuoso 5N (10 mL) cuidadosamente y se agita la mezcla durante la noche a temperatura ambiente. Se concentra *in vacuo* luego se disuelve la mezcla cruda en metanol y se filtra a través de una columna SCX eluyendo con metanol seguido por amoniaco 3M en metanol para obtener el compuesto del título (250 mg, 40%). EM (ER+) *m/z*: 153 $(M+H)^+$.

Preparación 305

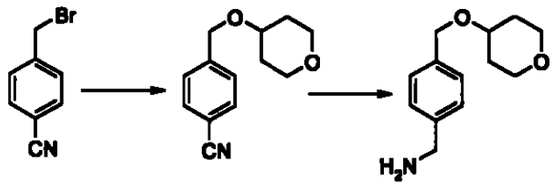
4-Etoxi-3-cloro-bencilamina



El compuesto de la Preparación 305 se puede preparar esencialmente como se describe en la Preparación 304 usando el fluoruro de arilo apropiado (38% de rendimiento, EM (ER+) *m/z* 169 $(M+H-NH_3)^+$).

Preparación 306

4-(Tetrahidro-piran-4-iloximetil)-bencilamina



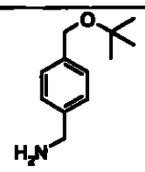
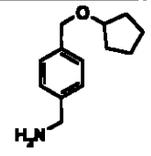
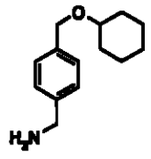
4-(Tetrahidro-piran-4-iloximetil)-benzonitrilo: Se agrega bis(trimetilsilil)amida de sodio (2.8 mL, 5.61 mmol, solución 2M en THF) a una solución de tetrahidro-piran-4-ol (572 mg, 5.61 mmol) en THF anhidro (20 mL) y se agita durante 30 min. Se agrega una solución de 4-bromometil-benzonitrilo (1 g, 5.1 mmol) en THF anhidro (5 mL) y se agita la mezcla resultante durante la noche a temperatura ambiente. Se concentra *in vacuo* y se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con ciclohexano/EtOAc (98:2 hasta 1:1 gradiente) para obtener el intermediario deseado como un sólido blanco (845 mg, 76%). CG-EM *m/z*: 217 (M^+).

4-(Tetrahidro-piran-4-iloximetil)-bencilamina: Se usa un método similar al Procedimiento General 6-5 para reducir 4-(tetrahidro-piran-4-iloximetil)-benzonitrilo (845 mg, 4 mmol). Se pone a reflujo durante la noche para obtener el compuesto del título (812 mg, 91%). EM (ER+) *m/z*: 222.2 $(M+H)^+$.

1359

Preparaciones 307-309

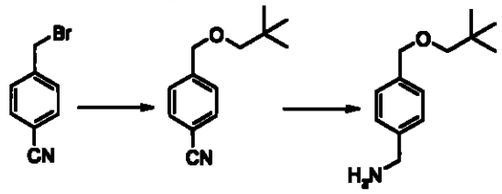
Los compuestos de las Preparaciones 307-309 se pueden preparar esencialmente como se describe en la Preparación 306 usando 4-bromometil-benzonitrilo y el alcohol apropiado. Los rendimientos totales y datos EM (ER+) se muestran en la Tabla a continuación.

Prep.	Estructura	**Compuesto**	**Rendimiento (%)**	**EM (ER+) m/z**
307		4-*tert*-Butoximetil-bencilamina	22	194 $(M+H)^+$
308		4-Ciclopentiloximetil-bencilamina	72	206 $(M+H)^+$
309		4-Ciclohexiloximetil-bencilamina	58	220 $(M+H)^+$

1360

Preparación 310

4-(2,2-Dimetil-propoximetil)-bencilamina



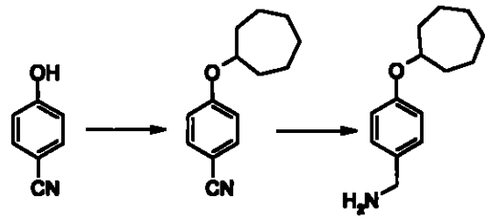
4-(2,2-Dimetil-propoximetil)-benzonitrilo: Se agrega bis(trimetilsilil)amida de sodio (3 mL, 6 mmol, solución 2M en THF) a una solución de 2,2-dimetil-1-propanol (528 mg, 6 mmol) en 1,4-dioxano anhidro. Se agita hasta que la suspensión se vuelve homogénea. Luego se agrega una solución de bromuro de 4-cianobencilo (980 mg, 5 mmol) en 1,4-dioxano anhidro (3 mL). Se calienta la mezcla en un horno de microondas a 100°C durante 30 min. Se enfría a temperatura ambiente, se agrega agua (50 mL) y se extrae con EtOAc (3 x 50 mL). Se secan los extractos orgánicos combinados sobre $MgSO_4$, y se concentran *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con isohexano/EtOAc (95:5 hasta 1:1 gradiente) para obtener el intermediario deseado (811 mg, 80%).

4-(2,2-Dimetil-propoximetil)-bencilamina: Se agrega complejo BH_3-THF 1M en THF (16 mL, 16 mmol) a 4-(2,2-dimetil-propoximetil)-benzonitrilo puro (3.043 g, 15 mmol) y se agita la mezcla durante la noche a temperatura ambiente. Se agrega metanol y se agita hasta que la evolución de hidrógeno se

detiene. Se concentra la solución *in vacuo*. Se disuelve la mezcla cruda en metanol y se filtra a través de una columna SCX eluyendo con metanol seguido por amoniaco 3M en metanol. Se concentra *in vacuo* para obtener el compuesto del título (3 g, 96%).

Preparación 311

4-Cicloheptiloxi-bencilamina



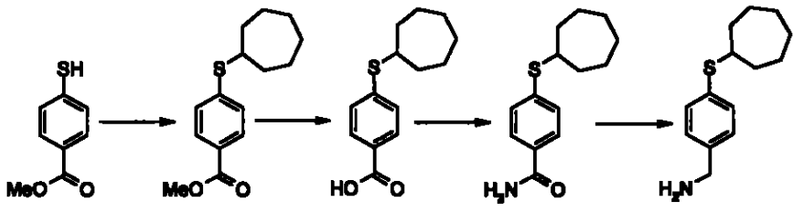
4-Cicloheptiloxi-benzonitrilo: Bajo una atmósfera de nitrógeno, se agrega 4-hidroxibenzonitrilo (4 g, 33.5 mmol), cicloheptanol (2.55 g, 22.3 mmol), tri-*n*-butilfosfina (8.25 mL, 33.5 mmol), y dipiperidina de azodicarboxilato (8.45 g, 33.5 mmol) a THF anhidro (60 mL) a 0°C. Se agita la mezcla a 0°C durante 1 h y luego a temperatura ambiente durante 12 h. se diluye con EtOAc (50 mL) y agua (50 mL). Se separan las capas y se extrae la fase acuosa con EtOAc (4 × 30 mL). Se lavan los extractos orgánicos combinados con agua (30 mL) y salmuera (20 mL). Se secan sobre Na_2SO_4, se filtran y se concentran *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de sílice (columna RediSep 120 g) eluyendo con hexano/EtOAc (gradiente 1:0 hasta 1:1 durante

1.25 h; 80 mL/min) para proporcionar el intermediario deseado como un aceite incoloro (2.77 g, 58%). EM (APCI) *m/z*: 216 $(M+H)^+$.

4-Cicloheptiloxi-bencilamina: Se disuelve 4-cicloheptiloxi-benzonitrilo (2 g, 9.29 mmol) en THF anhidro (20 mL) y se enfría hasta 0°C. Se agrega complejo de dimetilsulfuro de borano (2.8 mL, 27.9 mmol, solución 10-12 M), se agita a 0°C durante 0.5 h y luego se calienta a reflujo durante 1 h. Se enfría la mezcla a 0°C, se agrega metanol (5 mL) y se agita durante 15 min. Se agrega HCl acuoso 2M (15 mL) y se agita durante 30 min a temperatura ambiente. Se concentra la mezcla *in vacuo* y se purifica el residuo por cromatografía en gel de sílice (columna RediSep 45 g) eluyendo con un gradiente de diclorometano en cloroformo/metanol/hidróxido de amonio concentrado (80:18:2) durante 30 min (80 mL/min) para proporcionar el compuesto del título como un aceite incoloro (1.87 g, 97%). EM (APCI) *m/z*: 220 $(M+H)^+$.

Preparación 312

4-Cicloheptiltio-bencilamina



4-Cicloheptiltio-benzoato de metilo: Bajo una atmósfera de nitrógeno, se agrega 4-mercaptobenzoato de metilo (2.5 g, 15 mmol), cicloheptanol (2.55 g, 22.3 mmol), tri-*n*-butilfosfina (5.26 g, 26 mmol) y dipiperidina de azodicarboxilato (6.56 g, 26 mmol) a THF anhidro (50 mL) a 0°C. Se agita la mezcla a 0°C durante 1 h y luego a temperatura ambiente durante 12 h. se diluye con EtOAc (50 mL) y agua (50 mL) y se extrae la fase acuosa con EtOAc (4 × 30 mL). Se lavan los extractos orgánicos combinados con agua (30 mL) y salmuera (20 mL). Se seca la fase orgánica sobre Na_2SO_4, se filtra y se concentra *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de sílice (columna RediSep 120 g) eluyendo con hexano/EtOAc (gradiente 1:0 hasta 1:1 durante 1.25 h; 80 mL/min) para proporcionar el intermediario deseado como un aceite incoloro (1.12 g, 40%). EM (APCI) *m/z*: 265 $(M+H)^+$.

Ácido 4-cicloheptiltio-benzoico: Se agrega 4-cicloheptiltio-benzoato de metilo (1.1 g, 4.16 mmol) e hidróxido de sodio (500 mg, 12.5 mmol) a metanol (20 mL) y se agita durante la noche. Se agrega HCl acuoso 2M (20 mL) y se extrae la fase acuosa con diclorometano. Se lavan los extractos orgánicos combinados con agua (20 mL) y salmuera (20 mL). Se seca la solución orgánica sobre Na_2SO_4, se filtra y se concentra *in vacuo* para proporcionar el intermediario deseado como un sólido blanco (984 mg, 94%). EM (APCI) *m/z*: 251 $(M+H)^+$.

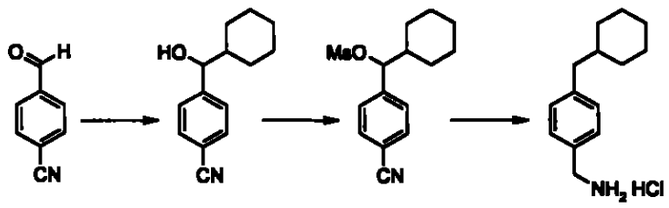
4-Cicloheptiltio-benzamida: Se agrega cloruro de tionilo (1.35 mL, 18.4 mmol) a una mezcla de ácido 4-cicloheptiltio-benzoico (984 mg, 3.93 mmol) en diclorometano (15 mL) a 0°C. Se calienta la mezcla a reflujo durante 1 h. Se enfría la mezcla a temperatura ambiente y se concentra *in vacuo*. Se disuelve el residuo en diclorometano (20 mL) y se enfría a 0°C. Se agrega trietilamina (1.1 mL, 7.86 mmol) y se burbujea gas de amoniaco a través de la solución. Se entibia la mezcla a temperatura ambiente y se agita durante 1 h. Se diluye con agua (20 mL) y se extrae la fase acuosa con diclorometano (3 × 20 mL). Se lavan los extractos orgánicos combinados con $NaHCO_3$ acuoso saturado (20 mL). Se seca la solución orgánica sobre Na_2SO_4, se filtra y se concentra *in vacuo* para proporcionar el intermediario deseado como un sólido blanco opaco (976 mg, 99%). EM (APCI) *m/z*: 250 $(M+H)^+$.

4-Cicloheptiltio-bencilamina: Bajo una atmósfera de nitrógeno, se agrega 4-cicloheptiltio-benzamida (976 mg, 3.91 mmol) a una mezcla espesa de hidruro de aluminio litio (0.398 mg, 11.7 mmol) en THF anhidro (25 mL) a 0°C. Se calienta la mezcla durante 1 h. Se enfría la mezcla a 0°C y se agrega éter de dietilo (50 mL). Cuidadosamente se agrega agua (0.4 mL), NaOH acuoso 3M (0.4 mL) y agua (1.2 mL). Se filtra el residuo sólido y se concentra el filtrado *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de sílice

(columna RediSep 45 g) eluyendo con un gradiente de diclorometano en cloroformo/metanol/hidróxido de amonio concentrado (80:18:2) durante 45 min (80 mL/min) para dar el compuesto del título como un aceite incoloro (530 mg, 57%). EM (ER+) *m/z*: 236 $(M+H)^+$.

Preparación 313

Clorohidrato 4-ciclohexilmetil-bencilamina



4-(Ciclohexil-hidroxi-metil)-benzonitrilo: Se disuelve 4-formil-benzonitrilo (5 g, 38.1 mmol) en tolueno anhidro (50 mL). Se agrega clorodiciclohexilborano (39 mL, 39 mmol, solución 1M en hexano) y 2,6-lutidina (4.25 mL, 39 mmol) y se agita la mezcla durante la noche a temperatura ambiente. Se enfría a 0°C, se agrega peróxido de hidrógeno acuoso (5.4 mL, 48 mmol, 30%) y NaOH acuoso 3M (16 mL, 48 mmol) y se agita durante 15 min. Se agrega EtOAc y se extrae la fase acuosa con EtOAc. Se lavan los extractos orgánicos combinados con agua y salmuera. Se seca la solución orgánica sobre Na_2SO_4, se filtra y se concentra *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de sílice (columna RediSep 45 g)

eluyendo con hexano/EtOAc (gradiente 1:0 hasta 1:1 durante 60 min; 80 mL/min) para proporcionar el intermediario deseado como un aceite claro (2.3 g, 23%). EM (APCI) *m/z*: 197 $(M-H_2O)^+$.

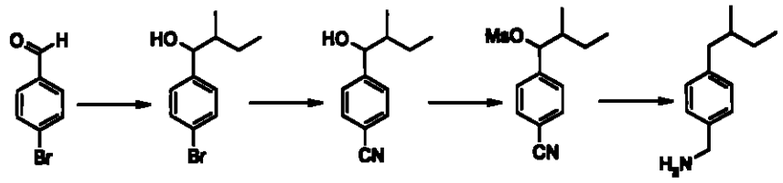
4-(Ciclohexil-metansulfoniloxi-metil)-benzonitrilo: Se disuelve 4-(ciclohexil-hidroxi-metil)-benzonitrilo (1 g, 4.66 mmol), y trietilamina (1.3 mL, 9.3 mmol) en diclorometano (20 mL). Se enfría la mezcla a 0°C, se agrega cloruro de metansulfonilo (1.49 mL, 5.34 mmol) y se agita la solución durante 2 h a 0°C. Se agrega agua (10 mL) y $NaHCO_3$ acuoso saturado (10 mL). Se separan las capas y se extrae nuevamente la fase acuosa con diclorometano (3 × 20 mL). Se combinan las capas orgánicas, se lava con agua (20 mL), se seca sobre Na_2SO_4, se filtra y se concentra *in vacuo* para proporcionar el intermediario deseado como un aceite amarillo (1.29 g, 94%). EM (APCI) *m/z*: 294 $(M+H)^+$.

Clorohidrato de 4-ciclohexilmetil-bencilamina: Se disuelve 4-(ciclohexil-metansulfoniloxi-metil)-benzonitrilo (1.36 g, 4.64 mmol) en éter de dietilo (20 mL) y se enfría la solución a 0°C. Se agrega hidruro de aluminio litio (528 mg, 13.9 mmol) y se agita la mezcla a 0°C durante 2 h y luego a temperatura ambiente durante 3 h. Se enfría la mezcla a 0°C y cuidadosamente se agrega agua (0.5 mL), NaOH acuoso 3M (0.55

mL), y agua (1.5 mL). Se filtra el residuo sólido y se concentra el filtrado *in vacuo*. Se disuelve la mezcla cruda en éter de dietilo y se burbujea cloruro de hidrógeno para formar un precipitado blanco. Se filtra y se seca el sólido in *vacuo* para proporcionar el compuesto del título como un sólido blanco (420 mg, 44%). EM (APCI) *m/z*: 204 $(M+H)^+$.

Preparación 314

4-(2-Metil-butil)-bencilamina



4-(1-Hidroxi-2-metil-butil)-1-bromo-benceno: Se agrega lentamente una solución de 2-bromo-butano (4.8 g, 35 mmol) en THF anhidro (20 mL) a una mezcla agitada de magnesio (980 mg, 37 mmol) y THF anhidro (10 mL) bajo una atmósfera de nitrógeno. Se calienta la mezcla a reflujo durante 30 min. Se enfría la mezcla a temperatura ambiente y se agrega 4-bromo-benzaldehído (5.36 g, 29 mmol). Después de agitar durante 5 min, Se enfría la mezcla en un baño de hielo y se acidifica con HCl acuoso 3N (50 mL). Se diluye la mezcla con agua y se extrae dos veces con éter de dietilo. Se lavan los extractos orgánicos combinados con agua y salmuera. Se seca la fase orgánica sobre Na_2SO_4, se filtra y se concentra *in vacuo*. Se

purifica por cromatografía en gel de sílice eluyendo con hexano/EtOAc (1:0, 20:1 y 1:1) para proporcionar el intermediario deseado como un aceite claro (2 g, 28%). EM (APCI) *m/z*: 243 $(M+H)^+$.

4-(1-Hidroxi-2-metil-butil)-benzonitrilo: Se agrega 4-(1-hidroxi-2-metil-butil)-1-bromo-benceno (1.9 g, 7.8 mmol), cianuro de zinc (1.82 g, 15.6 mmol), y tetraquistrifenilfosfina paladio(0) (260 mg, 0.22 mmol) a DMF anhidro (40 mL) bajo una atmósfera de nitrógeno. Se calienta la mezcla a 90°C durante 12 h. Se enfría la mezcla a temperatura ambiente, se diluye con agua y se extrae la fase acuosa dos veces con diclorometano. Se lavan los extractos orgánicos combinados con agua y salmuera. Se seca la solución orgánica sobre Na_2SO_4, se filtra y se concentra *in vacuo*. Se purifica por cromatografía en gel de sílice eluyendo con hexano/EtOAc (1:0 y 20:1) para proporcionar el intermediario deseado (1.2 g, 75%). EM (APCI) *m/z*: 190 $(M+H)^+$.

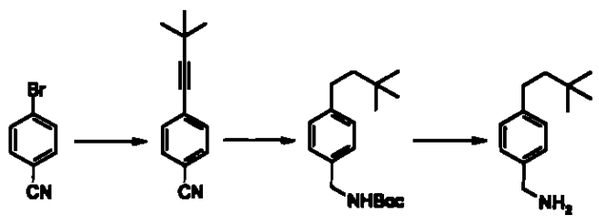
4-(1-Metansulfoniloxi-2-metil-butil)-benzonitrilo: Se agrega cloruro de metansulfonilo (540 mg, 4.72 mmol) a una solución de 4-(1-hidroxi-2-metil-butil)-benzonitrilo (800 mg, 4.23 mmol) y trietilamina (0.88 mL, 6.35 mmol) en diclorometano (10 mL) a 0°C. Se entibia la mezcla a temperatura ambiente y se agita durante 1 h. se diluye la mezcla con agua y

diclorometano. Se extrae la capa acuosa con diclorometano. Se lavan los extractos orgánicos combinados con agua. Se seca la solución orgánica sobre Na_2SO_4, se filtra y se concentra *in vacuo* para proporcionar el intermediario deseado como un aceite claro (1.38 g) que se usó sin purificación adicional. EM (APCI) *m/z*: 268 $(M+H)^+$.

4-(2-Metil-butil)-bencilamina: Bajo una atmósfera de nitrógeno, se agrega una mezcla de 4-(1-metansulfoniloxi-2-metil-butil)-benzonitrilo (1.3 g, 4.9 mmol) en éter de dietilo (5 mL) a una mezcla espesa de hidruro de aluminio litio (820 mg, 19.5 mmol) en éter de dietilo (25 mL) a 0°C. Se calienta la mezcla bajo reflujo durante 1 h. Se enfría la mezcla en un baño de hielo y se agrega agua (0.9 mL), NaOH acuoso 15% (0.9 mL) y agua (2.8 mL). Se aplica la mezcla a una columna de gel de sílice eluyendo con diclorometano y 5:1 diclorometano en cloroformo/metanol/hidróxido de amonio concentrado (80:18:2) para proporcionar el compuesto del título (450 mg, 52%). EM (ER+) *m/z*: 178 $(M+H)^+$.

Preparación 315

4-(3,3-Dimetil-butil)-bencilamina



4-(3,3-Dimetil-but-1-inil)-benzonitrilo: Se disuelve 4-bromobenzonitrilo (3 g, 16.48 mmol) en DMF anhidro (30 mL) en un tubo sellado. Se desgasifica la solución, se purga con nitrógeno y se agrega tris(dibencilidenoacetona)dipaladio(0) (453 mg, 0.49 mmol), yoduro de cobre(I) (188 mg, 0.99 mmol), trifenilfosfina (1.08 g, 4.12 mmol), trietilamina (10 mL) y 3,3-dimetilbutina (6.1 mL, 49.44 mmol). Se calienta la mezcla a 90°C durante la noche. Se enfría a temperatura ambiente, se agrega agua y se extrae la fase acuosa dos veces con EtOAc. Se secan los extractos orgánicos combinados sobre $MgSO_4$, se filtra y se concentra *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con hexano y hexano/EtOAc (19:1, 9:1) para dar el intermediario deseado como un sólido (2.75 g, 92%).

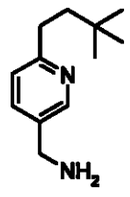
***N*-(*tert*-Butoxicarbonil)-4-(3,3-dimetil-butil)-bencilamina**: Se disuelve 4-(3,3-dimetil-but-1-inil)-benzonitrilo (0.85 g, 4.64 mmol) en metanol (50 mL). Se agrega Pd/C 10% (tipo Degussa E101, 0.68 g) y di-*tert*-butil-dicarbonato (1.21 g, 5.57 mmol). Se somete la mezcla a hidrogenación bajo presión atmosférica (globo) durante 6 h. Se filtra el catalizador a través de Celite® y se concentra el filtrado *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con hexano y hexano/EtOAc (9:1, 4:1) para

proporcionar el intermediario deseado como un aceite (1.25 g, 93%). EM (ER+) *m/z*: 314 $(M+Na)^+$.

4-(3,3-Dimetil-butil)-bencilamina: Se agrega cloruro de hidrógeno 4N en dioxano (15 mL) a una solución agitada de *N*-(*tert*-butoxicarbonil)-4-(3,3-dimetil-butil)-bencilamina (1.25 g, 4.29 mmol) en metanol (20 mL) y se agita a temperatura ambiente durante la noche. Se concentra *in vacuo* y se lava el sólido con éter de dietilo. Se suspende el sólido en diclorometano y $NaHCO_3$ acuoso saturado y se agita hasta que ambas fases se limpian (15 min). Se extrae la fase acuosa dos veces con diclorometano. Se secan los extractos orgánicos combinados sobre $MgSO_4$, se filtran y se concentran *in vacuo* para dar el compuesto del título como un aceite (0.654 g, 80%) que se usó sin ninguna purificación adicional. EM (ER+) *m/z*: 192 $(M+H)^+$.

Preparación 316

3-Aminometil-6-(3,3-dimetil-butil)-piridina

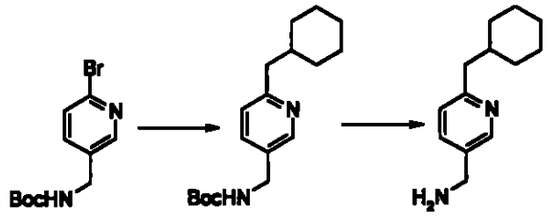


El compuesto del título se puede preparar esencialmente como se describe en la Preparación 315 al usar 6-

bromonicotinonitrilo (45% de rendimiento, EM (ER+) *m/z* 193 $(M+H)^+$).

Preparación 317

3-Aminometil-6-ciclohexilmetil-piridina



3-*tert*-Butoxicarbonilaminometil-6-ciclohexilmetil-piridina:

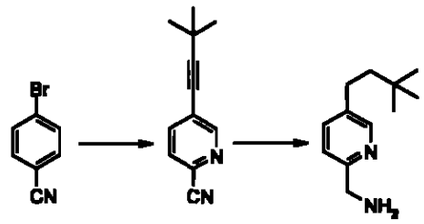
Se disuelve 2-bromo-5-*tert*-butoxicarbonilaminometil-piridina (500 mg, 1.74 mmol) en THF anhidro (5 mL) en un tubo sellado. Se desgasifica la solución, se purga con nitrógeno y se agrega 1,1'-[bis(difenilfosfina)ferroceno]dicloropaladio(II) (127 mg, 0.174 mmol) y bromuro de ciclohexilmetilzinc 0.5M en THF (10.4 mL, 5.22 mmol). Se calienta la mezcla a 60°C durante la noche. Se enfría a temperatura ambiente y se diluye la mezcla de reacción con EtOAc. Se agrega agua y se filtra el precipitado sobre Celite®. Se seca la fase orgánica sobre $MgSO_4$, se filtra y se concentra *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con hexano y hexano/EtOAc (4:1, 3:2) para dar el intermediario deseado como un aceite (359 mg, 68%). EM (ER+) *m/z*: 305 $(M+H)^+$.

1373

3-Aminometil-6-ciclohexilmetil-piridina: Se agrega cloruro de hidrógeno 4N en dioxano (10 mL) a una solución de 3-*tert*-butoxicarbonilaminometil-6-ciclohexilmetil-piridina (345 mg, 1.13 mmol) en EtOAc (10 mL) y se agita durante la noche. Se concentra *in vacuo*, se suspende el sólido obtenido en éter de dietilo y se agrega hexano. Se filtra y se lava el sólido con hexano. Se suspende el sólido en diclorometano, se agrega $NaHCO_3$ acuoso saturado y se agita hasta que ambas fases se limpian (15 min). Se extrae la fase acuosa dos veces con dichorometano. Se secan los extractos orgánicos combinados sobre $MgSO_4$, se filtran y se concentran *in vacuo* para obtener el compuesto del título como un aceite (205 mg, 97%) que se usó sin ninguna purificación adicional. EM (ER+) *m/z*: 205 $(M+H)^+$.

Preparación 318

2-Aminometil-5-(3,3-dimetil-butil)-piridina



5-(3,3-Dimetil-but-1-inil)-2-ciano-piridina: Se disuelve 5-bromo-2-ciano-piridina (316 mg, 1.72 mmol) en DMF

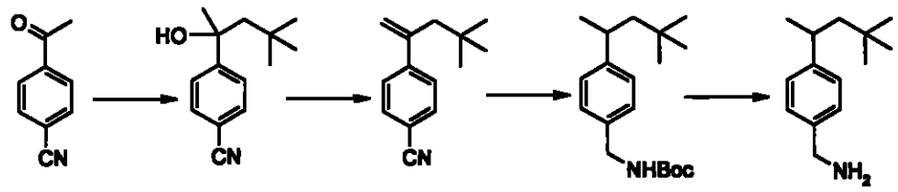
anhidro (7 mL) en un tubo sellado. Se desgasifica la solución, se purga con nitrógeno y se agrega tris(dibencilidenoacetona)dipaladio(0) (47 mg, 0.05 mmol), yoduro de cobre(I) (20 mg, 0.1 mmol), trifenilfosfina (113 mg, 0.43 mmol), trietilamina (2 mL) y 3,3-dimetilbutino (0.64 mL, 5.16 mmol). Se calienta la mezcla a 90°C durante la noche. Se enfría a temperatura ambiente, se agrega agua y se extrae la fase acuosa dos veces con EtOAc. Se secan los extractos orgánicos combinados sobre $MgSO_4$, se filtran y se concentran *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con hexano y hexano/EtOAc (19:1) para dar el intermediario deseado como un sólido (310 mg, 97%).

2-Aminometil-5-(3,3-dimetil-butil)-piridina: Se disuelve 5-(3,3-dimetil-but-1-inil)-2-ciano-piridina (255 mg, 1.5 mmol) en metanol (15 mL). Se agrega Pd/C 10% (tipo Degussa E101, 230 mg) y se expone la mezcla a hidrogenación bajo presión atmosférica (globo) durante la noche. Se filtra el catalizador a través de Celite® y se concentra el filtrado *in vacuo* para proporcionar el compuesto del título como un sólido (231 mg, 87%) que se usó sin ninguna purificación adicional. EM (ER+) *m/z*: 193 $(M+H)^+$.

1335

Preparación 319

4-(1,3,3-Trimetil-butil)-bencilamina



4-(1-Hidroxi-1,3,3-trimetil-butil)-benzonitrilo: se disuelve 4-acetilbenzonitrilo (1 g, 6.88 mmol) en éter de dietilo/THF (1:1, 60 mL) y se enfría la solución a 0°C. Se agrega cloruro de neopentilmagnesio 1M en éter de dietilo (8.3 mL, 8.3 mmol) bajo nitrógeno y se agita la mezcla a temperatura ambiente durante la noche. Se agrega NH_4Cl acuoso saturado y se extrae la mezcla dos veces con EtOAc. Se secan los extractos orgánicos combinados sobre $MgSO_4$, se filtran y se concentran *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con hexano y hexano/EtOAc (19:1, 9:1) para dar el intermediario deseado (364 mg, 24%).

4-(3,3-Dimetil-1-metilen-butil)-benzonitrilo: Se agrega monohidrato del ácido *p*-toluensulfónico (308 mg, 1.62 mmol) a una solución de 4-(1-hidroxi-1,3,3-trimetil-butil)-benzonitrilo (352 mg, 1.62 mmol) en tolueno (10 mL). Se calienta la solución hasta 100°C durante 30 min. Se enfría la mezcla de reacción a temperatura ambiente, se diluye la

mezcla de reacción con EtOAc y se lava la fase orgánica con $NaHCO_3$ acuoso saturado. Se seca la fase orgánica sobre $MgSO_4$, se filtra y se concentra *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con hexano y hexano/EtOAc (98:2, 19:1) para dar el intermediario deseado como un aceite (200 mg, 62%).

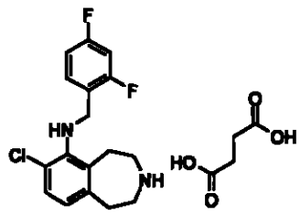
N-(*tert*-Butoxicarbonil)-4-(1,3,3-trimetil-butil)-bencilamina: Se disuelve 4-(3,3-dimetil-1-metilen-butil)-benzonitrilo (164 mg, 0.82 mmol) en metanol (15 mL). Se agrega Pd/C 10% (tipo Degussa E101, 130 mg) y di-*tert*-butil-dicarbonato (197 mg, 0.902 mmol). Se somete la mezcla a hidrogenación bajo presión atmosférica (globo) durante 3 h. Se filtra el catalizador a través de Celite® y se concentra el filtrado *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con hexano y hexano/EtOAc (19:1, 9:1) para proporcionar el intermediario deseado como un aceite (227 mg, 90%). EM (ER+) *m/z*: 328 $(M+Na)^+$.

4-(1,3,3-Trimetil-butil)-bencilamina: Se agrega cloruro de hidrógeno 4N en dioxano (10 mL) a una solución agitada de *N*-(*tert*-butoxicarbonil)-4-(1,3,3-trimetil-butil)-bencilamina (225 mg, 0.74 mmol) en EtOAc (15 mL) y se agita la mezcla a temperatura ambiente durante la noche. Se concentra *in vacuo* y se lava el sólido con éter de dietilo. Se suspende el

sólido en diclorometano y $NaHCO_3$ acuoso saturado y se agita hasta que ambas fases se limpian (15 min). Se extrae la fase acuosa dos veces con diclorometano. Se secan los extractos orgánicos combinados sobre $MgSO_4$, se filtran y se concentran *in vacuo* para dar el compuesto del título como un aceite (0.136 g, 90%) que se usó sin ninguna purificación adicional. EM (ER+) *m/z*: 206 $(M+H)^+$.

Ejemplo 537

Succinato de 7-cloro-6-(2,4-difluorobencilamino)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



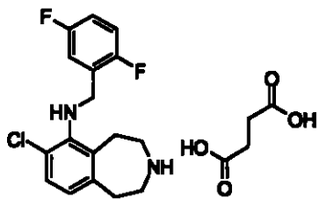
Se usa un método similar al Procedimiento General 5-1 para reaccionar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (3 g, 7.06 mmol), acetato de paladio(II) (0.16 g, 0.71 mmol), BINAP (0.88 g, 1.41 mmol), 2,4-difluorobencilamina (3.03 g, 21.18 mmol) y carbonato de cesio (3.22 g, 9.88 mmol) en tolueno desgasificado (120 mL). Se desgasifica la mezcla con purga vacío/nitrógeno y se calienta a 100°C durante 16 h. Se enfría la mezcla a

temperatura ambiente, se diluye con EtOAc, se filtra a través de Celite® y se concentra *in vacuo* para dar un aceite café. Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con hexano y luego hexano/THF (95:5) para obtener 7-cloro-6-(2,4-difluorobencilamino)-3-(2,2,2,trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina como aceite (2.25 g, 76%). EM (ER+) *m/z*: 419 $(M+H)^+$.

Se usa un método similar al Procedimiento General 1-2, usando 7-cloro-6-(2,4-difluorobencilamino)-3-(2,2,2,trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (2.2 g, 5.26 mmol), para dar la base libre del compuesto del título como un aceite (1.66 g, 98%) que se solidifica durante el reposo a temperatura ambiente y se usó sin purificación adicional. EM (ER+) *m/z*: 323 $(M+H)^+$. Se usa un método similar al Procedimiento General 2-1, usando 7-cloro-6-(2,4-difluorobencilamino)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (1.66 g, 5.14 mmol) para dar el compuesto del título como un sólido blanco (2.03 g, 90%). EM (ER+) *m/z*: 323 $(M+H)^+$.

Ejemplo 538

Succinato de 7-cloro-6-(2,5-difluorobencilamino)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina

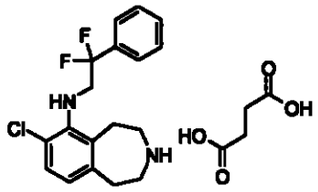


1399

El Ejemplo 538 se puede preparar esencialmente como se describe en el Ejemplo 537 usando 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina y 2,5-difluorobencilamina (68% de rendimiento, EM (ER+) *m/z* 323 $(M+H)^+$).

Ejemplo 539

Succinato de 7-cloro-6-(2,2-difluoro-2-fenil-etilamino)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



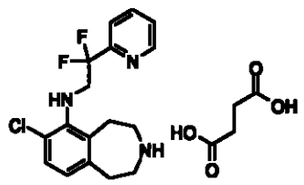
Se usa un método similar al Procedimiento General 5-3 para reaccionar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (541 mg, 1.274 mmol), acetato de paladio(II) (57 mg, 0.225 mmol), tris(dibencilidenoacetona)dipaladio(0) (117 mg, 0.127 mmol), BINAP (0.506 g, 0.764 mmol), 2,2-difluoro-2-fenil-etilamina (400 mg, 2.547 mmol) y carbonato de cesio (830 mg, 2.548 mmol) en tolueno desgasificado (35 mL). Se desgasifica la mezcla con purga vacío/nitrógeno y se calienta a 100°C durante 16 h. Se enfría la mezcla a temperatura ambiente, se diluye con EtOAc y se filtra sobre Celite®. Se purifica la mezcla cruda por cromatografía en gel

de sílice eluyendo con hexano y hexano/EtOAc (19:1) para obtener 7-cloro-6-(2,2-difluoro-2-fenil-etilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina como aceite (335 mg, 61%). EM (ER+) *m/z*: 433 $(M+H)^+$.

Se usa un método similar al Procedimiento General 1-2, usando 7-cloro-6-(2,2-difluoro-2-fenil-etilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (317 mg, 0.734 mmol), para dar la base libre del compuesto del título como un aceite (215 mg, 87%) que se usó sin purificación adicional. EM (ER+) *m/z*: 337 $(M+H)^+$. Se usa un método similar al Procedimiento General 2-1, usando 7-cloro-6-(2,2-difluoro-2-fenil-etilamino)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (215 mg, 0.64 mmol) para dar el compuesto del título como un sólido blanco (220 mg, 76%). EM (ER+) *m/z*: 337 $(M+H)^+$.

Ejemplo 540

Succinato de 7-cloro-6-(2,2-difluoro-2-piridin-2-il-etilamino)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina

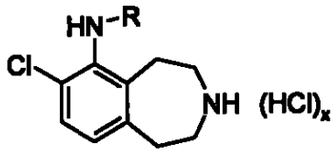


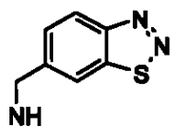
El Ejemplo 540 se puede preparar esencialmente como se describe en el Ejemplo 539 usando 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-

tetrahidro-1*H*-benzo[*d*]azepina y 2,2-difluoro-2-piridin-2-il-etilamina (preparado al seguir el procedimiento descrito en *J. Med. Chem.* 2003, *46*, 461-473), (37% de rendimiento, EM (ER+) *m/z* 338 $(M+H)^+$).

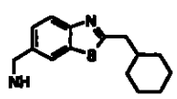
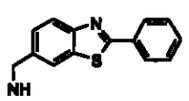
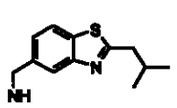
Ejemplos 541-544

Los Ejemplos 541-544 se pueden preparar esencialmente como se describe en el Ejemplo 262 al usar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina y la amina apropiada. Los rendimientos totales y datos EM (ER+) se muestran en la Tabla a continuación.



Ej.	NH-R	Compuesto	Rendimiento (%)	EM (ER+) *m/z*
541		Clorohidrato 7-cloro-6-(benzo[1,2,3]tiadiazol-6-il-metilamino)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	12	345 $(M+H)^+$

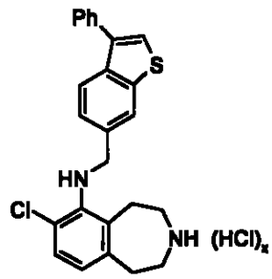
1382

542		Clorohidrato 7-cloro-6-(2-ciclohexilmetil-benzotiazol-6-il-metilamino)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	50	441 $(M+H)^+$
543		Clorohidrato 7-cloro-6-[(2-fenil-benzotiazol-6-il-metil)-amino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	27	420 $(M+H)^+$
544		Clorohidrato 7-cloro-6-(2-isobutil-benzotiazol-5-il-metilamino)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	37	400 $(M+H)^+$

1383

Ejemplo 545

Clorohidrato de 7-cloro-6-(3-fenil-benzotiofen-6-il-metilamino)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



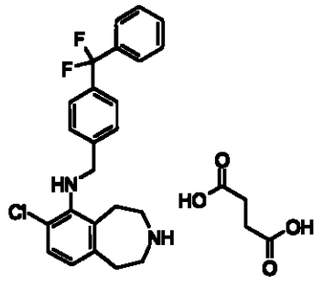
Se usa un método similar al Procedimiento General 5-2, usando 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (0.28 g, 0.66 mmol) y 6-aminometil-3-fenil-benzotiofeno (0.19 g, 0.8 mmol) con tris(dibencilidenoacetona)dipaladio(0) (120 mg, 0.13 mmol), BINAP (165 mg, 0.26 mmol) y carbonato de cesio (0.3 g, 0.93 mmol) a 90°C durante 17 h, para obtener 7-cloro-6-(3-fenil-benzotiofen-6-il-metilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina, que se usa sin purificación adicional (234 mg, 69%). EM (ER+) *m/z*: 515 (M+H)+.

Se usa un procedimiento similar al Procedimiento General 1-1 para desproteger 7-cloro-6-(3-fenil-benzotiofen-6-il-metilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (234 mg, 0.45 mmol) en amoniaco 7M en metanol

(20 mL). Se purifica por CLAR de fase inversa (Vydac C18 5 x 25 cm, 30% hasta 100% acetonitrilo en solución TFA-agua 0.1%). Se recubre la base libre por cromatografía SCX y forma la sal de conformidad con el Procedimiento General 2-3 para obtener el compuesto del título (38 mg, 17%). EMAR (ER+) *m/z*: 419.1340 $(M+H)^+$.

Ejemplo 546

Succinato 7-cloro-6-[(difluoro-fenil-metil)-bencilamino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina

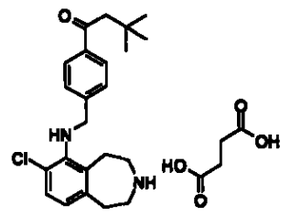


Se usa un procedimiento similar al Ejemplo 262 usando 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina y 4-(difluoro-fenil-metil)-bencilamina, seguido por desprotección de conformidad con el Procedimiento General 1-2 y formación de sal de conformidad con el Procedimiento General 2-1 para obtener el compuesto del título (175 mg, 77%). EM (ER+) *m/z* 413 $(M+H)^+$.

1305

Ejemplo 547

Succinato de 7-cloro-6-[4-(3,3-dimetil-butiril)-bencilamino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



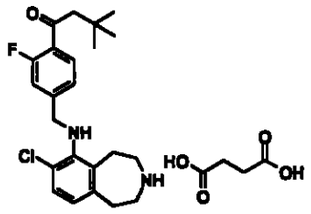
Se usa un método similar al Procedimiento General 5-3 para reaccionar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (250 mg, 0.588 mmol), acetato de paladio(II) (26 mg, 0.118 mmol), tris(dibencilidenoacetona)dipaladio(0) (53 mg, 0.059 mmol), BINAP (0.22 g, 0.353 mmol), 4-(3,3-dimetil-butiril)-bencilamina (241 mg, 1.176 mmol) y carbonato de cesio (383 mg, 1.176 mmol) en tolueno desgasificado (10 mL). Se desgasifica la mezcla con purga vacío/nitrógeno y se calienta hasta 100°C durante 16 h. Se enfría la mezcla a temperatura ambiente, se diluye con EtOAc y se lava con $NaHCO_3$ acuoso saturado. Se seca la capa orgánica sobre Na_2SO_4, se filtra y se concentra *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con hexano y luego hexano/EtOAc (90:10, 85:15) para obtener 7-cloro-6-[4-(3,3-dimetil-butiril)-bencilamino]-3-(2,2,2-

trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina como aceite (185 mg, 65%). EM (ER+) *m/z*: 481 $(M+H)^+$.

Se usa un método similar al Procedimiento General 1-2, usando 7-cloro-6-[4-(3,3-dimetil-butiril)-bencilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (165 mg, 0.343 mmol), para dar la base libre del compuesto del título como un aceite (130 mg, 98%) que se usó sin purificación adicional. EM (ER+) *m/z*: 385 $(M+H)^+$. Se usa un método similar al Procedimiento General 2-1, usando 7-cloro-6-[4-(3,3-dimetil-butiril)-bencilamino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (130 mg, 0.338 mmol) para dar el compuesto del título como un sólido blanco (128 mg, 76%). EM (ER+) *m/z*: 385 $(M+H)^+$.

Ejemplo 548

Succinato de 7-cloro-6-[4-(3,3-dimetil-butiril)-3-fluoro-bencilamino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



Se usa un método similar al Procedimiento General 5-2 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-

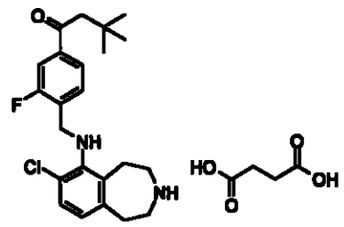
benzo[*d*]azepina (96 mg, 0.225 mmol) con 4-(3,3-dimetil-butiril)-3-fluoro-bencilamina (105 mg, 0.45 mmol) al usar tris(dibencilidenoacetona)dipaladio(0) (41 mg, 0.045 mmol), BINAP (56 mg, 0.09 mmol) y carbonato de cesio (103 mg, 0.315 mmol) en tolueno anhidro (15 mL). Se purifica por cromatografía en gel de sílice eluyendo con hexano/EtOAc (9:1) para dar 7-cloro-6-[4-(3,3-dimetil-butiril)-3-fluoro-bencilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina como un aceite amarillo (54 mg, 49%). EM (ER+) *m/z*: 499 $(M+H)^+$.

Se usa un método similar al Procedimiento General 1-2, usando 7-cloro-6-[4-(3,3-dimetil-butiril)-3-fluoro-bencilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (53 mg, 0.11 mmol) para dar la base libre del compuesto del título como un aceite amarillo (42 mg, 96%) que se usó sin purificación adicional. Se usa un método similar al Procedimiento General 2-1, usando 7-cloro-6-[4-(3,3-dimetil-butiril)-3-fluoro-bencilamino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (42 mg, 0.105 mmol) para dar el compuesto del título como un sólido blanco (30 mg, 60%). EM (ER+) *m/z*: 403 $(M+H)^+$.

1388

Ejemplo 549

Succinato de 7-cloro-6-[4-(3,3-dimetil-butiril)-2-fluoro-bencilamino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



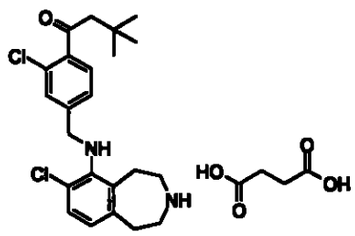
Se usa un método similar al Procedimiento General 5-2 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (127 mg, 0.3 mmol) con 4-(3,3-dimetil-butiril)-2-fluoro-bencilamina (120 mg, 0.54 mmol) al usar tris(dibencilidenoacetona)dipaladio(0) (27 mg, 0.03 mmol), BINAP (40 mg, 0.06 mmol) y carbonato de cesio (137 mg, 0.42 mmol) en tolueno anhidro (20 mL). Se purifica por cromatografía en gel de sílice eluyendo con hexano/EtOAc (19:1 y 9:1) seguido por CLAR de fase inversa [Zorbax Bonus RP, 5 □M 21.2 x 100 mm, eluyendo con agua/acetonitrilo (TFA 0.05% en cada uno) (35:65 hasta 15:85 gradiente durante 5 min), relación de flujo 25 mL/min, detector UV (230 nm)] para dar 7-cloro-6-[4-(3,3-dimetil-butiril)-2-fluoro-bencilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-

benzo[*d*]azepina como un aceite (72 mg, 49%). EM (ER+) ***m/z***: 499 $(M+H)^+$.

Se usa un método similar al Procedimiento General 1-2, usando 7-cloro-6-[4-(3,3-dimetil-butiril)-2-fluoro-bencilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (26 mg, 0.052 mmol) para dar la base libre del compuesto del título como un aceite amarillo (19 mg, 91%) que se usó sin purificación adicional. Se usa un método similar al Procedimiento General 2-1, usando 7-cloro-6-[4-(3,3-dimetil-butiril)-2-fluoro-bencilamino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (18 mg, 0.045 mmol) para dar el compuesto del título como un sólido blanco (20 mg, 86%). EM (ER+)m/z: 403 $(M+H)^+$.

Ejemplo 550

Succinato de 7-cloro-6-[3-cloro-4-(3,3-dimetil-butiril)-bencilamino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



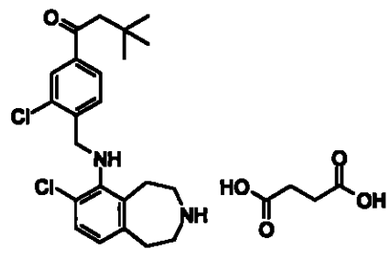
Se usa un método similar al Procedimiento General 5-2 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-

trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (90 mg, 0.212 mmol) con 3-cloro-4-(3,3-dimetil-butiril)-bencilamina (102 mg, 0.43 mmol) al usar tris(dibencilidenoacetona)dipaladio(0) (39 mg, 0.0424 mmol), BINAP (53 mg, 0.0848 mmol) y carbonato de cesio (97 mg, 0.297 mmol) en tolueno anhidro (10 mL). Se purifica por cromatografía en gel de sílice eluyendo con hexano/EtOAc (9:1) para dar 7-cloro-6-[3-cloro-4-(3,3-dimetil-butiril)-bencilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina como un aceite (72 mg, 49%). EM (ER+) *m/z*: 516 $(M+H)^+$.

Se usa un método similar al Procedimiento General 1-2, usando 7-cloro-6-[3-cloro-4-(3,3-dimetil-butiril)-bencilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (70 mg, 0.136 mmol) para dar la base libre del compuesto del título como un aceite amarillo (57 mg, 99%) que se usó sin purificación adicional. Se usa un método similar al Procedimiento General 2-1, usando 7-cloro-6-[3-cloro-4-(3,3-dimetil-butiril)-bencilamino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (57 mg, 0.136 mmol) para dar el compuesto del título como un sólido blanco (50 mg, 68%). EM (ER+) *m/z*: 420 $(M+H)^+$.

Ejemplo 551

Succinato de 7-cloro-6-[2-cloro-4-(3,3-dimetil-butiril)-bencilamino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



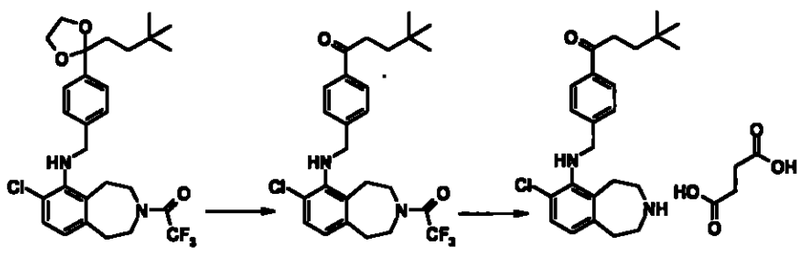
Se usa un método similar al Procedimiento General 5-2 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (300 mg, 0.71 mmol) con 1-(4-aminometil-3-cloro-fenil)-3,3-dimetil-butan-1-ona (338 mg, 1.41 mmol) al usar tris(dibencilidenoacetona)dipaladio(0) (130 mg, 0.142 mmol), BINAP (177 mg, 0.284 mmol) y carbonato de cesio (324 mg, 0.994 mmol) en tolueno anhidro (31 mL). Se purifica por cromatografía en gel de sílice eluyendo con hexano/EtOAc (92:8) seguido por CLAR de fase inversa [Hichrom Kromasil C18, 5 □M 21.2 x 100 mm, eluyendo con agua/acetonitrilo (TFA 0.05% en cada uno) (1:4 hasta 1:19 gradiente durante 5 min), relación de flujo 25 mL/min, detector UV (230 nm)] para dar 7-cloro-6-[2-cloro-4-(3,3-dimetil-butiril)-bencilamino]-3-

(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina como un aceite (77 mg, 21%). EM (ER+) *m/z*: 516 $(M+H)^+$.

Se usa un método similar al Procedimiento General 1-2, usando 7-cloro-6-[2-cloro-4-(3,3-dimetil-butiril)-bencilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (77 mg, 0.15 mmol) para dar la base libre del compuesto del título como un aceite amarillo (93 mg, 99%) que se usó sin purificación adicional. Se usa un método similar al Procedimiento General 2-1, usando 7-cloro-6-[2-cloro-4-(3,3-dimetil-butiril)-bencilamino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (63 mg, 0.15 mmol) para dar el compuesto del título como un sólido blanco (52 mg, 65%). EM (ER+) *m/z*: 420 $(M+H)^+$.

Ejemplo 552

Succinato de 7-cloro-6-[4-(4,4-dimetil-pentanoil)-bencilamino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



Se usa un método similar al Procedimiento General 5-2 para reaccionar 7-cloro-3-(2,2,2-trifluoroacetil)-6-

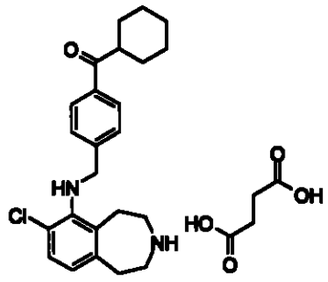
trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (233 mg, 0.55 mmol), tris(dibencilidenoacetona)dipaladio(0) (50 mg, 0.055 mmol), BINAP (73 mg, 0.11 mmol), 4-[2-(3,3-dimetil-butil)-[1,3]dioxolan-2-il]-bencilamina (263 mg, 1 mmol) y carbonato de cesio (250 mg, 0.77 mmol) en tolueno desgasificado (20 mL). Se desgasifica la mezcla con purga vacío/nitrógeno y se calienta a 100°C durante 14 h. Se enfría la mezcla a temperatura ambiente, se diluye con EtOAc y se filtra a través de Celite®. Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con hexano y luego hexano/EtOAc (19:1, 9:1 y 4:1) para obtener 7-cloro-6-{4-[2-(3,3-dimetil-butil)-[1,3]dioxolan-2-il]-bencilamina}-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina como aceite (185 mg, 63%). EM (ER+) *m/z*: 539 $(M+H)^+$.

Se disuelve 7-cloro-6-{4-[2-(3,3-dimetil-butil)-[1,3]dioxolan-2-il]-bencilamina}-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (185 mg, 0.34 mmol) en metanol (10 mL) y se agrega HCl acuoso 1N (2 mL). Se agita la mezcla durante 2 h y se concentra *in vacuo*. Se disuelve el residuo en diclorometano y se lava con $NaHCO_3$ acuoso saturado. Se seca la fase orgánica sobre $MgSO_4$, se filtra y se concentra *in vacuo* para obtener 7-cloro-6-[4-(4,4-dimetil-pentanoil)-bencilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina como un aceite (150 mg, 89%).

Se usa un método similar al Procedimiento General 1-2, usando 7-cloro-6-[4-(4,4-dimetil-pentanoil)-bencilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (150 mg, 0.3 mmol), para dar la base libre del compuesto del título como un aceite (100 mg, 83%) que se usó sin purificación adicional. Se usa un método similar al Procedimiento General 2-1, usando 7-cloro-6-[4-(4,4-dimetil-pentanoil)-bencilamino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (100 mg, 0.25 mmol) para dar el compuesto del título como un sólido (100 mg, 78%). EM (ER+) *m/z*: 399 $(M+H)^+$.

Ejemplo 553

Succinato de 7-cloro-6-(4-ciclohexanocarbonil-bencilamino)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



Se usa un método similar al Procedimiento General 5-2 para reaccionar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (150 mg, 0.353 mmol), tris(dibencilidenoacetona)dipaladio(0) (64 mg, 0.071 mmol),

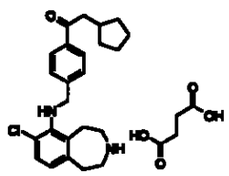
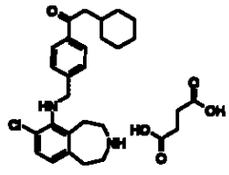
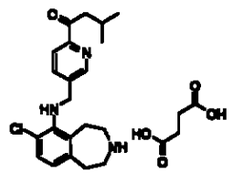
BINAP (88 mg, 0.141 mmol), 4-ciclohexanocarbonil-bencilamina (125 mg, 0.576 mmol) y carbonato de cesio (230 mg, 0.706 mmol) en tolueno desgasificado (10 mL). Se desgasifica la mezcla con purga vacío/nitrógeno y se calienta a 100°C durante 6 h. Se enfría la mezcla a temperatura ambiente, se diluye con EtOAc y se filtra a través de Celite®. Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con hexano y luego hexano/EtOAc (90:10 y 85:15) para obtener 7-cloro-6-(4-ciclohexanocarbonil-bencilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina como aceite (130 mg, 75%). EM (ER+) *m/z*: 493 $(M+H)^+$.

Se usa un método similar al Procedimiento General 1-2, usando 7-cloro-6-(4-ciclohexanocarbonil-bencilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (120 mg, 0.243 mmol), para dar la base libre del compuesto del título como un aceite (86 mg, 89%) que se usó sin purificación adicional. EM (ER+) *m/z*: 397 $(M+H)^+$. Se usa un método similar al Procedimiento General 2-1, usando 7-cloro-6-(4-ciclohexanocarbonil-bencilamino)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (86 mg, 0.217 mmol) para dar el compuesto del título como un sólido (85 mg, 77%). EM (ER+) *m/z*: 397 $(M+H)^+$.

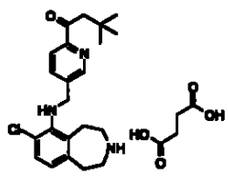
Ejemplos 554-557

Los Ejemplos 554-557 se pueden preparar esencialmente como se describe en el Ejemplo 553 usando 7-cloro-3-(2,2,2-

trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina y la amina apropiada. Los rendimientos totales y datos EM (ER+) se muestran en la Tabla a continuación.

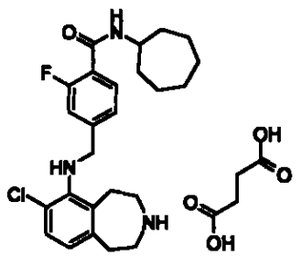
Ej.	Estructura	Compuesto	Rendimiento (%)	EM (ER+) m/z
554		Succinato de 7-cloro-6-[4-(2-ciclopentil-acetil)-bencilamino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	64	397 $(M+H)^+$
555		Succinato de 7-cloro-6-[4-(2-ciclohexil-acetil)-bencilamino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	30	411 $(M+H)^+$
556		Succinato de 7-cloro-6-[6-(3-metil-butiril)-piridin-3-il-metilamino]-	35	372 $(M+H)^+$

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		2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina		
557		Succinato de 7-cloro-6-[6-(3,3-dimetil-butiril)-piridin-3-il-metilamino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	30	386 $(M+H)^+$

Ejemplo 558

Succinato de 7-cloro-6-(4-cicloheptilcarbamoil-3-fluoro-bencilamino)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



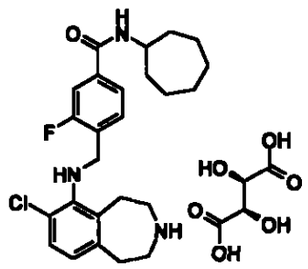
Se usa un método similar al Procedimiento General 5-2 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (1.1 g, 2.5 mmol) con 4-aminometil-*N*-cicloheptil-2-fluoro-benzamida (1.35 g, 5.1 mmol) en

tolueno anhidro (25 mL). Se purifica por cromatografía en gel de sílice eluyendo con hexano/EtOAc (gradiente 19:1 hasta 1:1) seguido por cromatografía SCX para obtener 7-cloro-6-[4-cicloheptilcarbamoil-3-fluoro-bencilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (720 mg, 53%). EM (ER+) *m/z*: 540.2 $(M+H)^+$.

Se usa un método similar al Procedimiento General 1-2 para desproteger 7-cloro-6-[4-cicloheptilcarbamoil-3-fluoro-bencilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina. Se purifica por cromatografía en gel de sílice eluyendo con diclorometano/amoniaco 2M en metanol (99:1 hasta 90:10 gradiente) para obtener la base libre del compuesto del título. Se usa un método similar al Procedimiento General 2-1 para obtener el compuesto del título (665 mg, 89%). EM (ER+) *m/z*: 444.2 $(M+H)^+$.

Ejemplo 559

(*L*)-Tartrato de 7-cloro-6-(4-cicloheptilcarbamoil-2-fluoro-bencilamino)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina

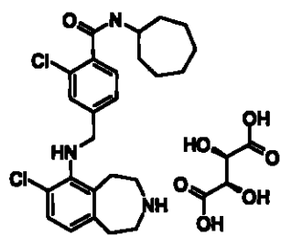


Se usa un método similar al Procedimiento General 5-2 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (640 mg, 1.5 mmol) con 4-aminometil-*N*-cicloheptil-3-fluoro-benzamida (795 mg, 3 mmol) en tolueno anhidro (20 mL). Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con hexano/EtOAc (19:1 hasta 3:2 gradiente) para obtener 7-cloro-6-(4-cicloheptilcarbamoil-2-fluoro-bencilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (568 mg, 70%). EM (ER+) *m/z*: 540.2 $(M+H)^+$.

Se usa un método similar al Procedimiento General 1-2 para desproteger 7-cloro-6-(4-cicloheptilcarbamoil-2-fluoro-bencilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina. Se purifica por cromatografía en gel de sílice eluyendo con diclorometano/amoniaco 2M en metanol (99/1 hasta 93/7 gradiente) para dar la base libre del compuesto del título. Se disuelve la base libre (400 mg, 0.9 mmol) y ácido *L*-tartárico (135 mg, 0.9 mmol) en metanol. Se concentra *in vacuo* a un aceite. Se tritura el aceite con diclorometano y se remueve el solvente *in vacuo* para obtener el compuesto del título como un sólido (460 mg, 74%). EM (ER+) *m/z*: 444.2 $(M+H)^+$.

Ejemplo 560

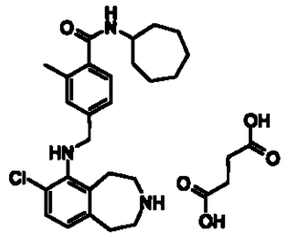
(*L*)-Tartrato de 7-cloro-6-(3-cloro-4-cicloheptilcarbamoil-bencilamino)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



El Ejemplo 560 se puede preparar esencialmente como se describe en el Ejemplo 559 al usar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina y 4-aminometil-2-cloro-*N*-cicloheptil-benzamida (50% de rendimiento, EM (ER+) *m/z* 460.2 $(M+H)^+$).

Ejemplo 561

Succinato de 7-cloro-6-(4-cicloheptilcarbamoil-3-metil-bencilamino)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



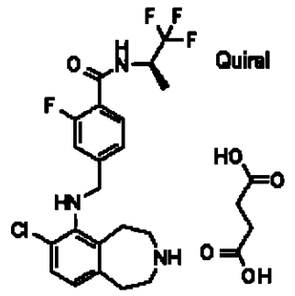
Se usa un método similar al Procedimiento General 5-2 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-

trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (660 mg, 1.6 mmol) con 4-aminometil-*N*-cicloheptil-2-metil-benzamida (810 mg, 3.1 mmol) en tolueno anhidro (18 mL). Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con hexano/THF (19:1 hasta 7:3 gradiente) para obtener 7-cloro-6-(4-cicloheptilcarbamoil-3-metil-bencilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (690 mg, 83%). EM (ER+) *m/z*: 536.3 $(M+H)^+$.

Se usa un método similar al Procedimiento General 1-3 para desproteger 7-cloro-6-(4-cicloheptilcarbamoil-3-metil-bencilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (680 mg, 1.3 mmol). Se purifica por cromatografía en gel de sílice eluyendo con diclorometano/amoniaco 2M en metanol (99:1 hasta 97:3 gradiente) para dar la base libre del compuesto del título. Se usa un método similar al Procedimiento General 2-1 para obtener el compuesto del título (473 mg, 65%). EM (ER+) *m/z*: 440.3 $(M+H)^+$.

Ejemplo 562

Succinato de (*R*)-7-cloro-6-[3-fluoro-4-(2,2,2-trifluoro-1-metil-etilcarbamoil)-bencilamino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



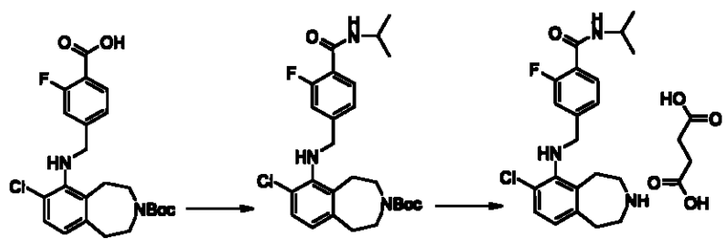
Se usa un método similar al Procedimiento General 5-2 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (0.561 g, 1.319 mmol) con (*R*)-4-aminometil-2-fluoro-*N*-(2,2,2-trifluoro-1-metil-etil)-benzamida (0.698 g, 2.642 mmol) al usar tris(dibencilidenoacetona)dipaladio(0) (0.241 g, 0.264 mmol), BINAP (0.33 g, 0.53 mmol) y carbonato de cesio (1.51 g, 4.63 mmol) en tolueno anhidro (13 mL). Se purifica por cromatografía en gel de sílice (columna RediSep® 40 g) eluyendo con hexano/EtOAc (gradiente 19:1 hasta 1:1 durante 30 min; 35 mL/min) y luego por cromatografía SCX para proporcionar (*R*)-7-cloro-6-[3-fluoro-4-(2,2,2-trifluoro-1-metil-etilcarbamoil)-bencilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina como un aceite incoloro (0.444 g, 62%). EM (ER+) *m/z*: 540.1 $(M+H)^+$.

Se usa un método similar al Procedimiento General 1-3 para desproteger (*R*)-7-cloro-6-[3-fluoro-4-(2,2,2-trifluoro-1-metil-etilcarbamoil)-bencilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (0.224 g, 0.415 mmol). Se purifica por cromatografía en gel de

sílice (solumna RediSep® 12 g) eluyendo con diclorometano/amoniaco 2M en metanol (99:1 hasta 90:10 gradiente durante 30 min; 35 mL/min) para proporcionar la base libre del compuesto del título como una espuma blanca (0.142 g, 77%). Se usa un método similar al Procedimiento General 2-1, usando (*R*)-7-cloro-6-[3-fluoro-4-(2,2,2-trifluoro-1-metil-etilcarbamoil)-bencilamino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (0.132 g, 0.299 mmol) para proporcionar el compuesto del título como un sólido blanco (0.135 g, 80%). EM (ER+) *m/z*: 444.2 $(M+H)^+$.

Ejemplo 563

Succinato de 7-cloro-6-(3-fluoro-4-isopropilcarbamoil-bencilamino)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



Se agrega isopropilamina (0.15 mL, 1.8 mmol), HOBT (0.24 g, 1.8 mmol), diisopropiletilamina (0.63 mL, 3.6 mmol) y EDC (0.34 g, 1.8 mmol) a una mezcla de 3-*tert*-butoxicarbonil-6-(4-carboxi-3-fluoro-bencilamino)-7-cloro-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (0.403 g, 0.9 mmol) en THF anhidro (11.8 mL) a temperatura ambiente. Se agita durante la noche a

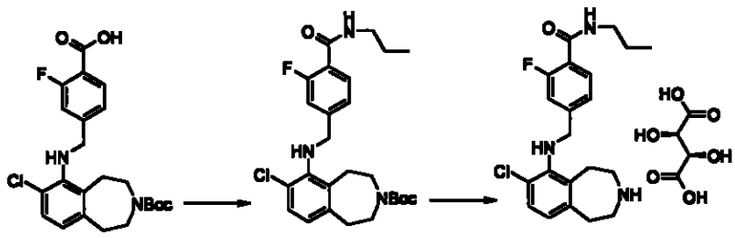
temperatura ambiente y se divide la mezcla entre EtOAc (250 mL) y $NaHCO_3$ acuoso saturado (100 mL). Se seca la fase orgánica sobre Na_2SO_4, se filtra y se concentra *in vacuo*. Se purifica por cromatografía en gel de sílice (columna RediSep® 40 g) eluyendo con hexano/EtOAc (gradiente 19:1 hasta 1:1 durante 30 min; 50 mL/min) para proporcionar 3-*tert*-butoxicarbonil-7-cloro-6-(3-fluoro-4-isopropilcarbamoil-bencilamino)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina como un aceite incoloro espeso (0.439 g, 100%). EM (ER+) *m/z*: 490.2 $(M+H)^+$.

Se usa un método similar al Procedimiento General 1-4 para desproteger 3-*tert*-butoxicarbonil-7-cloro-6-(3-fluoro-4-isopropilcarbamoil-bencilamino)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (0.406 g, 0.83 mmol) en 1,4-dioxano (12.8 mL). Se purifica por cromatografía SCX eluyendo con diclorometano y diclorometano/amoniaco 2M en metanol (1:1) seguido por cromatografía en gel de sílice (columna RediSep 40 g) eluyendo con diclorometano/amoniaco 2M en metanol (99:1 hasta 90:10 durante 30 min) y luego diclorometano/amoniaco 2M en metanol (90:10 durante 30 min; 35 mL/min) para proporcionar 7-cloro-6-(3-fluoro-4-isopropilcarbamoil-bencilamino)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina como un aceite incoloro (0.3237 g). EM (ER+) *m/z*: 390.1 $(M+H)^+$. Se usa un método similar al Procedimiento General 2-1, usando 7-cloro-6-(3-fluoro-4-isopropilcarbamoil-bencilamino)-2,3,4,5-

tetrahidro-1*H*-benzo[*d*]azepina (0.301 g, 0.772 mmol) para proporcionar el compuesto del título como un sólido beige (0.328 g, 84%). EM (ER+) *m/z*: 390.1 $(M+H)^+$.

Ejemplo 564

(*L*)-Tartrato de 7-cloro-6-(3-fluoro-4-propilcarbamoil-bencilamino)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



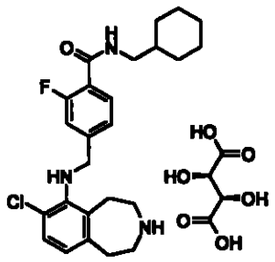
Se agrega una solución de *n*-propilamina (6.3 mg, 0.11 mmol) en THF anhidro (0.5 mL), HOBT (14.5 mg, 0.11 mmol), una solución de diisopropilamina (27.7 mg, 0.21 mmol) en THF anhidro (0.5 mL) y EDC (20.5 mg, 0.11 mmol) a una mezcla de 3-*tert*-butoxicarbonil-6-(4-carboxi-3-fluoro-bencilamino)-7-cloro-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (48.1 mg, 0.11 mmol) en THF anhidro (1.4 mL) a temperatura ambiente. Se agita durante la noche a temperatura ambiente y se divide la mezcla entre EtOAc (50 mL) y $NaHCO_3$ acuoso saturado (20 mL). Se seca la fase orgánica sobre Na_2SO_4, se filtra y se concentra *in vacuo*. Se purifica por cromatografía en gel de sílice (columna RediSep® 12 g) eluyendo con hexano/EtOAc

(gradiente 19:1 hasta 1:1 durante 30 min; 35 mL/min) para proporcionar 3-*tert*-butoxicarbonil-7-cloro-6-(3-fluoro-4-propilcarbamoil-bencilamino)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina como un aceite incoloro espeso (37.1 mg, 71%). EM (ER+) *m/z*: 490.2 $(M+H)^+$.

Se usa un método similar al Procedimiento General 1-4 para desproteger 3-*tert*-butoxicarbonil-7-cloro-6-(3-fluoro-4-propilcarbamoil-bencilamino)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (33.1 mg, 0.83 mmol) en 1,4-dioxano (1 mL). Se purifica por cromatografía SCX eluyendo con diclorometano y diclorometano/amoniaco 2M en metanol (1:1) para proporcionar 7-cloro-6-(3-fluoro-4-propilcarbamoil-bencilamino)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina como un aceite incoloro (25.2 mg, 96%). EM (ER+) *m/z*: 390.1 $(M+H)^+$. Se usa un método similar al Procedimiento General 2-6, usando 7-cloro-6-(3-fluoro-4-propilcarbamoil-bencilamino)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (25 mg, 0.064 mmol) para proporcionar el compuesto del título como una espuma blanca (31.4 mg, 91%). EM (ER+) *m/z*: 390.1 $(M+H)^+$.

Ejemplo 565

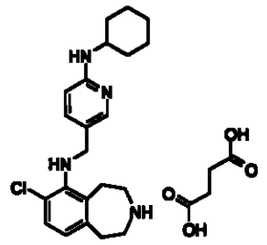
(*L*)-Tartrato de 7-cloro-6-[4-(ciclohexilmetilcarbamoil)-3-fluoro-bencilamino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



El Ejemplo 565 se puede preparar esencialmente como se describe en el Ejemplo 564 al usar 3-*tert*-butoxicarbonil-6-(4-carboxi-3-fluoro-bencilamino)-7-cloro-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina y ciclohexilmetilamina (67% de rendimiento, EM (ER+) *m/z* 444 $(M+H)^+$).

Ejemplo 566

Succinato de 7-cloro-6-(6-ciclohexilamino-piridin-3-ilmetilamino)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



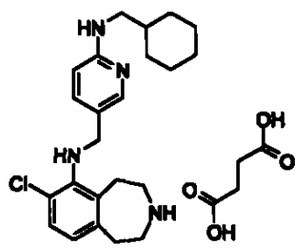
Se usa un método similar al Procedimiento General 5-2 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (800 mg, 1.9 mmol) con 5-aminometil-2-ciclohexilamino-piridina (910 mg, 4.4 mmol) en tolueno anhidro (15 mL). Se purifica el residuo por cromatografía en gel de sílice eluyendo con hexano/EtOAc (19:1 hasta 3:2 gradiente) para obtener 7-cloro-6-(6-ciclohexilamino-piridin-3-

ilmetilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (520 mg, 58%). EM (ER+) *m/z*: 481.0 $(M+H)^+$.

Se usa un método similar al Procedimiento General 1-3 para desproteger 7-cloro-6-(6-ciclohexilamino-piridin-3-ilmetilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina. Se purifica por cromatografía en gel de sílice eluyendo con diclorometano/amoniaco 2M en metanol (99/1 hasta 85/15 gradiente) para dar la base libre del compuesto del título. Se usa un método similar al Procedimiento General 2-1 para obtener el compuesto del título (360 mg, 66%). EM (ER+) *m/z*: 385.1 $(M+H)^+$.

Ejemplo 567

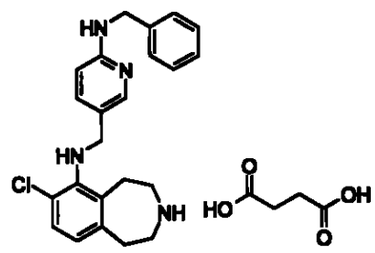
Succinato de 7-cloro-6-(6-ciclohexilmetilamino-piridin-3-ilmetilamino)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



El compuesto del título se pueden preparar esencialmente como se describe en el Ejemplo 566 al usar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina y 5-aminometil-2-ciclohexilmetilamino-piridina (22% de rendimiento, EM (ER+) *m/z* 399.1 $(M+H)^+$).

Ejemplo 568

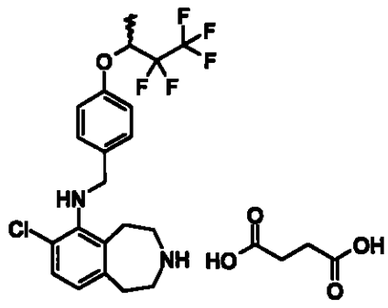
Succinato de 6-[6-(Bencilamino)-piridin-3-ilmetilamino]-7-cloro-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



Se usa un método similar al Procedimiento General 5-2 para acoplar 6-bencilamino-piridin-3-ilmetilamina y 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina para dar, después de la desprotección y formación de sal por métodos similares a los Procedimientos Generales 1-3 y 2-1, el compuesto del título como un sólido blanco opaco (45% rendimiento general). EMAR (ER+) *m/z*: 393.1836 $(M+H)^+$.

Ejemplo 569

Succinato de (±)-7-cloro-6-{4-[1-(1,1,2,2,2-pentafluoroetil)-etoxi]-bencilamino}-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



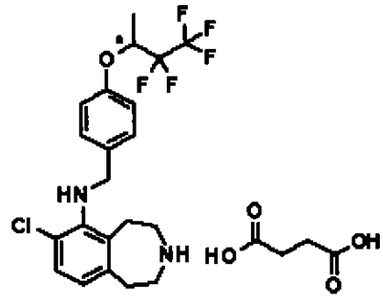
Se usa un método similar al Procedimiento General 5-2 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (751 mg, 1.8 mmol) con (±)-4-[1-(1,1,2,2,2-pentafluoroetil)-etoxi]-bencilamina (950 mg, 3.5 mmol) en tolueno anhidro (20 mL). Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo secuencialmente con hexano/EtOAc (10:1, 5:1, 3:1) para obtener (±)-7-cloro-6-{4-[1-(1,1,2,2,2-pentafluoroetil)-etoxi]-bencilamino}-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (990 mg, 99%).

Se usa un método similar al Procedimiento General 1-3 para desproteger (±)-7-cloro-6-{4-[1-(1,1,2,2,2-pentafluoroetil)-etoxi]-bencilamino}-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (980 mg, 1.8 mmol). Se purifica por cromatografía en gel de sílice eluyendo con diclorometano/amoniaco 2M en metanol (99:1 hasta 90:10 gradiente) para dar la base libre del compuesto del título. Se usa un método similar al Procedimiento General 2-1

para obtener el compuesto del título (650 mg, 64%). EM (ER+) *m/z*: 449.1 $(M+H)^+$.

Ejemplo 570

Succinato de (-)-7-cloro-6-{4-[1-(1,1,2,2,2-pentafluoroetil)-etoxi]-bencilamino}-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



Quiral

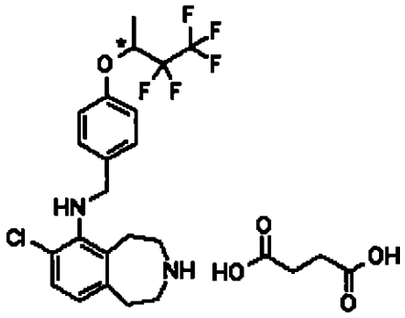
Se usa un método similar al Procedimiento General 5-2 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (9 g, 21.1 mmol) con 4-[1-(1,1,2,2,2-pentafluoroetil)-etoxi]-bencilamina isómero 2 (11.4 g, 42.3 mmol) en tolueno anhidro (270 mL). Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con hexano/EtOAc (19:1 hasta 4:1 gradiente) para obtener 7-cloro-6-{4-[1-(1,1,2,2,2-pentafluoroetil)-etoxi]-bencilamino}-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina isómero 2 (9.5 g, 83%).

Se usa un método similar al Procedimiento General 1-3 para desproteger 7-cloro-6-{4-[1-(1,1,2,2,2-pentafluoroetil)-

etoxi]-bencilamino}-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina isómero 2 (9.5 g, 17.4 mmol). Se purifica por cromatografía en gel de sílice eluyendo con diclorometano/amoniaco 2M en metanol (99:1 hasta 90:10 gradiente) para dar la base libre del compuesto del título. Se usa un método similar al Procedimiento General 2-1 para obtener el compuesto del título (5.9 g, 60%). EM (ER+) *m/z*: 449.1 $(M+H)^+$. $[\alpha]^{20}_D$ -11.6° (c 0.5, MeOH).

Ejemplo 571

Succinato de (+)-7-cloro-6-{4-[1-(1,1,2,2,2-pentafluoroetil)-etoxi]-bencilamino}-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



Quiral

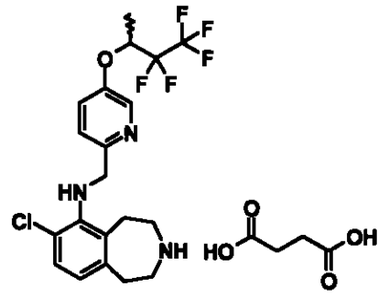
Se usa un método similar al Procedimiento General 5-2 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (3.4 g, 8 mmol) con 4-[1-(1,1,2,2,2-pentafluoroetil)-etoxi]-bencilamina isómero 1 (4.3 g, 16 mmol) en tolueno anhidro (100 mL). Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con hexano/EtOAc (19:1 hasta 3:1 gradiente) para obtener 7-cloro-6-{4-[1-(1,1,2,2,2-

pentafluoroetil)-etoxi]-bencilamino}-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina isómero 1 (3.7 g, 85%).

Se usa un método similar al Procedimiento General 1-3 para desproteger 7-cloro-6-{4-[1-(1,1,2,2,2-pentafluoroetil)-etoxi]-bencilamino}-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina isómero 1 (3.7 g, 6.8 mmol). Se purifica por cromatografía en gel de sílice eluyendo con diclorometano/amoniaco 2M en metanol (99:1 hasta 97:3 gradiente) para dar la base libre del compuesto del título. Se usa un método similar al Procedimiento General 2-1 para obtener el compuesto del título (2.8 g, 74%). EM (ER+) *m/z*: 449.1 $(M+H)^+$. $[\alpha]^{20}_D$ +13.0° (c 0.5, MeOH).

Ejemplo 572

Succinato de (±)-7-cloro-6-{4-[1-(1,1,2,2,2-pentafluoroetil)-etoxi]-piridin-2-ilmetilamino}-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



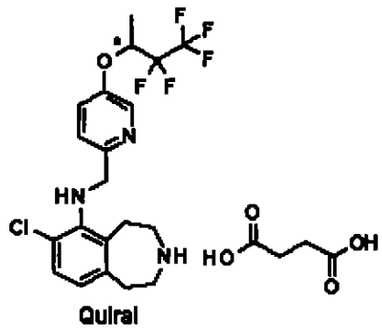
Se usa un método similar al Procedimiento General 5-2 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-

benzo[*d*]azepina (268 mg, 0.6 mmol) con (±)-2-aminometil-5-[1-(1,1,2,2,2-pentafluoroetil)-etoxi]-piridina (170 mg, 0.6 mmol) en tolueno anhidro (3 mL). Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo secuencialmente con hexano/EtOAc (10:1, 5:1, 3:1) para obtener (±)-7-cloro-6-{4-[1-(1,1,2,2,2-pentafluoroetil)-etoxi]-piridin-2-ilmetilamino}-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (270 mg, 79%). EM (ER+) *m/z*: 546.1 $(M+H)^+$.

Se usa un método similar al Procedimiento General 1-3 para desproteger (±)-7-cloro-6-{4-[1-(1,1,2,2,2-pentafluoroetil)-etoxi]-piridin-2-ilmetilamino}-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (265 mg, 0.5 mmol). Se purifica por cromatografía en gel de sílice eluyendo con diclorometano/amoniaco 2M en metanol (99:1 hasta 90:10 gradiente) para dar la base libre del compuesto del título. Se usa un método similar al Procedimiento General 2-1 para obtener el compuesto del título (172 mg, 63%). EM (ER+) *m/z*: 450.1 $(M+H)^+$.

Ejemplo 573

Succinato de (-)-7-cloro-6-{4-[1-(1,1,2,2,2-pentafluoroetil)-etoxi]-piridin-2-ilmetilamino}-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina

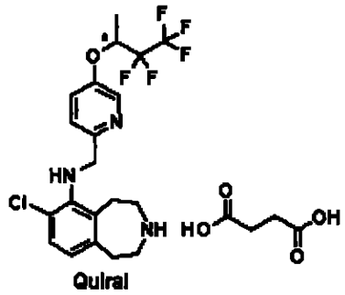


Quiral

Se separa succinato de (±)-7-cloro-6-{4-[1-(1,1,2,2,2-pentafluoroetil)-etoxi]-piridin-2-ilmetilamino}-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (172 mg) por cromatografía quiral de fase normal (Chiralcel OD, 8 x 35 cm, eluyendo con heptano/isopropanol 4:1 con DMEA 0.2%). Se colecta el 1er isómero eluido, luego se usa un método similar al Procedimiento General 2-1 para obtener el compuesto del título [50 mg, 96.3% ee (Chiralcel OD-H, 4.6 x 150 mm, eluyendo con heptano/isopropanol 4:1 con DMEA 0.2%, 0.6 mL/min)]. EM (ER+) *m/z*: 450.1 $(M+H)^+$. $[\alpha]^{20}_D$ -10.5° (c 0.5, MeOH).

Ejemplo 574

Succinato de (+)-7-cloro-6-{4-[1-(1,1,2,2,2-pentafluoroetil)-etoxi]-piridin-2-ilmetilamino}-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina

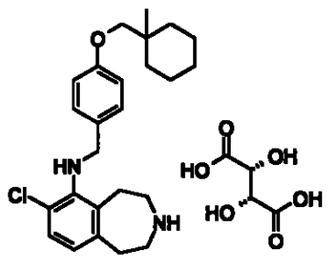


Quiral

Se separa succinato de (±)-7-cloro-6-{4-[1-(1,1,2,2,2-pentafluoroetil)-etoxi]-piridin-2-ilmetilamino}-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (172 mg) por cromatografía quiral de fase normal (Chiralcel OD, 8 x 35 cm, eluyendo con heptano/isopropanol 4:1 con DMEA 0.2%). Se colecta el 2do isómero eluido, luego se usa un método similar al Procedimiento General 2-1 para obtener el compuesto del título [41 mg, 95.6% ee (Chiralcel OD-H, 4.6 x 150 mm, eluyendo con heptano/isopropanol 4:1 con DMEA 0.2%, 0.6 mL/min)]. EM (ER+) *m/z*: 450.1 $(M+H)^+$. $[\alpha]^{20}_D$ +13.1° (c 0.5, MeOH).

Ejemplo 575

(*L*)-Tartrato de 7-cloro-6-[4-(1-metil-ciclohexilmetoxi)-bencilamino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina

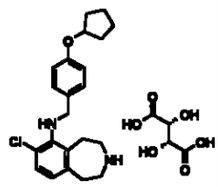
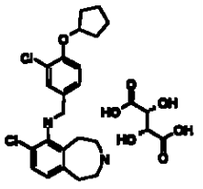
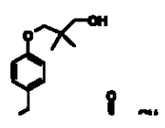


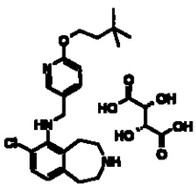
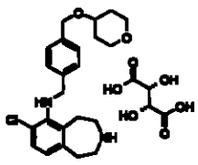
Se usa un método similar al Procedimiento General 5-2 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (200 mg, 0.47 mmol) con 4-(1-metil-ciclohexilmetoxi)-bencilamina (120 mg, 0.51 mmol) en 1,4-dioxano anhidro (7 mL). Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con isohexano/EtOAc (19:1 hasta 4:1 gradiente) para obtener 7-cloro-6-[4-(1-metil-ciclohexilmetoxi)-bencilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (101 mg, 39%).

Se usa un método similar al Procedimiento General 1-1 para desproteger 7-cloro-6-[4-(1-metil-ciclohexilmetoxi)-bencilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (100 mg, 0.19 mmol). Se purifica por cromatografía SCX eluyendo con metanol y amoniaco 3M en metanol. Se usa un método similar al Procedimiento General 2-6 para obtener el compuesto del título (78 mg, 73%). EM (ER+) *m/z*: 413.2 $(M+H)^+$.

Ejemplos 576-580

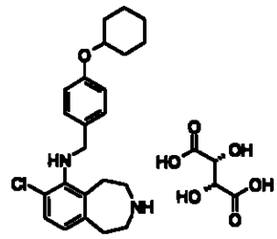
Los Ejemplos 576-580 se pueden preparar esencialmente como se describe en el Ejemplo 575 al usar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina y la amina apropiada. Los rendimientos totales y datos EM (ER+) se muestran en la Tabla a continuación.

Ej.	**Estructura**	**Compuesto**	**Rendimiento (%)**	**EM (ER+) m/z**
576		(*L*)-Tartrato de 7-cloro-6-(4-ciclopentiloxi-bencilamino)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	39	371 (M+H)$^+$
577		(*L*)-Tartrato de 7-cloro-6-(3-cloro-4-ciclopentiloxi-bencilamino)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	6	405 (M+H)$^+$
578		(*L*)-Tartrato de 7-	6	389

		cloro-6-[4-(2,2,dimetil-3-hidroxi-propoxi)-bencilamino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina		(M+H)+
579		(*L*)-Tartrato de 7-cloro-6-[6-(3,3-dimetil-butoxi)-piridin-3-ilmetilamino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	50	388 (M+H)+
580		(*L*)-Tartrato de 7-cloro-6-[4-(tetrahidro-piran-4-iloximetil)-bencilamino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	37	401 (M+H)+

Ejemplo 581

(*L*)-Tartrato de 7-cloro-6-(4-ciclohexiloxi-bencilamino)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



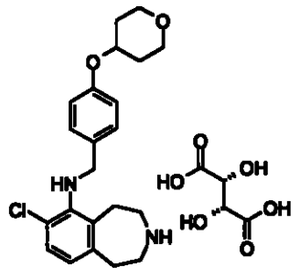
Se usa un método similar al Procedimiento General 5-1 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (100 mg, 0.43 mmol) con 4-ciclohexiloxi-bencilamina (58 mg, 0.285 mol) en tolueno anhidro (1 mL). Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con ciclohexano/EtOAc (9:1) para dar 7-cloro-6-(4-ciclohexiloxi-bencilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (78 mg, 69%).

Se usa un método similar al Procedimiento General 1-1 para desproteger 7-cloro-6-(4-ciclohexiloxi-bencilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (237 mg, 0.49 mmol) para obtener la base libre del compuesto del título. Se usa un método similar al Procedimiento General 2-6 para obtener el compuesto del título (208 mg, 80%). EM (ER+) *m/z*: 385.2 $(M+H)^+$.

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Ejemplo 582

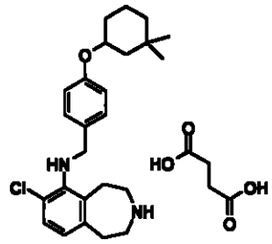
(*L*)-Tartrato de 7-cloro-6-[4-(tetrahidro-piran-4-iloxi)-bencilamino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



El Ejemplo 582 se pueden preparar esencialmente como se describe en el Ejemplo 581 al usar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina y 4-(tetrahidro-piran-4-iloxi)-bencilamina (4% de rendimiento, EM (ER+) *m/z* 387 $(M+H)^+$).

Ejemplo 583

Succinato de (±)-7-cloro-6-[4-(3,3-dimetil-ciclohexiloxi)-bencilamino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



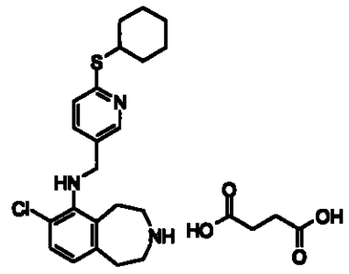
Se usa un método similar al Procedimiento General 5-2 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-

trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (387 mg, 0.91 mmol) con (±)-4-(3,3-dimetil-ciclohexiloxi)-bencilamina (233 mg, 1 mmol) en 1,4-dioxano anhidro (14 mL). Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con ciclohexano/EtOAc (gradiente 19:1 hasta 1:1) para obtener (±)-7-cloro-6-[4-(3,3-dimetil-ciclohexiloxi)-bencilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (227 mg, 50%).

Se usa un método similar al Procedimiento General 1-1 para desproteger (±)-7-cloro-6-[4-(3,3-dimetil-ciclohexiloxi)-bencilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (220 mg, 0.43 mmol). Se purifica por cromatografía SCX eluyendo con metanol y amoniaco 3M en metanol. Se purifica además el residuo por CLAR preparativa. Se usa un método similar al Procedimiento General 2-1 para obtener el compuesto del título (65 mg, 13%). EM (ER+) *m/z*: 413.2 $(M+H)^+$.

Ejemplo 584

Succinato de 7-cloro-6-(4-ciclohexiltio-piridin-3-ilmetilamino)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



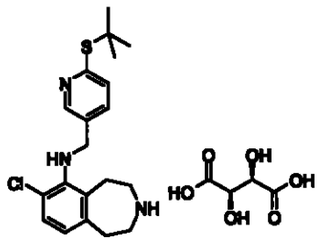
Se agrega carbonato de cesio (2.04 g, 6.27 mmol), acetato de paladio(II) (46 mg, 0.209 mmol) y BINAP (195.21 mg, 0.313 mmol) a una solución de 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (1.79 g, 4.18 mmol) y 5-aminometil-2-ciclohexiltio-piridina (1.11 g, 5.02 mmol) en tolueno anhidro (30 mL). Se sonica la suspensión resultante durante 30 min luego se calienta a 100°C durante 18 h. Se enfría la reacción a temperatura ambiente. Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con ciclohexano/EtOAc (98:2 hasta 60:40 gradiente) para dar 7-cloro-6-(4-ciclohexiltio-piridin-3-ilmetilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina como un aceite (1.1 g, 53%).

Se usa un método similar al Procedimiento General 1-1 para desproteger 7-cloro-6-(4-ciclohexiltio-piridin-3-ilmetilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (1.1 g, 2.21 mmol). Se purifica por cromatografía SCX eluyendo con metanol y amoniaco 3M en metanol. Se usa un método similar al Procedimiento General 2-

1 para obtener el compuesto del título como un sólido blanco (0.884 g, 77%). EM (ER+) *m/z*: 402 $(M+H)^+$.

Ejemplo 585

(*L*)-tartrato de 6-(4-*tert*-Butiltio-piridin-3-ilmetilamino)-7-cloro-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



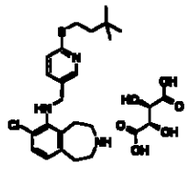
Se usa un método similar al Procedimiento General 5-2 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (990 mg, 2.32 mmol) con 5-aminometil-2-*tert*-butiltio-piridina (500 mg, 2.55 mmol) en tolueno anhidro (15 mL). Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con isohexano/EtOAc (1:0 hasta 3:1 gradiente) para obtener 6-(4-*tert*-butiltio-piridin-3-ilmetilamino)-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (650 mg, 59%). EM (ER+) *m/z*: 472 $(M+H)^+$.

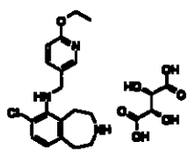
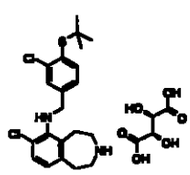
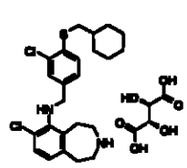
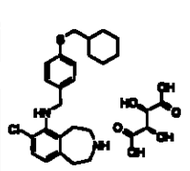
Se usa un método similar al Procedimiento General 1-2 para desproteger 6-(4-*tert*-butiltio-piridin-3-ilmetilamino)-7-cloro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (650 mg, 1.37 mmol). Se purifica por

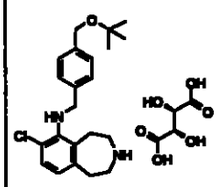
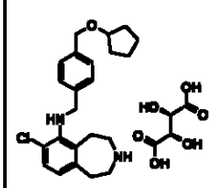
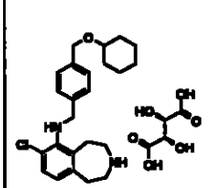
cromatografía SCX eluyendo con metanol y amoniaco 3M en metanol. Se usa un método similar al Procedimiento General 2-6 para obtener el compuesto del título (362 mg, 50%). EM (ER+) *m/z*: 376 $(M+H)^+$.

Ejemplos 586-593

Los Ejemplos 586-593 se pueden preparar esencialmente como se describe en el Ejemplo 585 al usar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina y la amina apropiada. Los rendimientos totales y datos EM (ER+) se muestran en la Tabla a continuación.

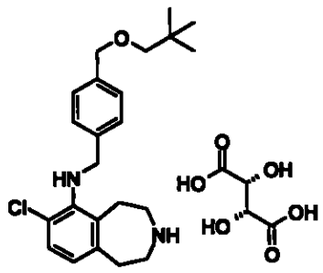
Ej.	Estructura	Compuesto	Rendimiento (%)	EM (ER+) *m/z*
586		(*L*)-Tartrato de 7-cloro-6-[4-(3,3-dimetilbutiltio)-piridin-3-ilmetilamino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	25	404 $(M+H)^+$

587		(*L*)-Tartrato de 7-cloro-6-(4-etoxi-piridin-3-ilmetilamino)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	30	332 $(M+H)^+$
588		(*L*)-Tartrato de 6-(4-*tert*-Butiltio-3-cloro-bencilamino)-7-cloro-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	37	409 $(M+H)^+$
589		(*L*)-Tartrato de 7-cloro-6-(3-cloro-4-ciclohexilmetiltio-bencilamino)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	27	472 $(M+Na)^+$
590		(*L*)-Tartrato de 7-cloro-6-(4-ciclohexilmetiltio-bencilamino)-2,3,4,5-tetrahidro-1*H*-	13	415 $(M+H)^+$

		benzo[*d*]azepina		
591		(*L*)-Tartrato de 6-(4-*tert*-Butoximetil-bencilamino)-7-cloro-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	16	373 $(M+H)^+$
592		(*L*)-Tartrato de 7-cloro-6-(4-ciclopentiloximetil-bencilamino)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	39	385 $(M+H)^+$
593		(*L*)-Tartrato de 7-cloro-6-(4-ciclohexiloximetil-bencilamino)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	33	399 $(M+H)^+$

Ejemplo 594

(*L*)-Tartrato de 7-cloro-6-[4-(2,2-dimetil-propoximetil)-bencilamino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina

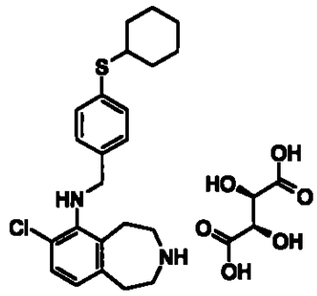


Se usa un método similar al Procedimiento General 5-2 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (426 mg, 1 mmol) con 4-(2,2-dimetil-propoximetil)-bencilamina (230 mg, 1.1 mmol) en tolueno anhidro (20 mL). Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con isohexano/EtOAc (gradiente 1:0 hasta 4:1) para obtener 7-cloro-6-[4-(2,2-dimetil-propoximetil)-bencilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (380 mg, 79%). EM (ER+) *m/z*: 483 $(M+H)^+$.

Se usa un método similar al Procedimiento General 1-2 para desproteger 7-cloro-6-[4-(2,2-dimetil-propoximetil)-bencilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (380 mg, 0.88 mmol). Se purifica por cromatografía SCX eluyendo con metanol y amoniaco 3M en metanol. Se usa un método similar al Procedimiento General 2-6 para obtener el compuesto del título (319.2 mg, 70%). EM (ER+) *m/z*: 387 $(M+H)^+$.

Ejemplo 595

(*L*)-Tartrato de 7-cloro-6-(4-ciclohexiltio-bencilamino)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



Se usa un método similar al Procedimiento General 5-2 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (167 mg, 0.392 mmol) con 4-ciclohexiltio-bencilamina (95.4 mg, 0.431 mmol) en 1,4-dioxano anhidro (5 mL). Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con isohexano/EtOAc (1:0 hasta 13:7 gradiente) para obtener 7-cloro-6-(4-ciclohexiltio-bencilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (155 mg, 79%). EM (ER+) *m/z*: 519 $(M+Na)^+$.

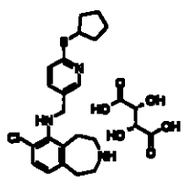
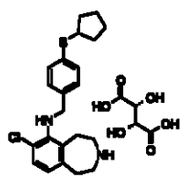
Se usa un método similar al Procedimiento General 1-2 para desproteger 7-cloro-6-(4-ciclohexiltio-bencilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (155 mg, 0.312 mmol). Se purifica por cromatografía SCX eluyendo con metanol y

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amoniaco 3M en metanol. Se usa un método similar al Procedimiento General 2-6 para obtener el compuesto del título (95 mg, 75%). EM (ER+) *m/z*: 401 $(M+H)^+$.

Ejemplos 596-597

Los Ejemplos 596-597 se pueden preparar esencialmente como se describe en el Ejemplo 595 al usar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina y la amina apropiada. Los rendimientos totales y datos EM (ER+) se muestran en la Tabla a continuación.

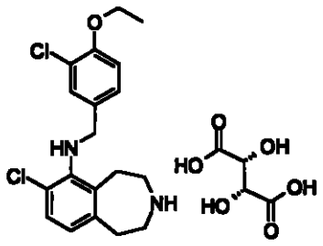
Ej.	**Estructura**	Compuesto	**Rendimiento (%)**	**EM (ER+) m/z**
596		(*L*)-Tartrato de 7-cloro-6-(4-ciclopentiltio-piridin-3-ilmetilamino)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	58	388 $(M+H)^+$
597		(*L*)-Tartrato de 7-cloro-6-(4-ciclopentiltio-bencilamino)-2,3,4,5-	66	387 $(M+H)^+$

(93)

		tetrahidro-1*H*-benzo[*d*]azepina		

Ejemplo 598

(*L*)-Tartrato de 7-cloro-6-(3-cloro-4-etoxi-bencilamino)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



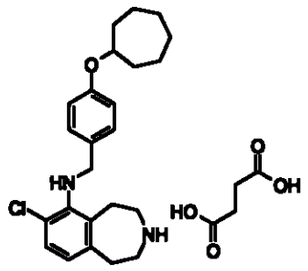
Se usa un método similar al Procedimiento General 5-2 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (150 mg, 0.35 mmol) con 4-etoxi-3-cloro-bencilamina (94.7 mg, 0.51 mmol) en 1,4-dioxano anhidro (10 mL). Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con isohexano/EtOAc (100:0 hasta 77:23 gradiente) para obtener 7-cloro-6-(3-cloro-4-etoxi-bencilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (111.3 mg, 68%). EM (ER+) *m/z*: 483 $(M+Na)^+$.

Se usa un método similar al Procedimiento General 1-1, pero agregando agua (10 mL) al amoniaco 7M en solución de metanol (20 mL), para desproteger 7-cloro-6-

(3-cloro-4-etoxi-bencilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (27 mg, 0.072 mmol) para dar la base libre del compuesto del título. Se usa un método similar al Procedimiento General 2-6 para dar el compuesto del título como un sólido (29 mg, 78%). EM (ER+) *m/z*: 365 $(M+H)^+$.

Ejemplo 599

Succinato de 7-cloro-6-(4-cicloheptiloxi-bencilamino)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



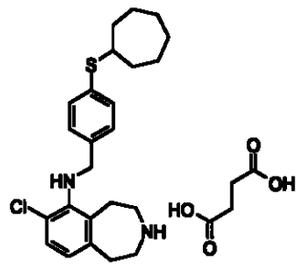
Bajo una atmósfera de nitrógeno, se agrega 4-cicloheptiloxi-bencilamina (451 mg, 2.06 mmol), 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (500 mg, 1.17 mmol), acetato de paladio(II) (26 mg, 0.117 mmol), BINAP (110 mg, 0.176 mmol), y carbonato de cesio (1.15 g, 3.52 mmol) a tolueno (20 mL). Se calienta la mezcla a 90°C durante 12 h. Se enfría la mezcla a temperatura ambiente y se diluye con EtOAc (25 mL). Se filtran los sólidos a través de celulosa (20 g) y se concentran *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de

sílice (columna RediSep 45 g) eluyendo con hexano/EtOAc (gradiente 1:0 hasta 4:1 durante 1 h; 80 mL/min) para proporcionar 7-cloro-6-(4-cicloheptiloxi-bencilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina como un aceite incoloro (384 mg, 61%). EM (APCI) *m/z*: 495 $(M+H)^+$.

Se disuelve 7-cloro-6-(4-cicloheptiloxi-bencilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (370 mg, 0.747 mmol) y monohidrato de hidróxido litio (153 mg, 3.73 mmol) en metanol (5 mL) y se agita durante 6 h. Se concentra la mezcla *in vacuo* y se disuelve el residuo en agua (20 mL). Se extrae la mezcla con EtOAc (3 × 20 mL). Se secan los extractos orgánicos combinados sobre Na_2SO_4, se filtran y se concentran *in vacuo*. Se purifica la mezcla cruda por CLAR de fase inversa [columna Phenomonex C18(2), 5 × 25 cm, eluyendo con un gradiente de agua/acetonitrilo (TFA 0.1% en cada uno) (9:1 a través de 1:9 durante 40 min), 118 mL/min] para proporcionar la sal de trifluoroacetato del compuesto del título. Se disuelve el residuo en metanol y se eluye a través de una columna SCX con amoniaco saturado en metanol para proporcionar la base libre del compuesto del título (197 mg, 65%). Se usa un método similar al Procedimiento General 2-1 para dar el compuesto del título como un sólido blanco opaco (250 mg, 100%). EM (APCI) *m/z*: 399 $(M+H)^+$.

Ejemplo 600

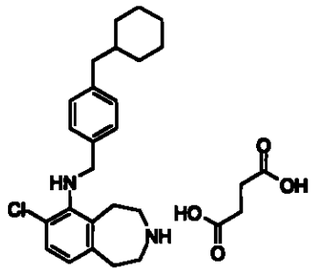
Succinato de 7-cloro-6-(4-cicloheptiltio-bencilamino)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



El Ejemplo 600 se puede preparar esencialmente como se describe en el Ejemplo 599 al usar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina y 4-cicloheptiltio-bencilamina (6% de rendimiento, EM (ER+) *m/z* 415 $(M+H)^+$).

Ejemplo 601

Succinato de 7-cloro-6-(4-ciclohexilmetil-bencilamino)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



Bajo una atmósfera de nitrógeno, se agrega clorohidrato de 4-ciclohexilmetil-bencilamina (352 mg, 1.47 mmol), 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (500 mg, 1.17 mmol),

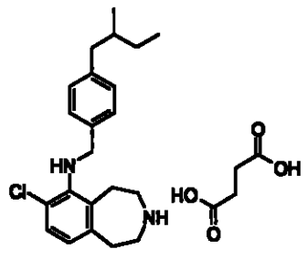
acetato de paladio(II) (52.7 mg, 0.235 mmol), BINAP (293 mg, 0.47 mmol) y carbonato de cesio (1.53 g, 4.7 mmol) a tolueno (20 mL). Se calienta la mezcla a 90°C durante 12 h. Se enfría la mezcla a temperatura ambiente y se diluye con EtOAc (25 mL). Se filtran los sólidos a través de celulosa (20 g) y se concentra el filtrado *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de sílice (columna RediSep 45 g) eluyendo con hexano/EtOAc (gradiente 1:0 hasta 4:1 durante 1 h; 80 mL/min) para proporcionar 7-cloro-6-(4-ciclohexilmetil-bencilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina como un aceite incoloro (354 mg, 63%). EM (APCI) *m/z*: 479 $(M+H)^+$.

Se disuelve 7-cloro-6-(4-ciclohexilmetil-bencilamino)-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (354 mg, 0.739 mmol) y monohidrato de hidróxido litio (100 mg, 2.43 mmol) en metanol (5 mL) y se agita durante la noche. Se concentra la mezcla *in vacuo* y se disuelve el residuo en agua (20 mL). Se extrae la mezcla con EtOAc (3 × 20 mL). Se secan los extractos orgánicos combinados sobre Na_2SO_4, se filtran, y se concentran *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de sílice (columna RediSep 40 g) eluyendo con un gradiente de diclorometano y cloroformo/metanol/hidróxido de amonio concentrado (80:18:2) durante 1 h (80 mL/min) seguido por CLAR de fase inversa [columna Phenomonex C18(2) (5 × 25 cm), eluyendo con

agua/acetonitrilo (TFA 0.1% en cada uno) (9:1 hasta 1:9 gradiente durante 40 min), 118 mL/min] para obtener la sal de trifluoroacetato del compuesto del título. Se disuelve el residuo en metanol y se eluye a través de columna SCX con amoniaco saturado en metanol para proporcionar 7-cloro-6-(4-ciclohexilmetil-bencilamino)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (184 mg, 64%). Se usa un método similar al Procedimiento General 2-1 para dar el compuesto del título como un sólido blanco (240 mg, 100%). EM (ES) ***m/z***: 383 $(M+H)^+$.

Ejemplo 602

Succinato de 7-cloro-6-[4-(2-metil-butil)-bencilamino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



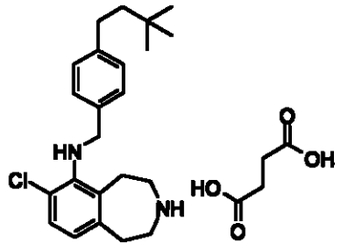
Bajo una atmósfera de nitrógeno, se agrega 4-(2-metil-butil)-bencilamina (450 mg, 2.54 mmol), 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (720 mg, 1.7 mmol), acetato de paladio(II) (40 mg, 0.17 mmol), BINAP (222 mg, 0.34 mmol) y carbonato de cesio (1.4 g, 4.3 mmol) a tolueno (20 mL). Se

calienta la mezcla a 95°C durante 12 h. Se enfría la mezcla a temperatura ambiente y se aplica la mezcla a una columna de gel de sílice eluyendo con hexano/EtOAc (10:1) para proporcionar 7-cloro-6-[4-(2-metil-butil)-bencilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (450 mg, 59%). EM (ER+) *m/z*: 453 $(M+H)^+$.

Se disuelve 7-cloro-6-[4-(2-metil-butil)-bencilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (450 mg, 1 mmol) e hidróxido de amonio concentrado (5 mL) en metanol (10 mL) y se agita durante la noche. Se concentra la mezcla *in vacuo*. Se purifica la mezcla cruda por cromatografía SCX eluyendo con metanol y amoniaco 3M en metanol. Se concentra el producto *in vacuo* y se purifica el residuo por CLAR de fase inversa [Phenomonex Luna C18(2), 50 mm × 250 mm, eluyendo con acetonitrilo/agua con TFA 0.1% (2:3)]. Se concentra *in vacuo*, se basifica con carbonato de potasio y se extrae en diclorometano. Se seca la solución orgánica sobre Na_2SO_4, se filtra y se concentra *in vacuo* para proporcionar la base libre del compuesto del título (205 mg, 57%). Se usa un método similar al Procedimiento General 2-1 para dar el compuesto del título como un sólido blanco (280 mg, 59%). EM (APCI) *m/z*: 357 $(M+H)^+$.

Ejemplo 603

Succinato de 7-cloro-6-[4-(3,3-dimetil-butil)-bencilamino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina

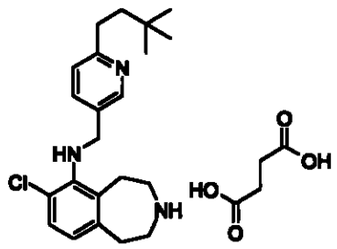


Se usa un método similar al Procedimiento General 5-1 para reaccionar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (623 mg, 1.46 mmol), acetato de paladio(II) (33 mg, 0.146 mmol), BINAP (182 mg, 0.292 mmol), 4-(3,3-dimetil-butil)-bencilamina (560 mg, 2.93 mmol) y carbonato de cesio (666 mg, 2.04 mmol) en tolueno desgasificado (40 mL). Se desgasifica la mezcla con purga vacío/nitrógeno y se calienta a 100°C durante 16 h. Se enfría la mezcla a temperatura ambiente, se diluye con EtOAc y se lava con agua. Se seca la fase orgánica sobre $MgSO_4$, se filtra y se concentra *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con hexano y luego hexano/EtOAc (19:1, 9:1) para obtener 7-cloro-6-[4-(3,3-dimetil-butil)-bencilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina como aceite (622 mg, 91%). EM (ER+) *m/z*: 467 $(M+H)^+$.

Se usa un método similar al Procedimiento General 1-2, usando 7-cloro-6-[4-(3,3-dimetil-butil)-bencilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (448 mg, 0.96 mmol), para dar la base libre del compuesto del título como un aceite (320 mg, 90%) que se usó sin purificación adicional. EM (ER+) *m/z*: 371 $(M+H)^+$. Se usa un método similar al Procedimiento General 2-1, usando 7-cloro-6-[4-(3,3-dimetil-butil)-bencilamino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (315 mg, 0.85 mmol) para dar el compuesto del título como un sólido blanco (340 mg, 82%). EM (ER+) *m/z*: 371 $(M+H)^+$.

Ejemplo 604

Succinato de 7-cloro-6-[6-(3,3-dimetil-butil)-piridin-3-il-metilamino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



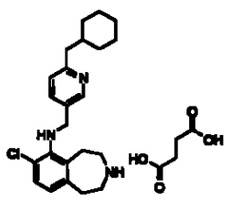
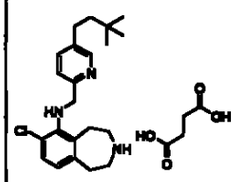
Se usa un método similar al Procedimiento General 5-2 para reaccionar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (166 mg, 0.39 mmol), tris(dibencilidenoacetona)dipaladio(0) (71 mg, 0.078 mmol),

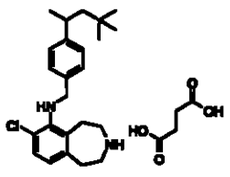
BINAP (103 mg, 0.156 mmol), 3-aminometil-6-(3,3-dimetil-butil)-piridina (150 mg, 0.78 mmol) y carbonato de cesio (178 mg, 0.546 mmol) en tolueno desgasificado (20 mL). Se desgasifica la mezcla con purga vacío/nitrógeno y se calienta a 100°C durante 14 h. Se enfría la mezcla a temperatura ambiente, se diluye con EtOAc y se filtra a través de Celite®. Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con hexano y luego hexano/EtOAc (19:1, 9:1 y 4:1) para obtener 7-cloro-6-[6-(3,3-dimetil-butil)-piridin-3-il-metilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina como aceite (149 mg, 82%). EM (ER+) *m/z*: 468 $(M+H)^+$.

Se usa un método similar al Procedimiento General 1-2, usando 7-cloro-6-[6-(3,3-dimetil-butil)-piridin-3-il-metilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (140 mg, 0.29 mmol), para dar la base libre del compuesto del título como un aceite (96 mg, 86%) que se usó sin purificación adicional. EM (ER+) *m/z*: 372 $(M+H)^+$. Se usa un método similar al Procedimiento General 2-1, usando 7-cloro-6-[6-(3,3-dimetil-butil)-piridin-3-il-metilamino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (96 mg, 0.258 mmol) para dar el compuesto del título como un sólido (119 mg, 94%). EM (ER+) *m/z*: 372 $(M+H)^+$.

Ejemplos 605-607

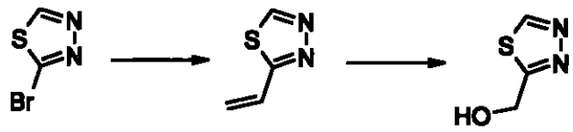
Los Ejemplos 605-607 se pueden preparar esencialmente como se describe en el Ejemplo 604 usando 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina y la amina apropiada. Los rendimientos totales y datos EM (ER+) se muestran en la Tabla a continuación.

Ej.	**Estructura**	**Compuesto**	**Rendimiento (%)**	**EM (ER+) m/z**
605		Succinato de 7-cloro-6-(6-ciclohexilmetil-piridin-3-il-metilamino)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	42	384 $(M+H)^+$
606		Succinato de 7-cloro-6-[5-(3,3-dimetil-butil)-piridin-2-il-metilamino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	34	372 $(M+H)^+$

607		Succinato de 7-cloro-6-[4-(1,3,3-trimetil-butil)-bencilamino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	47	385 $(M+H)^+$

Preparación 320

2-Hidroximetil-[1,3,4]-tiadiazol



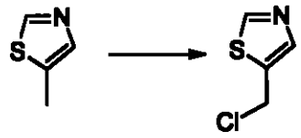
2-Vinil-[1,3,4]-tiadiazol: Se combina 2-bromo-[1,3,4]-tiadiazol (3.5 g, 21.2 mmol), tributilvinilestaño (6.20 mL, 21.2 mmol) y tetraquis(trifenilfosfina)paladio(0) (735 mg, 0.6 mmol) en tolueno anhidro (141 mL). Se calienta la mezcla a reflujo durante 18 h. Se agrega metanol y diclorometano hasta disolver el residuo y se evapora sobre gel de sílice. Se purifica el residuo por cromatografía en gel de sílice eluyendo con hexano/EtOAc (1:0 hasta 1:4 gradiente) para dar el intermediario deseado (0.49 g, 21%). CG-EM *m/z*: 112 (M^+).

2-Hidroximetil-[1,3,4]-tiadiazol: A -10°C se burbujea ozono a través de una solución de 2-vinil-[1,3,4]-tiadiazol (400 mg,

3.57 mmol) en metanol (18 mL). Después de 20 min el material de partida se consume. Se agrega luego borohidruro de sodio (37 mg, 0.98 mmol) y se entibia a temperatura ambiente. Se evapora la mezcla y se purifica el residuo al pasar a través de una almohadilla de gel de sílice eluyendo con metanol/diclorometano (98:2 hasta 96:4 gradiente) para dar el compuesto del título (0.24 g, 60%). EM (ER+) *m/z*: 117 $(M+H)^+$.

Preparación 321

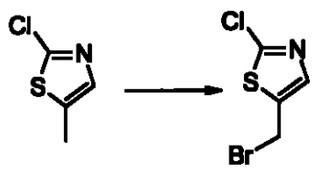
5-clorometiltiazol



Se combina 5-metiltiazol (1.5 g, 15.1 mmol), *N*-clorosuccinimida (2.6 g, 19.4 mmol) y AIBN (0.26 g, 1.6 mmol) en tetracloruro de carbono (15 mL). Se pone a reflujo bajo nitrógeno durante 3 h. Se enfría la mezcla de reacción y se concentra *in vacuo*. Se purifica por cromatografía en gel de sílice eluyendo con hexano/EtOAc (4:1) para dar el compuesto del título como un aceite amarillo (0.38 g, 19%).

Preparación 322

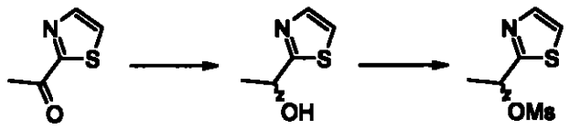
5-Bromometil-2-clorotiazol



5-clorometil-2-clorotiazol: se combina 5-metil-2-clorotiazol (1.05 g, 7.5 mmol), NBS (1.7 g, 9.6 mmol) y AIBN (0.12 g, 0.73 mmol) en tetracloruro de carbono (10 mL). Se pone a reflujo bajo nitrógeno durante 7 h. Se enfría y se concentra *in vacuo*. Se purifica por cromatografía en gel de sílice eluyendo con hexano/EtOAc (9:1) para dar el compuesto del título como un aceite amarillo (0.82 g, 51%).

Preparación 323

(±)-1-Metansulfoniloxi-1-tiazol-2-il-etil

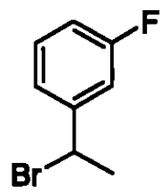


(±)-1-Tiazol-2-il-etanol: Se agrega borohidruro de sodio (357 mg, 9.4 mmol) en porciones, durante 5 min, a una solución de 2-acetiltiazol (1.0 g, 7.8 mmol) en metanol (25 mL) a 0°C bajo una atmósfera de nitrógeno. Se agita la mezcla durante 2 h a temperatura ambiente. Se concentra la mezcla *in vacuo*, se diluye el residuo con salmuera (30 mL) y se ajusta la mezcla a un pH 6 con HCl acuoso 5N (10 mL). Se extrae la mezcla con EtOAc (40 mL). Se seca la capa orgánica sobre Na_2SO_4, se filtra y se concentra *in vacuo* para obtener el intermediario deseado (1.0 g, 99%). CG-EM *m/z*: 129 (M^+).

(±)-1-Metansulfoniloxi-1-tiazol-2-il-etilo: Se disuelve 1-tiazol-2-il-etanol (1.0 g, 7.7 mmol) en diclorometano (30 mL) y trietilamina (1.2 mL, 8.5 mmol). Se enfría la solución a 0°C, luego se agrega cloruro de metanosulfonilo (690 µl, 8.9 mmol) bajo una atmósfera de nitrógeno. Se agita la solución durante 1.5 h a temperatura ambiente, luego se lava con $NaHCO_3$ acuoso saturado (30 mL). Se seca la capa orgánica sobre Na_2SO_4, se filtra y se concentra *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con diclorometano/hexano/metanol (50:45:5) para obtener el compuesto del título (1.3 g, 81%). CG-EM *m/z*: 207 (M^+).

Preparación 324

Bromuro de (±)-1-(3-Fluorofenil)etilo



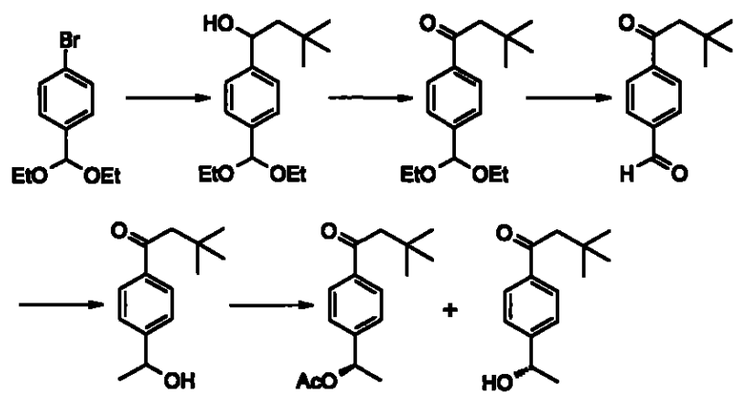
Se disuelve (±)-1-(3-fluorofenil)etanol (250 mg, 1.786 mmol) en tetracloruro de carbono (10 mL). Se agrega tribromuro de fósforo (0.1 mL, 1.786 mmol) a 0°C y se agita la solución a temperatura ambiente durante

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la noche. Se diluye la mezcla de reacción con diclorometano y se lava con salmuera. Se seca la fase orgánica sobre Na_2SO_4, se filtra y se concentra *in vacuo* para obtener el compuesto del título (285 mg) que se usó sin ninguna purificación adicional.

Preparación 325

(*S*)-1-[4-(1-Hidroxietil)-fenil]-3,3-dimetilbutan-1-ona



1-[4-(Dietoximetil)-fenil]-3,3-dimetilbutan-1-ol: Se disuelve 1-bromo-4-(dietoximetil)-benceno (6.1 g, 23.55 mmol) en THF anhidro (150 mL) y se enfría la solución a -78°C. Se agrega *n*-butil litio (11.3 mL, 28.26 mmol, solución 2.5M en hexano) y se agita la mezcla durante 30 min. Se agrega 3,3-dimetilbutiraldehído (4.7 mL, 35.33 mmol) y se agita la mezcla durante 1 h. Se agrega agua y EtOAc. Se entibia la solución a temperatura ambiente y se extrae la capa acuosa tres veces con EtOAc. Se secan los extractos orgánicos

combinados con Na_2SO_4, se filtran y se concentran *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con hexano/EtOAc (93:7) para dar el intermediario deseado como un aceite incoloro (3.8 g, 58%).

1-[4-(Dietoximetil)-fenil]-3,3-dimetilbutan-1-ona: Se disuelve 1-[4-(dietoximetil)-fenil]-3,3-dimetilbutan-1-ol (3.8 g, 13.57 mmol) en hexano (50 mL). Se agrega dióxido de manganeso (3.5 g, 40.71 mmol) y se agita la mezcla a 60°C durante la noche. Se filtra el sólido y se concentra el filtrado *in vacuo* para dar el intermediario deseado como un aceite incoloro (3.49 g, 93%).

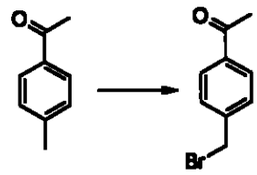
4-(3,3-Dimetil-butiril)-benzaldehído: Se disuelve 1-[4-(dietoximetil)-fenil]-3,3-dimetilbutan-1-ona (3.49 g, 12.55 mmol) en acetona (50 mL). Se agrega monohidrato del ácido p-toluensulfónico (238 mg, 1.256 mmol). Se calienta la mezcla bajo reflujo durante 3 h. Se concentra *in vacuo* y se divide el residuo entre agua y EtOAc. Se extrae la fase acuosa tres veces con EtOAc. Se secan los extractos orgánicos combinados sobre Na_2SO_4, se filtran y se concentran *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con hexano/EtOAc (9:1) para dar el intermediario deseado como un aceite incoloro (1.67 g, 65%).

1-[4-(1-Hidroxietil)-fenil]-3,3-dimetilbutan-1-ona: Se disuelve 4-(3,3-dimetil-butiril)-benzaldehído (1.67 g, 8.186 mmol) en THF anhidro (20 mL) y se enfría la solución a -10°C. Se agrega bromuro de metil magnesio (2.7 mL, 8.186 mmol, solución 3M en éter de dietilo) y se agita la mezcla durante 30 min. Se agrega agua a 0°C, se diluye con EtOAc y se extrae la capa acuosa tres veces con EtOAc. Se secan los extractos orgánicos combinados sobre Na_2SO_4, se filtran a través de una almohadilla corta de gel de sílice y se concentra *in vacuo* para dar el intermediario deseado como aceite amarillo (1.519 g, 84%).

(*S*)-1-[4-(1-hidroxietil)-fenil]-3,3-dimetilbutan-1-ona: Se disuelve 1-[4-(1-hidroxietil)-fenil]-3,3-dimetilbutan-1-ona (1.519 g, 6.905 mmol) en éterde diisopropilo (20 mL). Se agrega polvo de mallas moleculares 4Å (1.5 g), acetato de vinilo (2 mL) y resina acrílica de lipasa Candida Antarctica (150 mg). Se agita la mezcla a temperatura ambiente durante la noche. Se remueve el residuo sólido por filtración. Se concentra el filtrado *in vacuo* y se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con hexano/EtOAc (4:1) para dar (R)-1-(1-acetoxi-etil)-4-(3,3-dimetil-butiril)-benceno como aceite incoloro (0.661 g, 36%) y (*S*)-1-[4-(1-hidroxietil)-fenil]-3,3-dimetilbutan-1-ona como un aceite amarillo ligero (0.737 g, 49%).

Preparación 326

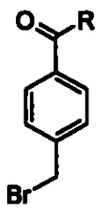
Bromuro de 4-Acetil-bencilo



Se calienta una mezcla de 4'-metilacetofenona (5 g, 37.26 mmol), NBS (6.964 g, 39.12 mmol), y AIBN (153 mg, 0.93 mmol) en tetracloruro de carbono (120 mL) durante 14 h a reflujo. Se enfría a temperatura ambiente y se lava secuencialmente con agua (100 mL), HCl acuoso 1M (100 mL), $NaHCO_3$ acuoso 5% (100 mL) y salmuera (100 mL). Se seca la fase orgánica sobre Na_2SO_4, se filtra y se concentra *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo secuencialmente con hexano y hexano/EtOAc (19:1, 9:1) para proporcionar el compuesto del título como aceite (5.191 g, 65%). CG-EM *m/z*: 213 (M^+).

Preparaciones 353-354

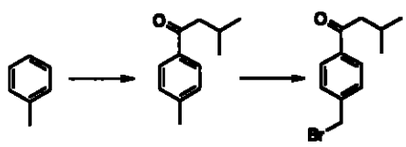
Los compuestos de las Preparaciones 353-354 se pueden preparar esencialmente como se describe en la Preparación 326 usando 4'-metilpropiofenona (Preparación 353) y 4'-metilbutirofenona (Preparación 354). Los rendimientos se muestran en la Tabla a continuación.



Prep.	R	Compuesto	Rendimiento (%)
353	Et	Bromuro de 4-Propionil-bencilo	92
354	*n*-Pr	Bromuro de 4-Butiril-bencilo	42

Preparación 329

Bromuro de 4-(3-Metil-butiril)-bencilo



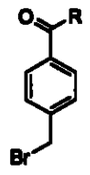
3,4'-Dimetilbutirofenona: Se agrega lentamente cloruro de isovalerilo (3.0 g, 24.88 mmol) a una solución agitada enfriada en hielo de tricloruro de aluminio (4.976 g, 37.32 mmol) en tolueno anhidro (60 mL). Se agita la mezcla de reacción a temperatura ambiente durante la noche. Se agrega lentamente agua enfriada en hielo y se extrae la mezcla dos veces con EtOAc. Se secan los extractos orgánicos combinados sobre Na_2SO_4, se filtran y se concentran *in vacuo* para dar el

intermediario deseado (4.38 g, 100%) que se usó sin ninguna purificación adicional. CG-EM *m/z*: 176 (M^+).

Bromuro de 4-(3-Metil-butiril)-bencilo: Se calienta una mezcla de 3,4'-dimetilbutirofenona (3 g, 17.02 mmol), NBS (3.787 g, 16.18 mmol), y AIBN (70 mg, 0.425 mmol) en tetracloruro de carbono (80 mL) durante 14 h a reflujo. Se enfría a temperatura ambiente y se filtra la mezcla. Se concentra el filtrado *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo secuencialmente con hexano y hexano/EtOAc (9:1) para proporcionar el compuesto del título como aceite (2.802 g, 65%). CG-EM *m/z*: 255 (M^+).

Preparaciones 356-357

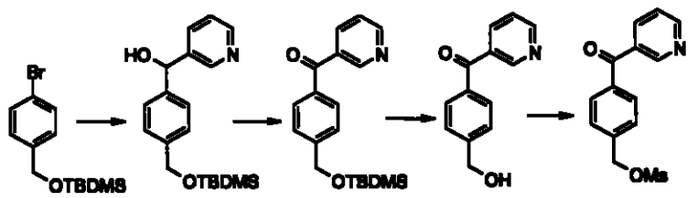
Los compuestos de las Preparaciones 356-357 se pueden preparar esencialmente como se describe en la Preparación 329 usando el cloruro de acilo apropiado. Los rendimientos totales y datos CG-EM se muestran en la Tabla a continuación.



Prep.	R	Compuesto	Rendimiento (%)	CG-EM m/z
330	*i*-Propilo	Bromuro de 4-Isobutiril-bencilo	32	241 $(M)^+$
357	2-Piridilo	Bromuro de 4-(Piridina-2-carbonil)-bencilo	9	276 $(M)^+$

Preparación 332

Metansulfonato de 4-(Piridina-3-carbonil)-bencilo



[4-(*tert*-Butildimetilsililoximetil)-fenil]-piridin-3-il-metanol: Se disuelve 4-(*tert*-butildimetilsililoximetil)bromobenceno (1 g, 3.319 mmol, preparado al seguir el procedimiento descrito en *J. Am. Chem. Soc.* 1995, *117*, 704-714) en THF anhidro (20 mL). Se enfría la solución a -78°C, se agrega *n*-BuLi (4.149 mL, 6.638 mmol, solución 1.6M en hexano) y se agita a esta temperatura durante 1.5 h. Se entibia a -60°C, se agita

durante 30 min adicionales y se agrega carboxaldehído 3-piridina. Se permite la mezcla de reacción hasta entibiar gradualmente a temperatura ambiente y se agita durante la noche. Se agrega salmuera y se extrae con EtOAc. Se seca la fase orgánica sobre Na_2SO_4, se filtra y se concentra *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo secuencialmente con hexano y EtOAc para dar el intermediario deseado (380 mg, 35%). EM (ER+) *m/z*: 330 $(M+H)^+$.

[4-(*tert*-Butildimetilsililoximetil)-fenil]-piridin-3-il-metanona: Se agrega dióxido de manganeso (1.44 g) a una solución agitada de [4-(*tert*-butildimetilsililoximetil)-fenil]-piridin-3-il-metanol (360 mg, 0.303 mmol) en 1,4-dioxano anhidro (25 mL). Se calienta la mezcla a 70°C durante la noche. Se enfría la mezcla de reacción a temperatura ambiente, se filtra a través de Celite® y se lava con EtOAc. Se concentra el filtrado *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo secuencialmente con hexano y hexano/EtOAc (1:1) para proporcionar el intermediario deseado (233 mg, 65%). CG-EM *m/z*: 327 (M^+).

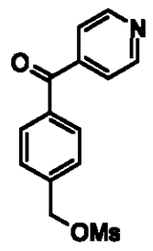
Alcohol de 4-(Piridina-3-carbonil)-bencilo: Se agrega fluoruro de tetrabutilamonio (1.37 mL, 1.37 mmol, solución 1M en THF) a una solución de [4-(*tert*-

butildimetilsililoximetil)-fenil]-piridin-3-il-metanona (225 mg, 0.687 mmol) en THF anhidro (10 mL) a 0°C y se agita a esta temperatura durante 1 h. Se concentra el solvente *in vacuo* y se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con EtOAc para proporcionar el intermediario deseado (85 mg, 58%). EM (ER+) *m/z*: 214 $(M+H)^+$.

Metansulfonato de 4-(Piridina-3-carbonil)-bencilo: Se disuelve alcohol de 4-(piridina-3-carbonil)-bencilo (85 mg, 0.399 mmol) en diclorometano (5 mL). Se enfría a 0°C y se agrega trietilamina (0.056 mL, 0.438 mmol) y cloruro de metansulfonilo (0.033 mL, 0.438 mmol). Se permite la mezcla entibiar hasta temperatura ambiente y se agita durante 2 h. Se diluye la mezcla de reacción con diclorometano y se lava con $NaHCO_3$ acuoso saturado. Se seca la fase orgánica sobre Na_2SO_4, se filtra y se concentra *in vacuo* para proporcionar el compuesto del título como aceite (115 mg, 100%). CG-EM *m/z*: 291 (M^+).

Preparación 333

Metansulfonato de 4-(Piridina-4-carbonil)-bencilo

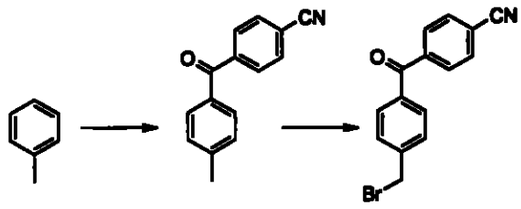


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El compuesto de la Preparación 333 se puede preparar esencialmente como se describe en la Preparación 332 usando 4-(*terț*-butildimetilsililoximetil)bromobenceno y carboxaldehído 4-piridina (CG-EM *m/z* 291 $(M)^+$).

Preparación 334

Bromuro de 4-(4-Ciano-benzoil)-bencilo

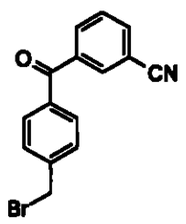


4-(4-Metil-benzoil)-benzonitrilo: Se suspende cloruro de 4-cianobenzoilo (2.0 g, 12 mmol) en tolueno anhidro (30 mL). Se agrega tricloruro de aluminio (2.4 g, 18 mmol) en tres porciones y se agita la mezcla de reacción a temperatura ambiente durante la noche. Se enfría a 0°C, se agrega cuidadosamente agua y se extrae la mezcla dos veces con EtOAc. Se secan los extractos orgánicos combinados sobre Na_2SO_4, se filtran y se concentran *in vacuo* para dar un sólido. Se suspende el sólido en éter de dietilo y se filtra para obtener el intermediario deseado (1.30 g, 49%) que se usó sin ninguna purificación adicional. CG-EM *m/z*: 221 (M^+).

Bromuro de 4-(4-Ciano-benzoil)-bencilo: Se calienta una mezcla de 4-(4-metil-benzoil)-benzonitrilo (300 mg, 1.356 mmol), NBS (386 mg, 2.169 mmol), y AIBN (22 mg, 0.136 mmol) en tetracloruro de carbono (10 mL) durante 14 h a reflujo. Se agrega NBS adicional (121 mg) y AIBN (11 mg) y se pone a reflujo la mezcla durante 3 h. Se enfría la mezcla de reacción a temperatura ambiente y se filtra la mezcla. Se concentra el filtrado *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo secuencialmente con hexano y hexano/EtOAc (9:1) para proporcionar el compuesto del título como un sólido (286 mg, 70%). CG-EM *m/z*: 300 (M^+).

Preparación 335

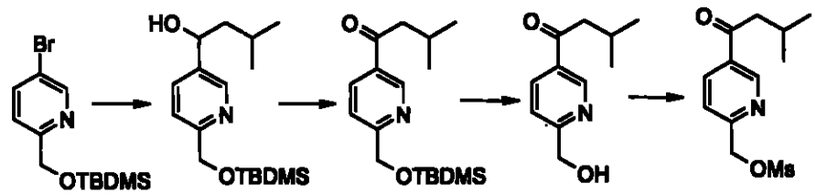
Bromuro de 4-(3-Ciano-benzoil)-bencilo



El compuesto de la Preparación 335 se puede preparar esencialmente como se describe en la Preparación 334 usando cloruro de 3-cianobenzoilo (CG-EM *m/z* 300 (M^+)).

Preparación 336

2-Metansulfoniloximetil-5-(3-metil-butiril)-piridina



2-(*tert*-Butildimetilsililoximetil)-5-(1-hidroxi-3-metil-butil)-piridina: Se disuelve 5-bromo-2-(*tert*-butildimetilsililoximetil)-piridina (0.5 g, 1.654 mmol, preparado al seguir el procedimiento descrito en *J. Med. Chem.* 1987, 30, 871-880) en THF anhidro (12 mL). Se enfría la solución a -78°C, se agrega *n*-BuLi (1.14 mL, 1.819 mmol, solución 1.6M en hexano) y se agita a esta temperatura durante 40 min. Se agrega lentamente aldehído isovalerilo (0.284 mL, 2.646 mmol) y se agita la mezcla durante 5 h a -78°C. Se agrega aldehído isovalerilo adicional (0.089 mL, 0.827 mmol) y se agita la mezcla durante 1.5 h a -78°C. Se agrega cloruro de amonio a -78°C y se entibia la mezcla a temperatura ambiente. Se agrega EtOAc y se extrae la capa acuosa dos veces con EtOAc. Se secan los extractos orgánicos combinados sobre Na_2SO_4, se filtran y se concentran *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con hexano y hexano/EtOAc (4:1) para dar el intermediario deseado como aceite (330 mg, 64%). CG-EM *m/z*: 309 (M^+).

2-(*tert*-Butildimetilsililoximetil)-5-(3-metil-butiril)-piridina: Se agrega dióxido de manganeso (1.32 g) a una solución agitada de 2-(*tert*-butildimetilsililoximetil)-5-(1-hidroxi-3-metil-butil)-piridina (330 mg, 1.066 mmol) en 1,4-dioxano anhidro (30 mL). Se calienta la mezcla a 70°C durante la noche. Se enfría la mezcla de reacción a temperatura ambiente, se filtra a través de Celite® y se lava con EtOAc. Se concentra el filtrado *in vacuo* para proporcionar el intermediario deseado como aceite (327 mg, 100%). CG-EM *m/z*: 307 (M^+).

2-Hidroximetil-5-(3-metil-butiril)-piridina: Se agrega fluoruro de tetrabutilamonio (2.13 mL, 2.13 mmol, solución 1M en THF) a una solución de 2-(*tert*-butildimetilsililoximetil)-5-(3-metil-butiril)-piridina (330 mg, 1.066 mmol) en THF anhidro (20 mL) a 0°C y se agita a esta temperatura durante 1 h. Se concentra el solvente *in vacuo* y se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con EtOAc para proporcionar el intermediario deseado (327 mg, 100%).

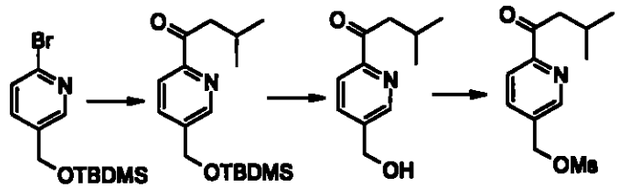
2-Metansulfoniloximetil-5-(3-metil-butiril)-piridina: Se disuelve 2-hidroximetil-5-(3-metil-butiril)-piridina (190 mg, 0.98 mmol) en diclorometano (10 mL). Se enfría a 0°C y se agrega trietilamina (0.151 mL, 1.08 mmol) y cloruro de metansulfonilo (0.083 mL, 1.08 mmol). Se permite la mezcla

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entibiar hasta temperatura ambiente y se agita durante 2 h. se diluye la mezcla de reacción con diclorometano y se lava con $NaHCO_3$ acuoso saturado. Se seca la fase orgánica sobre Na_2SO_4, se filtra y se concentra *in vacuo* para proporcionar el compuesto del título como aceite (263 mg, 98%).

Preparación 337

5-Metansulfoniloximetil-2-(3-metil-butiril)-piridina



5-(tert-Butildimetilsililoximetil)-2-(3-metil-butiril)-piridina: Se disuelve 2-bromo-5-(tert-butildimetilsililoximetil)piridina (1.99 g, 6.583 mmol, preparado al seguir el procedimiento descrito en *J. Org. Chem.* 2004, *69*, 250-262) en THF anhidro (20 mL). Se enfría la solución a -78°C, se agrega *n*-BuLi (4.32 mL, 6.912 mmol, solución 1.6M en hexano) y se agita a esta temperatura durante 40 min. Se agrega lentamente una solución de *N*-metoxi-*N*-metil-3-metil-butiramida (0.955 g, 6.583 mmol) en THF anhidro (5 mL). Se agita la mezcla durante 2 h a -78°C y luego se permite la mezcla entibiar hasta temperatura ambiente. Se agrega salmuera y se extrae la capa acuosa dos veces con EtOAc. Se secan los extractos orgánicos combinados sobre Na_2SO_4, se filtran y se

concentran *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con hexano y hexano/EtOAc (19:1) para dar el intermediario deseado como aceite amarillo (890 mg, 44%). CG-EM *m/z*: 307 (M^+).

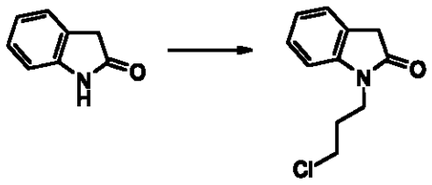
5-Hidroximetil-2-(3-metil-butiril)-piridina: Se agrega fluoruro de tetrabutilamonio (5.853 mL, 5.853 mmol, solución 1M en THF) a una solución de 5-(*tert*-butildimetilsililoximetil)-2-(3-metil-butiril)-piridina (900 mg, 2.927 mmol) en THF anhidro (30 mL) a 0°C y se agita a esta temperatura durante 2 h. Se concentra el solvente *in vacuo* y se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con hexano y hexano/EtOAc (3:2) para proporcionar el intermediario deseado (478 mg, 84%). EM (ER+) *m/z*: 194 $(M+H)^+$.

5-Metansulfoniloximetil-2-(3-metil-butiril)-piridina: Se disuelve 5-hidroximetil-2-(3-metil-butiril)-piridina (210 mg, 1.086 mmol) en diclorometano (5 mL). Se enfría a 0°C y se agrega trietilamina (0.167 mL, 1.195 mmol) y cloruro de metansulfonilo (0.093 mL, 1.195 mmol). Se permite la mezcla entibiar hasta temperatura ambiente y se agita durante 2 h. se diluye la mezcla de reacción con diclorometano y se lava con $NaHCO_3$ acuoso saturado. Se seca la fase orgánica sobre

Na_2SO_4, se filtra y se concentra *in vacuo* para proporcionar el compuesto del título (256 mg, 87%). CG-EM *m/z*: 271 (M^+).

Preparación 338

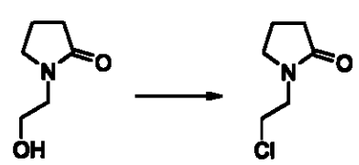
1-(3-cloro-propil)-1,3-dihidro-indol-2-ona



Se pone a reflujo junto con oxindol (2.66 g, 20.0 mmol), 1-bromo-3-cloropropano (2.56 mL, 26.0 mmol) y carbonato de potasio (5.52 g, 40.0 mmol) en acetonitrilo (300 mL) bajo nitrógeno durante 16 h. Se enfría la suspensión a temperatura ambiente y se filtra completamente el precipitado. Se concentra el filtrado *in vacuo* y se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con isohexano/EtOAc (1:0 hasta 3:2 gradiente durante 40 min) para dar el compuesto del título como un aceite anaranjado (1.65 g, 39%). EM (ER+) *m/z*: 210 $(M+H)^+$.

Preparación 339

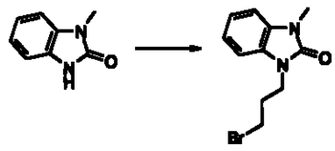
1-(2-cloro-etil)-pirrolidin-2-ona



Se agrega cloruro de tionilo (5 mL) a 1-(2-hidroxi-etil)-pirrolidin-2-ona (1.12 mL, 10.0 mmol) gota a gota luego se agita a temperatura ambiente durante 10 min. Se remueve solvente *in vacuo* para dar el compuesto del título como un aceite anaranjado. EM (ER+) *m/z*: 148 $(M+H)^+$.

Preparación 340

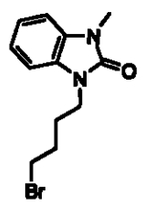
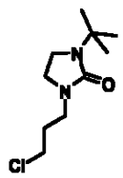
1-(3-Bromo-propil)-3-metil-1,3-dihidro-benzoimidazol-2-ona



Se agrega en porciones 3-metil-1,3-dihidro-benzoimidazol-2-ona (400 mg, 27.0 mmol) a una suspensión de hidruro de sodio (1.296 g, 32.4 mmol de dispersión 60% en aceite) en THF anhidro (200 mL) bajo nitrógeno durante 15 min, luego continua hasta agitar durante 30 min. Se agrega 1,3-dibromopropano (11.0 mL, 108 mmol) y se agita durante la noche. Luego se calienta a reflujo durante 3 días. Se enfría la suspensión a temperatura ambiente, Se vacía en salmuera (400 mL), se extrae con éter de dietilo (300 mL), se seca sobre $MgSO_4$ y se concentra *in vacuo*. Se purifica por cromatografía en gel de sílice eluyendo con isohexano/EtOAc (gradiente 1:0 hasta 1:1 durante 40 min) para dar el compuesto del título como un aceite incoloro (2.15 g, 30%).

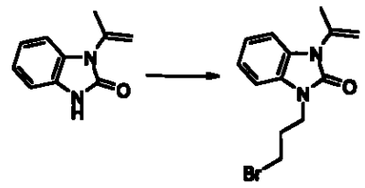
Preparaciones 341-342

El Compuesto de la Preparación 341 se puede preparar esencialmente como se describe en la Preparación 340 usando 3-metil-1,3-dihidro-benzoimidazol-2-ona y 1,4-dibromobutano. El Compuesto de la Preparación 342 se puede preparar esencialmente como se describe en la Preparación 340 usando 1-*tert*-butil-imidazolidin-2-ona y 1-bromo-3-cloropropano. Los rendimientos se muestran en la Tabla a continuación.

Prep.	Estructura	Compuesto	Rendimiento (%)
341		1-(4-Bromo-butil)-3-metil-1,3-dihidro-benzoimidazol-2-ona	56
342		1-*tert*-Butil-(3-cloro-propil)-imidazolidin-2-ona	5

Preparación 343

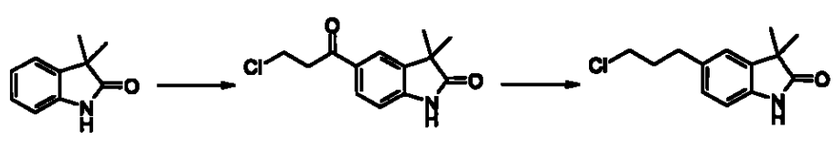
1-(3-Bromo-propil)-3-isopropenil-1,3-dihidro-benzoimidazol-2-ona



Se agrega hidruro de sodio (600 mg, 16.5 mmol de dispersión 60% en aceite) a una solución de 1-isopropenil-1,3-dihidro-benzoimidazol-2-ona (1.311 g, 7.53 mmol) en DMF anhidro (10 mL) bajo nitrógeno a temperatura ambiente y se agita durante 2 h. Se agrega 1-bromo-3-cloropropano (900 µL, 9.03 mmol) y se agita durante 3 días. Se vacía la suspensión en agua (100 mL), se extrae con éter de dietilo (2 x 50 mL). Se lava el extracto orgánico con salmuera (100 mL), se seca sobre $MgSO_4$ y se concentra *in vacuo* para dar el compuesto del título sin purifica con 1-(3-cloro-propil)-3-isopropenil-1,3-dihidro-benzoimidazol-2-ona (2.03 g, 1:1 mezcla). EM (ER+) *m/z*: 251 $(M+H)^+$, 293 $(M+H)^+$.

Preparación 344

5-(3-cloropropil)-3,3-dimetil-1,3-dihidro-indol-2-ona



5-(3-cloropropionil)-3,3-dimetil-1,3-dihidro-indol-2-ona:

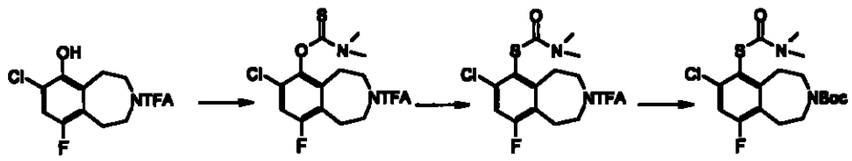
Bajo atmósfera de nitrógeno, se agrega cloruro de cloropropionilo (1.54 mL, 16.13 mmol) a una mezcla de 3,3-dimetil-1,3-dihidro-indol-2-ona (2.0 g, 12.41 mmol) y tricloruro de aluminio (10.26 g, 76.92 mmol) en disulfuro de carbono (70 mL). Se calienta bajo reflujo durante 3 h luego se permite enfriar. Se decanta completamente el solvente y se remplaza esto cuidadosamente con hielo/agua (200 mL). Se permite la suspensión resultante hasta agitar durante 20 min antes de filtrar completamente el producto y lavar con agua (80 mL). Se seca *in vacuo* para obtener el intermediario deseado como un sólido café pálido (3.08 g, 99%).

5-(3-cloropropil)-3,3-dimetil-1,3-dihidro-indol-2-ona: Bajo atmósfera de nitrógeno, se agrega 5-(3-cloropropil)-3,3-dimetil-1,3-dihidro-indol-2-ona (3.08 g, 12.24 mmol) a ácido trifluoroacético (9.4 mL, 122.4 mmol). Se enfría la suspensión resultante a 0°C y luego se agrega trietilsilano (4.5 mL, 28.2 mmol) gota a gota durante 2 min. Se calienta a 45°C durante 30 min luego se agita a temperatura ambiente durante la noche. Se vacía la mezcla de reacción sobre hielo/agua (100 mL) y se extrae con EtOAc (2 x 100 mL). Se secan los extractos combinados sobre $MgSO_4$, se filtran y se concentran *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con hexano/EtOAc

(gradiente 1:0 hasta 4:1), para dar el compuesto del título como un sólido amarillo anaranjado (2.12 g, 73%).

Preparación 345

3-*tert*-Butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-9-fluoro-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



7-cloro-6-(*O*-dimetiltiocarbamoil)-9-fluoro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina: Se calienta 7-cloro-9-fluoro-6-hidroxi-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (0.56 g, 1.8 mmol) a reflujo en 1,4-dioxano anhidro (18 mL) con trietilamina (1.01 mL, 7.2 mmol), *N*,*N*-dimetil-4-aminopiridina (22 mg, 0.18 mmol) y cloruro de dimetiltiocarbamoilo (0.67 g, 5.4 mmol) durante 16 h. Se enfría y se lava la mezcla con HCl acuoso 1N, $NaHCO_3$ acuoso saturado y salmuera. Se concentra *in vacuo* y se purifica por cromatografía en gel de sílice eluyendo con hexano/EtOAc (1:0 hasta 3:2 gradiente) para dar el intermediario deseado como un aceite amarillo que se solidifica en reposo (0.69 g, 96%). EM (ER+) *m/z*: 399 $(M+H)^+$.

1462

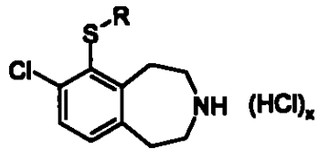
7-cloro-6-dimetilcarbamoiltio-9-fluoro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina: Se calienta 7-cloro-6-(*O*-dimetiltiocarbamoil)-9-fluoro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (0.69 g, 1.73 mmol) en éter de difenilo (6 mL) a 245°C durante 2.5 h. Se enfría la mezcla y se carga sobre una columna de gel de sílice. Se lava éter de difenilo apagado con hexano y eluyendo con hexano/EtOAc (1:0 hasta 3:2 gradiente) para dar el intermediario deseado (0.44 g, 64%). EM (ER+) *m/z*: 399 $(M+H)^+$.

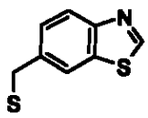
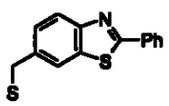
3-*tert*-Butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-9-fluoro-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina: Se calienta 7-cloro-6-dimetilcarbamoiltio-9-fluoro-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (0.2 g, 0.5 mmol) en metanol (50 mL) con carbonato de potasio (0.28 g, 2 mmol) a reflujo durante 5 h. Se enfría la mezcla, se agrega gota a gota una solución de di-*tert*-butil-dicarbonato (0.22 g, 1.0 mmol) en diclorometano (20 mL) y se agita 17 h. Se evapora la mezcla sobre gel de sílice y se purifica por cromatografía eluyendo con hexano/EtOAc (1:0 hasta 3:2 gradiente) para dar el compuesto del título (0.12 g, 62%). EM (ER+) *m/z*: 303 $(M+H-Boc)^+$.

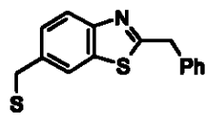
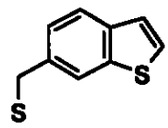
1468

Ejemplos 608-611

Los Ejemplos 608-611 se pueden preparar esencialmente como se describe en el Ejemplo 350 al usar 3-*tert*-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina y el clorometilheterociclo o bromometilheterociclo substituido apropiadamente. Los datos EM (ER+) se muestran en la Tabla a continuación.

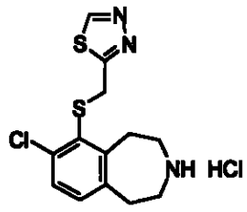


Ej.	Est.	Compuesto	EM (ER+ o APCI+)
608		Clorohidrato de 7-cloro-6-(benzotiazol-6-il-metiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	361 $(M+H)^+$
609		Clorohidrato de 7-cloro-6-(2-fenil-benzotiazol-6-il-metiltio)-2,3,4,5-tetrahidro-1*H*-	437 $(M+H)^+$

		benzo[*d*]azepina	
610		Clorohidrato de 7-cloro-6-(2-bencil-benzotiazol-6-il-metiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	451 $(M+H)^+$
611		Clorohidrato de 7-cloro-6-(benzotiofen-6-il-metiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	360 $(M+H)^+$

Ejemplo 612

Clorohidrato de 7-cloro-6-([1,3,4]tiadiazol-2-il-metiltio)-2,3,4,5-tetrahidro-1*H*-benzo [*d*]azepina



Se agita 2-hidroximetil-[1,3,4]-tiadiazol (241 mg, 2.1 mmol) en cloruro de tionilo (15 mL) durante 1 h y se concentra *in vacuo*. Se trata este residuo con el tiolato

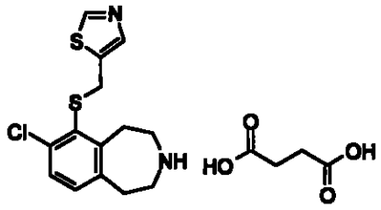
1470

preparado del 3-*tert*-butoxicarbonil-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (0.4 g, 1.04 mmol) e hidróxido de potasio (1.37 g, 24.5 mmol) en metanol (3.5 mL) de conformidad con el Procedimiento General 7 para dar 3-*tert*-butoxicarbonil-7-cloro-6-([1,3,4]tiadiazol-2-il-metiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (0.3 g, 70%). Se trata una alícuota con ácido trifluoroacético para obtener el espectro de masa. EM (ER+) *m/z*: 312 $(M+H)^+$.

Se usa un método similar al Procedimiento General 1-5 para desproteger 3-*tert*-butoxicarbonil-7-cloro-6-([1,3,4]tiadiazol-2-il-metiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (300 mg, 0.73 mmol). Se usa un método similar al Procedimiento General 2-2 para dar el compuesto del título (208 mg, 82%). EM (ER+) *m/z*: 312 $(M+H)^+$.

Ejemplo 613

Succinato de 7-cloro-6-(tiazol-5-ilmetiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina

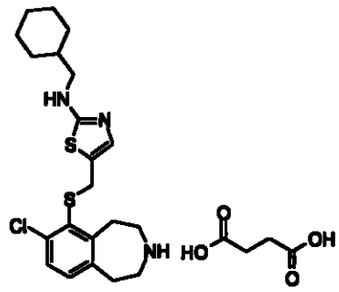


Se usa un método similar al Procedimiento General 7, usando 3-*tert*-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina y 5-clorometiltiazol

para dar, después de la desprotección y la formación de sal por métodos similares a los Procedimientos Generales 1-5 y 2-1, el compuesto del título como un sólido blanco (700 mg, 80% totales). EMAR (ER+) *m/z*: 311.0427 $(M+H)^+$.

Ejemplo 614

Succinato de 7-cloro-6-[2-(ciclohexilmetilamino)-tiazol-5-ilmetiltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina

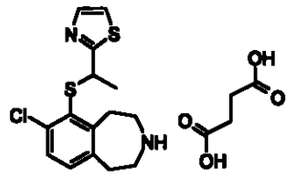


Se usa un método similar al Procedimiento General 7 usando 3-*tert*-butoxicarbonil-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina y 5-bromometil-2-clorotiazol para dar 3-*tert*-butoxicarbonil-7-cloro-6-(2-clorotiazol-5-ilmetiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina como un aceite amarillo (0.9 g, 71%). Se disuelve 3-*tert*-butoxicarbonil-7-cloro-6-(2-clorotiazol-5-ilmetiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (120 mg, 0.27 mmol) y ciclohexilmetilamina (1 mL, 7.7 mmol) en etanol absoluto (1 mL) en un tubo Pyrex de paredes gruesas. Se calienta la reacción en un baño de aceite a 82°C durante 24 h. Se enfría

la mezcla de reacción y se concentra *in vacuo*. Se purifica por cromatografía en gel de sílice eluyendo con hexano/EtOAc (4:1). Se usan métodos similares a los Procedimientos Generales 1-5 y 2-1 para desproteger y dar el compuesto del título como aceite amarillo (19 mg, 26% totales). EM (ER+) *m/z*: 422 $(M+H)^+$.

Ejemplo 615

Succinato de (-)-7-cloro-6-[1-(tiazol-2-il)-etiltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



Se agrega hidróxido de potasio (3.9 g, 70 mmol) a una solución de 3-*tert*-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (900 mg, 2.3 mmol) en metanol (25 mL) bajo una atmósfera de nitrógeno. Se calienta la mezcla a 80°C durante 1.5 h. Se enfría la mezcla a temperatura ambiente, luego se concentra *in vacuo* a un aceite. Se disuelve el aceite en EtOAc (50mL) y se lava con cloruro de amonio acuoso saturado (30 mL). Se separa la capa orgánica y se extrae la capa acuosa con EtOAc (3 x 50 mL). Se secan los extractos orgánicos combinados sobre Na_2SO_4, se filtran y se concentran *in vacuo* a un aceite

(735 mg). Se disuelve el aceite en DMSO anhidro (20 mL), luego se agrega trietilamina (1.9 mL, 14 mmol) y (±)-1-metansulfoniloxi-1-tiazol-2-il-etilo (1.3 g, 6.3 mmol) a temperatura ambiente bajo nitrógeno. Se calienta la mezcla a 40°C durante 1 h. Se enfría la reacción a temperatura ambiente, luego se diluye la mezcla con hexano/EtOAc (1:1, 50 mL) y se lava con cloruro de sodio 5% acuoso (3 x 50 mL). Se separa la capa orgánica y nuevamente se extrae la capa acuosa con EtOAc (3 x 50 mL). Se combinan los extractos orgánicos y se concentran *in vacuo*. Se purifica el residuo por cromatografía en gel de sílice eluyendo con hexano/EtOAc (19:1 hasta 7:3 gradiente) para obtener (±)-3-*tert*-butoxicarbonil-7-cloro-6-[1-(tiazol-2-il)-etiltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (779 mg, 79%). EM (ER+) *m/z*: 425.0 $(M+H)^+$.

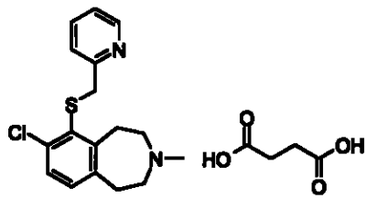
Se separa (±)-3-*tert*-butoxicarbonil-7-cloro-6-[1-(tiazol-2-il)-etiltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (770 mg, 1.8 mmol) por cromatografía quiral de fase normal [Chiralpak AD, 8 x 30 cm, eluyendo con heptano/etanol 3A (9:1)]. Se colecta el 2do isómero de elución de 3-*tert*-butoxicarbonil-7-cloro-6-[1-(tiazol-2-il)-etiltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina {348 mg, 99% ee [Chiralpak AD-H, 4.6 x 150 mm, eluyente heptano/etanol 3A (9:1)]}.

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Se usa un método similar al Procedimiento General 1-5 para desproteger 3-*tert*-butoxicarbonil-7-cloro-6-[1-(tiazol-2-il)-etiltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina isómero 2. Se purifica por cromatografía en gel de sílice eluyendo con diclorometano/amoniaco 2M en metanol (98:2 hasta 90:10 gradiente) para dar la base libre del compuesto del título. Se usa un método similar al Procedimiento General 2-1 para obtener el compuesto del título (350 mg, 96%). EM (ER+) *m/z*: 325.0 $(M+H)^+$. $[\alpha]^{20}_D$ - 160° (c 0.5, MeOH).

Ejemplo 616

Succinato de 7-cloro-3-metil-6-(piridin-2-ilmetiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



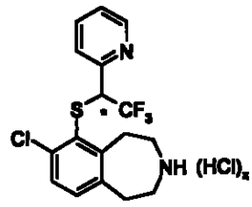
Se suspende clorohidrato de 7-cloro-6-(piridin-2-ilmetiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina en $NaHCO_3$ acuoso saturado y se extrae tres veces con EtOAc. Se secan los extractos orgánicos combinados sobre $MgSO_4$. Se filtran y se concentran in *vacuo* para dar la base libre como un aceite amarillo. Se combina la base libre (0.2 g, 0.66 mmol), triacetoxiborohidruro de sodio (0.78 g, 3.7 mmol),

formaldehído (solución 37% en agua, 0.2 mL, 2.7 mmol), y ácido acético (0.45 mL, 7.9 mmol), en 1,2-dicloroetano (5 mL). Se agita a temperatura ambiente durante 12 h. Se concentra la mezcla de reacción cruda *in vacuo* y se divide el residuo entre EtOAc/agua. Se separan las capas y se extrae la fase acuosa con EtOAc (3 x 30 mL). Se lavan los extractos orgánicos combinados con NaOH acuoso 1M. Se secan sobre $MgSO_4$, se filtran y se concentran *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con amoniaco 2M en metanol/diclorometano (4:96).

Se usa un método similar al Procedimiento General 2-1 para dar el compuesto del título como un cristal pegajoso (140 mg, 48%). EMAR (ER+) *m/z*: 319.1029 $(M+H)^+$.

Ejemplos 617 y 618

Clorohidrato de 7-cloro-6-(2,2,2-trifluoro-1-piridin-2-il-etiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina Isómero 1 y clorohidrato de 7-cloro-6-(2,2,2-trifluoro-1-piridin-2-il-etiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina Isómero 2



Se separan los dos enantiómeros de clorohidrato de (±)-7-cloro-6-(2,2,2-trifluoro-1-piridin-2-il-etiltio)-2,3,4,5-

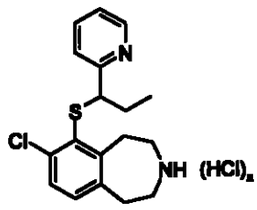
tetrahidro-1*H*-benzo[*d*]azepina por cromatografía quiral de fase normal (Chiralpak AD, 2 x 25 cm, eluyendo con heptano/etanol (85:15) con DMEA 0.2%).

Se somete el primer isómero de elución al Procedimiento General 1-4 para obtener clorohidrato de 7-cloro-6-(2,2,2-trifluoro-1-piridin-2-il-etiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina isómero 1 [99% ee (Chiralpak AD-H, 4.6 x 150 mm, eluyendo con heptano/etanol (85:15) con DMEA 0.2%, relación de flujo 0.6 mL/min)]. EM (ER+) *m/z*: 373.1 $(M+H)^+$.

Se somete el segundo isómero de elución al Procedimiento General 1-4 para obtener clorohidrato de 7-cloro-6-(2,2,2-trifluoro-1-piridin-2-il-etiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina isómero 2 [99% ee (Chiralpak AD-H, 4.6 x 150 mm, eluyendo con heptano/ etanol (85:15) con DMEA 0.2%, relación de flujo 0.6 mL/min)]. EM (ER+) *m/z* 373.1 $(M+H)^+$.

Ejemplo 619

Clorohidrato de (-)-7-cloro-6-(1-piridin-2-il-propiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



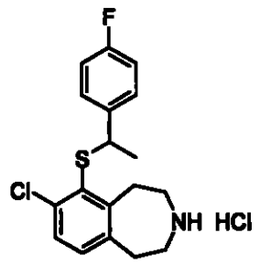
Se separan los dos enantiómeros de clorohidrato de (±)-7-cloro-6-(1-piridin-2-il-propiltio)-2,3,4,5-tetrahidro-1*H*-

benzo[*d*]azepina por cromatografía quiral de fase normal (Chiralcel OJ, 8 x 33 cm, eluyendo con heptano/metanol/etanol 3A (85:10:5) con DMEA 0.2%).

Se somete el segundo isómero de elución al Procedimiento General 1-4 para obtener el compuesto del título [93% ee (Chiralcel OJ, 4.6 x 250 mm, eluyendo con heptano/metanol/etanol 3A (90:5:5) con DMEA 0.2%, relación de flujo 0.6 mL/min)]. EM (ER+) *m/z*: 333.1 $(M+H)^+$. $[\alpha]^{20}_D$ -240.6° (c 0.5, MeOH).

Ejemplo 620

Clorohidrato de (±)-7-cloro-6-[1-(4-fluorofenil)etiltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



Se disuelve 3-*tert*-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (415 mg, 1.08 mmol) en metanol (20 mL) y se agrega hidróxido de potasio (1.938 g, 34.53 mmol). Se calienta a 60°C durante 4 h. Se enfría la mezcla de reacción a temperatura ambiente, se agrega cloruro de amonio saturado acuoso y se concentra *in vacuo*. Se divide el

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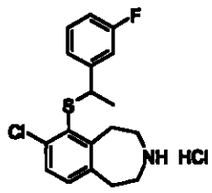
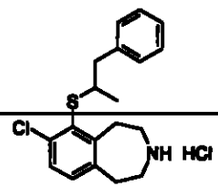
residuo entre EtOAc y agua. Se seca la fase orgánica sobre Na_2SO_4 anhidro y se concentra *in vacuo* para dar 3-*tert*-butoxicarbonil-7-cloro-6-mercapto-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (0.34 g, 1.086 mmol). Se disuelve la 3-*tert*-butoxicarbonil-7-cloro-6-mercapto-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina cruda (0.34 g, 1.086 mmol) en DMF anhidro (10 mL), se agrega hidruro de sodio (65 mg, 1.63 mmol, 60% en aceite mineral) y se agita la mezcla durante 5 min. Se agrega una solución de bromuro de (±)-1-(4-fluorofenil)etilo (332 mg, 1.63 mmol) en DMF anhidro (5 mL) y se calienta la solución a 45°C durante la noche. Se enfría a temperatura ambiente, se agrega agua y se extrae la fase acuosa dos veces con EtOAc. Se secan los extractos orgánicos combinados sobre Na_2SO_4 anhidro, se filtra y se concentra *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con hexano y hexano/EtOAc (19:1 y 9:1) para dar (±)-3-*tert*-butoxicarbonil-7-cloro-6-[1-(4-fluorofenil)etiltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina como aceite (397 mg, 84%). EM (ER+) *m/z*: 336 $(M+H-Boc)^+$.

Se usa un método similar al Procedimiento General 1-4 para desproteger (±)-3-*tert*-butoxicarbonil-7-cloro-6-[1-(4-fluorofenil)etiltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (47 mg, 0.108 mmol) y dar el compuesto del

título como un sólido (39 mg, 99%). EM (ER+) *m/z*: 336 $(M+H)^+$.

Ejemplos 621-622

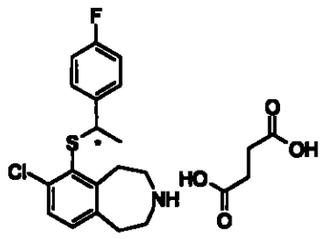
Los Ejemplos 621-622 se pueden preparar esencialmente como se describe en el Ejemplo 620 usando 3-*tert*-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina y el bromuro de alquilo apropiado. Los rendimientos totales y datos EM (ER+) se muestran en la Tabla a continuación.

Ej.	Estructura	Compuesto	Rendimiento (%)	EM (ER+) m/z
621		Clorohidrato de (±)-7-cloro-6-[1-(3-fluorofenil)etiltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	75	336 (M+H)+
622		Clorohidrato de (±)-7-cloro-6-(1-metil-2-fenil-	80	332 (M+H)+

		etiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina		

Ejemplos 623 y 624

Succinato de 7-cloro-6-[1-(4-fluorofenil)etiltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina Isómero 1 y Succinato de 7-cloro-6-[1-(4-fluorofenil)etiltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina Isómero 2



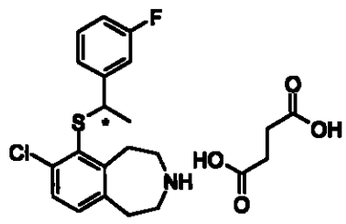
Se separan los dos enantiómeros de (±)-3-*tert*-butoxicarbonil-7-cloro-6-[1-(4-fluorofenil)etiltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina por CLAR quiral (columna Chiralcel OJ-H 4.6 x 150 mm, eluyendo con metanol a 0.6 mL/min).

Se somete el Isómero 1 (t_R = 7.3 min, ee > 99.9%) al Procedimiento General 2-1 para proporcionar succinato de 7-cloro-6-[1-(4-fluorofenil)etiltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina isómero 1 como un sólido blanco. EM (ER+) *m/z* 336 $(M+H)^+$.

Se somete el Isómero 2 (t_R = 12.9 min, ee = 99.9%) al Procedimiento General 2-1 para proporcionar succinato de 7-cloro-6-[1-(4-fluorofenil)etiltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina isómero 2 como un sólido blanco. EM (ER+) *m/z* 336 $(M+H)^+$.

Ejemplos 625 y 626

Succinato de 7-cloro-6-[1-(3-fluorofenil)etiltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina Isómero 1 y Succinato de 7-cloro-6-[1-(3-fluorofenil)etiltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina Isómero 2



Se separan los dos enantiómeros de (±)-3-*tert*-butoxicarbonil-7-cloro-6-[1-(3-fluorofenil)etiltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina por CLAR quiral (columna Chiralcel OJ-H 4.6 x 150 mm, eluyendo con metanol a 0.6 mL/min).

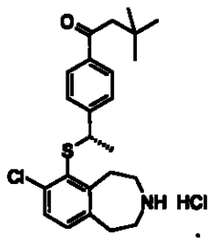
Se somete el Isómero 1 (t_R = 5.4 min, ee > 99.9%) al Procedimiento General 2-1 para proporcionar succinato de 7-cloro-6-[1-(3-fluorofenil)etiltio]-2,3,4,5-tetrahidro-1*H*-

benzo[*d*]azepina isómero 1 como un sólido blanco. EM (ER+) *m/z* 336 $(M+H)^+$.

Se somete el Isómero 2 (t_R = 11.2 min, ee = 99.7%) al Procedimiento General 2-1 para proporcionar succinato de 7-cloro-6-[1-(3-fluorofenil)etiltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina isómero 2 como un sólido blanco. EM (ER+) *m/z* 336 $(M+H)^+$.

Ejemplo 627

Clorohidrato de (S)-7-cloro-6-{1-[4-(3,3-dimetilbutiril)-fenil]-etiltio}-2,3,4,5-tetrahidro-1H-benzo[d]azepina



Se calienta la mezcla de 3-tert-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1H-benzo[d]azepina (310 mg, 0.807 mmol) e hidróxido de potasio (1.45 g, 25.83 mmol) en metanol (5 mL) a 50°C durante 3 h. Se enfría la mezcla de reacción a temperatura ambiente y se diluye con NH_4Cl acuoso saturado y EtOAc. Se separan las capas y se extrae la capa acuosa tres veces con EtOAc. Se secan los extractos orgánicos combinados sobre Na_2SO_4, se filtran y se concentran in vacuo. Se disuelve la 3-tert-butoxicarbonil-7-

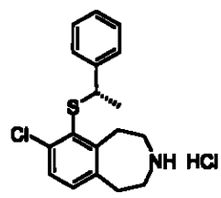
cloro-6-mercapto-2,3,4,5-tetrahidro-1H-benzo[d]azepina cruda en DMF anhidro (2 mL) y se enfría a 0°C. Se agrega hidruro de sodio (21 mg, 0.888 mmol) y una solución de (R)-1-[4-(1-bromoetil)-fenil]-3,3-dimetilbutan-1-ona {se prepara por la mezcla de (S)-1-[4-(1-hidroxietil)-fenil]-3,3-dimetilbutan-1-ona (213 mg, 0.969 mmol), trifenilfosfina (296 mg, 1.130 mmol) y NBS (201 mg, 1.13 mmol) en THF anhidro (5 mL) a 0°C y luego temperatura ambiente}. Se agita la mezcla a 0°C durante 30 min y se apaga con agua. Se diluye con EtOAc y se extrae la capa acuosa tres veces con EtOAc. Se secan los extractos orgánicos combinados sobre Na_2SO_4, se filtran y se concentran in vacuo. Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con hexano/EtOAc (85:15) para dar (S)-3-tert-butoxicarbonil-7-cloro-6-{1-[4-(3,3-dimetilbutiril)-fenil]-etiltio}-2,3,4,5-tetrahidro-1H-benzo[d]azepina como aceite amarillo (197 mg, 47%).

Se usa un método similar al Procedimiento General 1-4, usando (S)-3-tert-butoxicarbonil-7-cloro-6-{1-[4-(3,3-dimetilbutiril)-fenil]-etiltio}-2,3,4,5-tetrahidro-1H-benzo[d]azepina (197 mg, 0.382 mmol) para dar el compuesto del título como un sólido blanco (161 mg, 93%). EM (ER+) m/z: 416 $(M+H)^+$; ee = 92%, t_R = 11.27 min (Chiralcel OJ, 4.6 x 250 mm, 45°C, eluyente: isopropanol 20% con trietilamina 0.05% en SFC, relación de flujo 2 mL/min, detector UV a 234 nm).

1984

Ejemplo 628

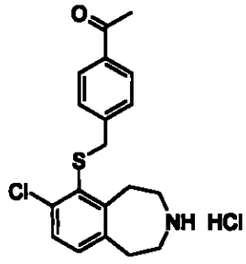
Clorohidrato de (*S*)-7-cloro-6-(1-fenil-etiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



El Ejemplo 628 se puede preparar esencialmente como se describe en el Ejemplo 627 usando 3-*tert*-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina y (*R*)-(1-bromo-etil)-benceno (64% de rendimiento, EM (ER+) *m/z* 318 $(M+H)^+$).

Ejemplo 629

Clorohidrato de 6-(4-Acetil-benciltio)-7-cloro-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



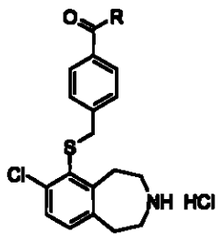
Se usa un método similar al Procedimiento General 7 para reaccionar 3-*tert*-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (200 mg, 0.521 mmol) con bromuro de 4-acetilbencilo (555 mg,

2.605 mmol). Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo secuencialmente con hexano y hexano/EtOAc (9:1, 4:1) para obtener 6-(4-acetil-benciltio)-3-*tert*-butoxicarbonil-7-cloro-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (190 mg, 82%).

Se usa un método similar al Procedimiento General 1-4 para desproteger 6-(4-acetil-benciltio)-3-*tert*-butoxicarbonil-7-cloro-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (170 mg, 0.381 mmol) y dar el compuesto del título como un sólido blanco (140 mg, 96%). EM (ER+) *m/z*: 346 $(M+H)^+$.

Ejemplos 630-634

Los Ejemplos 630-634 se pueden preparar esencialmente como se describe en el Ejemplo 629 usando 3-*tert*-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina y el bromuro de bencilo apropiado. Los rendimientos totales y datos EM (ER+) se muestran en la Tabla a continuación.

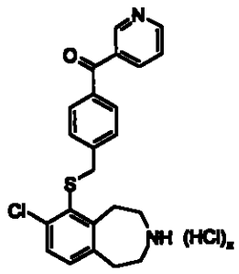


Ej.	R	Compuesto	Rendim	EM

			iento (%)	(ER+) m/z
630	Etilo	Clorohidrato de 7-cloro-6-(4-propionil-benciltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	87	360 $(M+H)^+$
631	*n*-Propilo	Clorohidrato de 6-(4-Butiril-benciltio)-7-cloro-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	81	374 $(M+H)^+$
632	*i*-Propilo	Clorohidrato de 7-cloro-6-(4-isobutiril-benciltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	69	374 $(M+H)^+$
633	*i*-Butil	Clorohidrato de 7-cloro-6-[4-(3-metil-butiril)-benciltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	68	388 $(M+H)^+$
634	2-Piridil	Clorohidrato de 7-cloro-6-[4-(piridina-2-carbonil)-benciltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	38	409 $(M+H)^+$

Ejemplo 635

Clorohidrato de 7-cloro-6-[4-(piridina-3-carbonil)-benciltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



Se disuelve 3-*tert*-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (150 mg, 0.39 mmol) en metanol (10 mL) y se agrega hidróxido de potasio (0.7 g, 12.47 mmol). Se calienta a 60°C durante 4 h. Se enfría la mezcla de reacción a temperatura ambiente, se agrega cloruro de amonio saturado acuoso y se concentra *in vacuo*. Se divide el residuo entre EtOAc y agua. Se seca la fase orgánica sobre Na_2SO_4 anhidro y se concentra *in vacuo* para dar 3-*tert*-butoxicarbonil-7-cloro-6-mercapto-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (0.12 g). Se disuelve la 3-*tert*-butoxicarbonil-7-cloro-6-mercapto-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina cruda (0.12 g, 5.2 mmol) en DEMO anhidro (6 mL) y se agrega trietilamina (0.325 mL, 2.34 mmol) y metansulfonato de 4-(piridina-3-carbonil)-bencilo (114 mg, 0.39 mmol). Se calienta la solución a 40°C durante la noche. Se enfría a temperatura ambiente, se diluye la mezcla con hexano/EtOAc (1:1, 100 mL), y se lava la solución orgánica

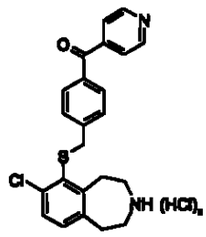
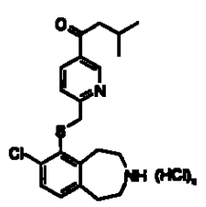
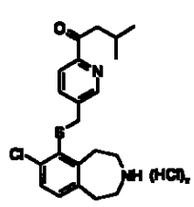
secuencialmente con salmuera y agua enfriada en hielo. Se seca la capa orgánica sobre Na_2SO_4 anhidro, se filtra y se concentra *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con hexano y hexano/EtOAc (1:1) para dar 3-*tert*-butoxicarbonil-7-cloro-6-[4-(piridina-3-carbonil)-benciltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina como aceite (123 mg, 64%).

Se usa un método similar al Procedimiento General 1-4 para desproteger 3-*tert*-butoxicarbonil-7-cloro-6-[4-(piridina-3-carbonil)-benciltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (113 mg, 0.22 mmol) y dar el compuesto del título como un sólido (105 mg, 99%). EM (ER+) *m/z*: 409 $(M+H)^+$.

Ejemplos 636-638

Los Ejemplos 636-638 se pueden preparar esencialmente como se describe en el Ejemplo 635 usando 3-*tert*-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina y el metansulfonato apropiado. Los rendimientos totales y datos EM (ER+) se muestran en la Tabla a continuación.

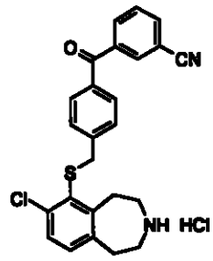
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Ej.	Estructura	Compuesto	rendimiento (%)	EM (ER+) m/z
636		Clorohidrato de 7-cloro-6-[4-(piridina-4-carbonil)-benciltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	39	409 (M+H)+
637		Clorohidrato de 7-cloro-6-[5-(3-metil-butiril)-piridin-2-il-metiltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	69	389 (M+H)+
638		Clorohidrato de 7-cloro-6-[6-(3-metil-butiril)-piridin-3-il-metiltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	57	389 (M+H)+

Ejemplo 639

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Clorohidrato de 7-cloro-6-[4-(3-cianobenzoil)-benciltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



Se disuelve 3-*tert*-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (200 mg, 0.52 mmol) en metanol (12 mL) y se agrega hidróxido de potasio (0.935 g, 16.66 mmol). Se calienta a 60°C durante 4 h. Se enfría la mezcla de reacción a temperatura ambiente, se agrega cloruro de amonio saturado acuoso y se concentra *in vacuo*. Se divide el residuo entre EtOAc y agua. Se seca la fase orgánica sobre Na_2SO_4 anhidro y se concentra *in vacuo* para dar 3-*tert*-butoxicarbonil-7-cloro-6-mercapto-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (0.16 g, 5.2 mmol). Se disuelve la 3-*tert*-butoxicarbonil-7-cloro-6-mercapto-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina cruda (0.16 g, 0.52 mmol) en DMSO anhidro (5 mL) y se agrega trietilamina (0.435 mL, 3.12 mmol) y bromuro de 4-(3-ciano-benzoil)bencilo (289 mg, 0.96 mmol). Se calienta la solución a 40°C durante la noche. Se enfría a temperatura ambiente, se diluye la mezcla con hexano/EtOAc (1:1, 100 mL), y se lava la solución orgánica secuencialmente con salmuera y agua enfriada en hielo. Se

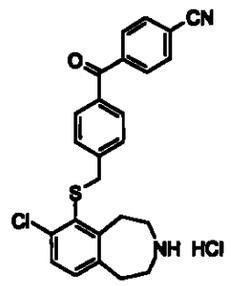
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seca la capa orgánica sobre Na_2SO_4 anhidro, se filtra y se concentra *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con hexano y hexano/EtOAc (9:1, 4:1) para dar 3-*tert*-butoxicarbonil-7-cloro-6-[4-(3-cianobenzoil)-benciltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina como aceite (212 mg, 77%).

Se usa un método similar al Procedimiento General 1-4 para desproteger 3-*tert*-butoxicarbonil-7-cloro-6-[4-(3-cianobenzoil)-benciltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (200 mg, 0.37 mmol) y dar el compuesto del título como un sólido (136 mg, 77%). EM (ER+) *m/z*: 433 $(M+H)^+$.

Ejemplo 640

Clorohidrato de 7-cloro-6-[4-(4-cianobenzoil)-benciltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



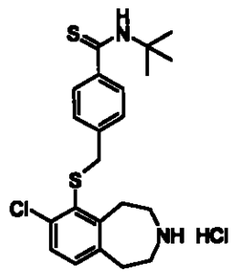
El Ejemplo 640 se puede preparar esencialmente como se describe en el Ejemplo 639 usando 3-*tert*-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1*H*-

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benzo[*d*]azepina y bromuro de 4-(4-ciano-benzoil)bencilo (49% de rendimiento, EM (ER+) *m/z* 433 $(M+H)^+$).

Ejemplo 641

Clorohidrato de 7-cloro-6-(4-*tert*-butiltiocarbamoil-benciltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



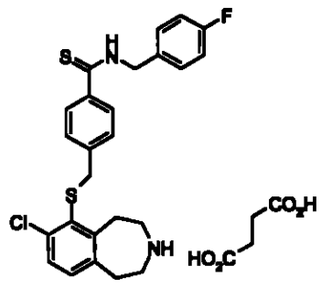
Se combina 7-cloro-6-(4-*tert*-butilcarbamoil-benciltio)-2,3,4,5-tetrahidro-1*H*-benzo [*d*]azepina (53 mg, 0.13 mmol) con 2,4-bis(4-metoxifenil)-1,3-dithia-2,4-difosfetano-2,4-disulfuro (reactivo Lawesson's) (53 mg, 0.13 mmol) en 1,4-dioxano anhidro (1 mL) en un tubo sellado y se calienta a 100°C durante 2 h. Se enfría la mezcla de reacción a temperatura ambiente, se concentra *in vacuo* y se purifica el residuo por cromatografía SCX para obtener 7-cloro-6-(4-*tert*-butiltiocarbamoil-benciltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina como un aceite amarillo. Se purifica por CLAR preparativa de fase inversa [Zorbax SB-Fenil 21.2 x 250 mm, 5 micras, 22 mL/min de HCl acuoso 0.1%/acetonitrilo (9:1 hasta 1:9) durante 30 min, detector a 230 nm].

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Se usa un método similar al Procedimiento General 2-2 para obtener el compuesto del título como un sólido amarillo (36 mg, 58%). EM (ER+) *m/z*: 419 $(M+H)^+$.

Ejemplo 642

Succinato de 7-cloro-6-[4-(4-fluorobenciltiocarbamoil)-benciltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



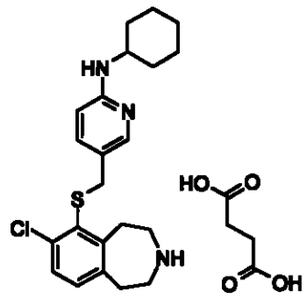
Se combina 7-cloro-6-[4-(4-fluorobencilcarbamoil)-benciltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (23 mg, 0.05 mmol) con 2,4-bis(4-metoxifenil)-1,3-ditia-2,4-difosfetano-2,4-disulfuro (reactivo de Lawesson) (23 mg, 0.05 mmol) en 1,4-dioxano anhidro (1 mL) en un tubo sellado y se calienta a 100°C durante 2 h. Se enfría la mezcla de reacción a temperatura ambiente, se concentra *in vacuo* y se purifica el residuo por cromatografía SCX para obtener 7-cloro-6-[4-(4-fluorobenciltiocarbamoil)-benciltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina como un aceite amarillo.

Se usa un método similar al Procedimiento General 2-1 para obtener el compuesto del título como un sólido blanco (10 mg, 42%). EM (ER+) *m/z*: 471 $(M+H)^+$.

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Ejemplo 643

Succinato de 7-cloro-6-(6-ciclohexilamino-piridin-3-ilmetiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



Se usa un método similar al Procedimiento General 7, usando 3-*tert*-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (2 g, 5.2 mmol) y 2-cloro-5-(clorometil)piridina (843 mg, 5.2 mmol) para dar 3-*tert*-butoxicarbonil-7-cloro-6-(6-cloro-piridin-3-ilmetiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (2.2 g, 95%). EM (ER+) *m/z*: 439.1 $(M+H)^+$.

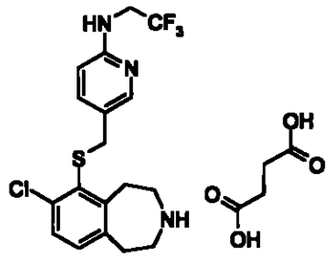
Se hace mezcla espesa de acetato de paladio(II) (434 mg, 1.9 mmol), BINAP (1.2 g, 1.9 mmol), *tert*-butóxido de sodio (644 mg, 6.7 mmol), ciclohexilamina (1.4 g, 14.4 mmol) y 3-*tert*-butoxicarbonil-7-cloro-6-(6-cloro-piridin-3-ilmetiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (2.1 g, 4.8 mmol) en tolueno anhidro (70 mL). Se desgasifica la mezcla espesa bajo alojamiento al vacío, luego se burbujea nitrógeno. Se calienta la mezcla a 95°C durante 16 h bajo una atmósfera de nitrógeno. Se enfría la mezcla a temperatura ambiente, se diluye con EtOAc (50 mL) y se filtra a través de Celite®. Se

concentra el filtrado a un aceite y se purifica por cromatografía en gel de sílice eluyendo con hexano/EtOAc (19:1 hasta 13:7 gradiente) para obtener 3-*tert*-butoxicarbonil-7-cloro-6-(6-ciclohexilamino-piridin-3-ilmetiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (800 mg, 33%). EM (ER+) *m/z*: 502.2 $(M+H)^+$.

Se usa un método similar al Procedimiento General 1-5 para desproteger 3-*tert*-butoxicarbonil-7-cloro-6-(6-ciclohexilamino-piridin-3-ilmetiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (790 mg, 1.6 mmol). Se purifica por cromatografía en gel de sílice eluyendo con diclorometano/amoniaco 2M en metanol (gradiente 99:1 hasta 95:5) para dar la base libre del compuesto del título. Se usa un método similar al Procedimiento General 2-1 para obtener el compuesto del título (670 mg, 82%). EM (ER+) *m/z*: 402.1 $(M+H)^+$.

Ejemplo 644

Succinato de 7-cloro-6-(6-trifluoroetilamino-piridin-3-ilmetiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina

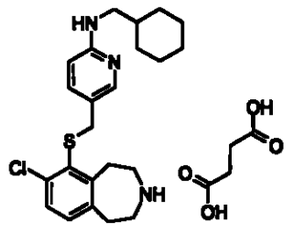


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El Ejemplo 644 se puede preparar esencialmente como se describe en el Ejemplo 643 al usar 3-*tert*-butoxicarbonil-7-cloro-6-(6-cloro-piridin-3-ilmetiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina y 2,2,2-trifluoroetilamina (10% de rendimiento, EM (ER+) *m/z* 502.2 $(M+H)^+$).

Ejemplo 645

Succinato de 7-cloro-6-(6-ciclohexilmetilamino-piridin-3-ilmetiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



Se agrega ciclohexilmetilamina (3 mL) a un matraz que contiene 3-*tert*-butoxicarbonil-7-cloro-6-(6-cloro-piridin-3-ilmetiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (340 mg, 0.8 mmol) y cloruro de amonio (50 mg, 0.92 mmol). Se calientan los contenidos en un matraz sellado a 170°C durante 7 h. Se enfría el matraz a temperatura ambiente, se diluye con EtOAc (50 mL) y se lava con agua (20 mL). Se colecta la capa orgánica y se concentra *in vacuo*. Se purifica el residuo por cromatografía en gel de sílice eluyendo con hexano/EtOAc (19:1 hasta 4:1 gradiente) para obtener 3-*tert*-butoxicarbonil-7-cloro-6-(6-ciclohexilmetilamino-piridin-3-

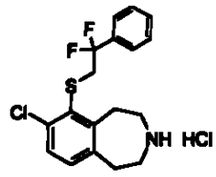
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ilmetiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (160 mg, 40%).

Se usa un método similar al Procedimiento General 1-5 para desproteger 3-*tert*-butoxicarbonil-7-cloro-6-(6-ciclohexilmetilamino-piridin-3-ilmetiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina. Se purifica por cromatografía en gel de sílice eluyendo con diclorometano/amoniaco 2M en metanol (99:1, 98:2, 96:4 gradiente) para dar la base libre del compuesto del título. Se usa un método similar al Procedimiento General 2-1 para obtener el compuesto del título (115 mg, 70%). EM (ER+) *m/z*: 416.0 $(M+H)^+$.

Ejemplo 646

Clorohidrato de 7-cloro-6-(2,2-difluoro-2-fenil-etiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



Se disuelve 3-*tert*-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (200 mg, 0.52 mmol) en metanol (10 mL) y se agrega hidróxido de potasio (0.934 g, 16.64 mmol). Se calienta a 60°C durante 4 h. Se enfría la mezcla de reacción a temperatura ambiente,

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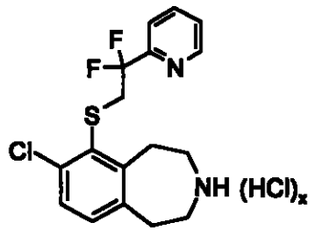
se agrega cloruro de amonio saturado acuoso y se concentra *in vacuo*. Se divide el residuo entre EtOAc y agua. Se seca la fase orgánica sobre Na_2SO_4 anhidro y se concentra *in vacuo* para dar 3-*tert*-butoxicarbonil-7-cloro-6-mercapto-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (0.163 g). Se disuelve la 3-*tert*-butoxicarbonil-7-cloro-6-mercapto-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina cruda (0.163 g, 0.52 mmol) en DMSO anhidro (5 mL) y se agrega trietilamina (0.43 mL, 3.12 mmol) y trifluorometansulfonato de 2,2-difluoro-2-feniletilo (151 mg, 0.52 mmol). Se calienta la solución a 40°C durante la noche. Se enfría a temperatura ambiente, se agrega agua y se extrae la fase acuosa dos veces con EtOAc. Se secan los extractos orgánicos combinados sobre Na_2SO_4 anhidro, se filtra y se concentra *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con hexano y hexano/EtOAc (19:1, 9:1 y 4:1) para dar 3-*tert*-butoxicarbonil-7-cloro-6-(2,2-difluoro-2-fenil-etiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina como aceite (132 mg, 56%).

Se usa un método similar al Procedimiento General 1-4 para desproteger 3-*tert*-butoxicarbonil-7-cloro-6-(2,2-difluoro-2-fenil-etiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (132 mg, 0.29 mmol) y dar el compuesto del título como un sólido (111 mg, 98%). EM (ER+) *m/z*: 354 $(M+H)^+$.

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Ejemplo 647

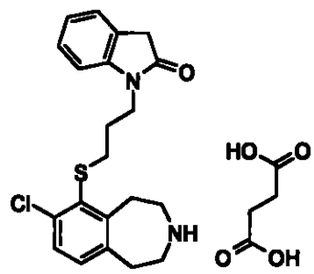
Clorohidrato de 7-cloro-6-(2,2-difluoro-2-piridin-2-il-etiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



El Ejemplo 647 se puede preparar esencialmente como se describe en el Ejemplo 646 usando 3-*tert*-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina y trifluorometansulfonato de 2,2-difluoro-2-piridin-2-il-etilo (preparado al seguir el procedimiento descrito en *J. Med. Chem.* 2003, *46*, 461-473) (66% de rendimiento, EM (ER+) *m/z* 355 $(M+H)^+$).

Ejemplo 648

Succinato de 7-cloro-6-[3-(2-oxo-2,3-dihidro-indol-1-il)-propiltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



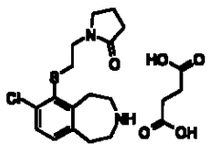
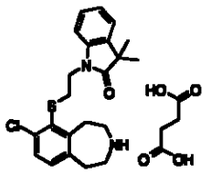
Se agrega hidróxido de potasio (899 mg, 16.64 mmol) en una porción a una solución de 3-*tert*-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (200 mg, 0.52 mmol) en metanol (10 mL). Se calienta la reacción a 50°C bajo nitrógeno durante 24 h, luego se enfría a temperatura ambiente y se agrega 1-(3-cloro-propil)-1,3-dihidro-indol-2-ona (217 mg, 1.04 mmol). Se agita la reacción a temperatura ambiente durante 4 días. Se remueven los solventes *in vacuo*, se agrega diclorometano (20 mL) y agua (20 mL). Se remueve la capa orgánica y se seca usando un separador de fase ISCO® luego se concentra *in vacuo* para dar 3-*tert*-butoxicarbonil-7-cloro-6-[3-(2-oxo-2,3-dihidro-indol-1-il)-propiltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina como polvo anaranjado. EM (ER+) *m/z*: 509 $(M+Na)^+$.

Se disuelve 3-*tert*-butoxicarbonil-7-cloro-6-[3-(2-oxo-2,3-dihidro-indol-1-il)-propiltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (0.52 mmol) en diclorometano (10 mL), luego se agrega TFA (2 mL) gota a gota y se agita durante 2 h. Se remueven los solventes in vacuo, luego la base libre usando una columna SCX, eluyendo con amoniaco 7M en metanol. Se purifica usando CLAR de fase inversa guiada por UV [columna Supelco Discovery C18 (21.2 x 100 mm, 5µm empacado), 20 mL/min

relación de flujo, eluyendo con agua/acetonitrilo/ácido acético gradiente durante 15 min, colección de fracción accionada usando detector UV (220 y 254 nm)] seguido por columna SCX, eluyendo con amoniaco 7M en metanol, luego CLAR de fase inversa guiada por masa [columna Supelco Discovery C18 (21.2 x 100 mm, empacado 5µm), relación de flujo 25 mL/min, eluyendo con agua/acetonitrilo/gradiente de ácido acético durante 12 min, colección de fracción accionada por Electrorocío EM] y columna SCX. Se concentra *in vacuo*, luego se usa un método similar al Procedimiento General 2-1 y se seca por congelado para dar el compuesto del título como un sólido rosa ligero (51 mg, 19%). EM (ER+) *m/z*: 387 $(M+H)^+$.

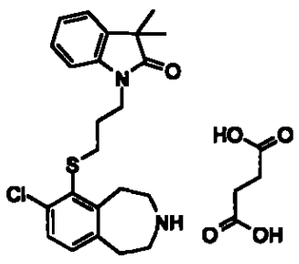
Ejemplos 649-650

Los Ejemplos 649-650 se pueden preparar esencialmente como se describe en el Ejemplo 648 usando 3-*tert*-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina y el cloruro de alquilo substituido apropiadamente. Los rendimientos totales y datos EM (ER+) se muestran en la Tabla a continuación.

Ej.	Estructura	Compuesto	Rendimiento (%)	EM (ER+) m/z
649		Succinato de 7-cloro-6-[2-(2-oxo-pirrolidin-1-il)-etiltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	71	325 (M+H)+
650		Succinato de 7-cloro-6-[2-(3,3-dimetil-2-oxo-2,3-dihidro-indol-1-il)-etiltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	32	401 (M+H)+

Ejemplo 651

Succinato de 7-cloro-6-[3-(3,3-dimetil-2-oxo-2,3-dihidro-indol-1-il)-propiltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina

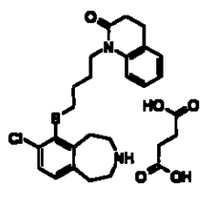
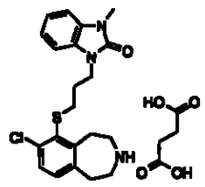
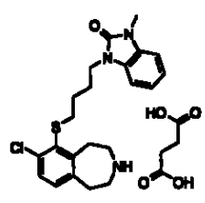


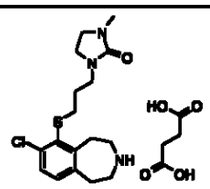
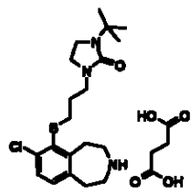
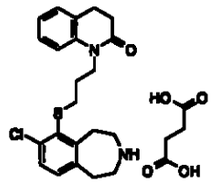
Se agrega hidróxido de potasio (170 mg, 3.03 mmol) en una porción a una solución de 3-*tert*-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (187 mg, 0.49 mmol) en metanol (10 mL). Se calienta la reacción a reflujo bajo nitrógeno durante la noche. Luego se agrega porción adicional de KOH (867 mg, 15.45 mmol) y se calienta a reflujo durante 3 h. Luego Se enfría a temperatura ambiente y se agrega 1-(3-bromo-propil)-1,3-dihidro-3,3-dimetil-indol-2-ona (274 mg, 0.97 mmol, preparado al seguir el procedimiento descrito en *Perkin 1* 2000, 769-774). Se agita la reacción a temperatura ambiente durante la noche. Se remueven los solventes *in vacuo*, se agrega agua y se extrae con éter de dietilo (2 x 50 mL). Se combinan los extractos orgánicos, se lava con agua (2 x 50 mL) y salmuera (50 mL). Se seca sobre $MgSO_4$ y se concentra *in vacuo*. Se purifica por cromatografía en gel de sílice eluyendo con isohexano/EtOAc (gradiente 1:0 hasta 1:1 durante 40 min) para dar 3-*tert*-butoxicarbonil-7-cloro-6-[3-(3,3-dimetil-2-oxo-2,3-dihidro-indol-1-il)-propiltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina como un aceite incoloro (330 mg), contaminado 50% con 1-(3-metoxipropil)-1,3-dihidro-3,3-dimetil-indol-2-ona. EM (ER+) *m/z*: 537 $(M+Na)^+$.

Se disuelve 3-tert-butoxicarbonil-7-cloro-6-[3-(3,3-dimetil-2-oxo-2,3-dihidro-indol-1-il)-propiltio]-2,3,4,5-tetrahidro-1H-benzo[d]azepina (240 mg, 0.52 mmol) en diclorometano (10 mL), luego se agrega TFA (1 mL) gota a gota y se agita a temperatura ambiente durante la noche. Se remueven los solventes in vacuo para dar un aceite color paja (580 mg), luego la base libre usando una columna SCX, eluyendo con amoniaco 7M en metanol. Se concentra in vacuo, luego se usa un método similar al Procedimiento General 2-1 y se seca por congelado para dar el compuesto del título como un sólido (196 mg, 82%). EM (ER+) m/z: 415 $(M+H)^+$.

Ejemplos 652-654

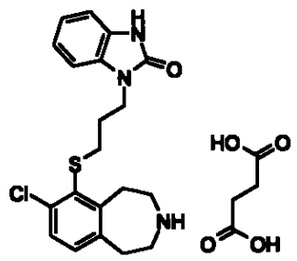
Los Ejemplos 652-654 se pueden preparar esencialmente como se describe en el Ejemplo 651 usando 3-*tert*-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina y el bromuro de alquilo apropiado. Los Ejemplos 655-657 se pueden preparar esencialmente como se describe en el Ejemplo 651 usando el cloruro de alquilo apropiado. Los rendimientos totales y datos EM (ER+) se muestran en la Tabla a continuación.

Ej.	Estructura	Compuesto	Rendimiento (%)	EM (ER+) m/z
652		Succinato de 7-cloro-6-[4-(2-oxo-3,4-dihidro-2*H*-quinolin-1-il)-butiltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	71	414 (M+H)+
653		Succinato de 7-cloro-6-[3-(3-metil-2-oxo-2,3-dihidro-benzoimidazol-1-il)-propiltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	31	402 (M+H)+
654		Succinato de 7-cloro-6-[4-(3-metil-2-oxo-2,3-dihidro-benzoimidazol-1-il)-butiltio]-2,3,4,5-tetrahidro-	31	416 (M+H)+

		1*H*-benzo[*d*]azepina		
655		Succinato de 7-cloro-6-[3-(3-metil-2-oxo-imidazolidin-1-il)-propiltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	29	354 (M+H)+
656		Succinato de 7-cloro-6-[3-(3-*tert*-butil-2-oxo-imidazolidin-1-il)-propiltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	31	396 (M+H)+
657		Succinato de 7-cloro-6-[3-(2-oxo-3,4-dihidro-2*H*-quinolin-1-il)-propiltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	66	400 (M+H)+

Ejemplo 658

Succinato de 7-cloro-6-[3-(2-oxo-2,3-dihidro-benzoimidazol-1-il)-propiltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



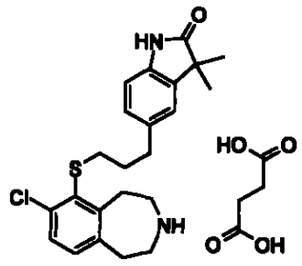
Se agrega hidróxido de potasio (933 mg, 16.6 mmol) en una porción a una solución de 3-*tert*-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (200 mg, 0.52 mmol) en metanol (10 mL). Se calienta la reacción a reflujo bajo nitrógeno 4 h. Luego Se enfría a temperatura ambiente y se agrega 1-(3-bromo-propil)-3-isopropenil-1,3-dihidro-benzoimidazol-2-ona (142 mg, 0.52 mmol). Se agita la reacción a temperatura ambiente durante la noche. Se remueven los solventes *in vacuo*, se extrae en éter de dietilo (2 x 50 mL), se lava con agua (2 x 50 mL) y salmuera (50 mL). Se seca sobre $MgSO_4$, se filtra y se concentra *in vacuo* para dar 3-*tert*-butoxicarbonil-7-cloro-6-[3-(2-oxo-2,3-dihidro-benzoimidazol-1-il)-propiltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina como un aceite (209 mg, 76%). EM (ER+) *m/z*: 550 $(M+Na)^+$.

Se disuelve 3-*tert*-butoxicarbonil-7-cloro-6-[3-(2-oxo-2,3-dihidro-benzoimidazol-1-il)-propiltio]-2,3,4,5-

tetrahidro-1*H*-benzo[*d*]azepina (209 mg, 0.396 mmol) en diclorometano (10 mL), luego se agrega TFA (0.5 mL) gota a gota y se agita a temperatura ambiente durante la noche. Se remueven los solventes *in vacuo* luego la base libre usando una columna SCX, eluyendo con amoniaco 7M en metanol. Se concentra *in vacuo*, luego se usa un método similar al Procedimiento General 2-1 y se seca por congelado para dar el compuesto del título como un sólido (140 mg, 70%). EM (ER+) *m/z*: 388 $(M+H)^+$.

Ejemplo 659

Succinato de 7-cloro-6-[3-(3,3-dimetil-2-oxo-2,3-dihidro-1*H*-indol-5-il)-propiltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



Bajo atmósfera de nitrógeno, se agrega hidróxido de potasio (138 mg, 2.46 mmol) a una solución agitada de 3-*tert*-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (375 mg, 0.97 mmol) en metanol (10 mL). Se calienta bajo reflujo durante 2 h luego se agrega hidróxido de potasio adicional (159 mg, 2.83 mmol) y se continua calentando bajo reflujo durante otras 6 h. Se enfría

1509

la mezcla de reacción y se agrega gota a gota por medio de cánula una solución de 5-(3-cloropropil)-3,3-dimetil-1,3-dihidro-indol-2-ona (245 mg, 1.03 mmol) en metanol (10 mL). Se agita a temperatura ambiente durante la noche luego se calienta a 50°C durante 5 h. Se agrega yoduro de potasio (186 mg, 1.12 mmol) a la mezcla de reacción y luego se calienta bajo reflujo durante 5 h. Se concentra *in vacuo* y se divide el residuo entre agua (100 mL) y EtOAc (50 mL). Se extrae la fase acuosa con EtOAc (2 x 50 mL). Se lavan los extractos combinados con salmuera (50 mL), se secan sobre $MgSO_4$, se filtran y se concentran *in vacuo* para obtener la mezcla cruda como un aceite amarillo. Se diluye este aceite con diclorometano luego se reconcentra *in vacuo* y se repite hasta que queda un sólido. Se seca el sólido en un horno al vacío para dar 3-*tert*-butoxicarbonil-7-cloro-6-[3-(3,3-dimetil-2-oxo-2,3-dihidro-1*H*-indol-5-il)-propiltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina como un sólido amarillo (481 mg) que se usó sin purificación adicional. EM (ER+) *m/z*: 537 $(M+Na)^+$.

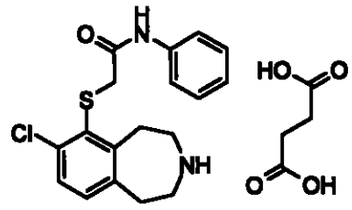
Se agrega ácido trifluoroacético (0.2 mL, 2.6 mmol) a una solución de 3-*tert*-butoxicarbonil-7-cloro-6-[3-(3,3-dimetil-2-oxo-2,3-dihidro-1*H*-indol-5-il)-propiltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (257 mg, 0.5 mmol) en diclorometano (5 mL) luego se agita a temperatura ambiente durante el fin de semana. Se concentra *in vacuo*. Se disuelve el residuo en metanol y se carga sobre una columna SCX.

Eluyendo con metanol seguido por amoniaco 7M en metanol. Se colecta la fracción básica y se concentra *in vacuo*. Se purifica el residuo por CLEM preparativa [columna Supelco Discovery C18 (21.2 x 100 mm, 5µm empacado), 25 mL/min relación de flujo, eluyendo con un gradiente agua/acetonitrilo que contiene ácido acético como modificador durante 12 min, colección de fracción accionada por Electrorocío EM] para dar 7-cloro-6-[3-(3,3-dimetil-2-oxo-2,3-dihidro-1*H*-indol-5-il)-propiltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina como un sólido blanco (101 mg, 25% durante 2 etapas). EM (ER+) *m/z*: 415 $(M+H)^+$.

Se disuelve 7-cloro-6-[3-(3,3-dimetil-2-oxo-2,3-dihidro-1*H*-indol-5-il)-propiltio]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (101 mg, 0.24 mmol) en una mezcla de éter de dietilo (3 mL) y metanol (2 mL). Se agrega ácido succínico (28.7 mg, 0.24 mmol) y se permite la suspensión resultante hasta agitar a temperatura ambiente durante 2 h. Se concentra *in vacuo* y se seca el residuo en un horno al vacío para proporcionar el compuesto del título como un sólido blanco. EM (ER+) *m/z*: 415 $(M+H)^+$.

Ejemplo 660

Succinato de 7-cloro-6-(*N*-fenilcarbamoil-metiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



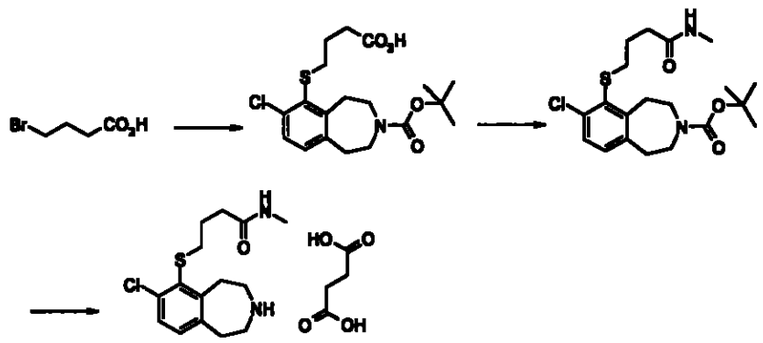
Se agrega hidróxido de potasio (890 mg, 15 mmol) en una porción a una solución de 3-*tert*-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (180 mg, 0.47 mmol) en metanol (10 mL). Se calienta la reacción a reflujo bajo nitrógeno 3 h. Luego Se enfría a temperatura ambiente, se agrega 2-cloro-*N*-fenil-acetamida (79 mg, 0.47 mmol) y se agita durante la noche. Se remueven los solventes *in vacuo*, se extraen en éter de dietilo (2 x 50 mL), se lavan con agua (2 x 50 mL) y salmuera (50 mL). Se secan sobre $MgSO_4$, se filtran y se concentran *in vacuo* para dar 3-*tert*-butoxicarbonil-7-cloro-6-(*N*-fenilcarbamoil-metiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina como un aceite claro (210 mg, 100%). EM (ER+) *m/z*: 460 $(M+Na)^+$.

Se disuelve 3-*tert*-butoxicarbonil-7-cloro-6-(*N*-fenilcarbamoil-metiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (210 mg, 0.47 mmol) en diclorometano (10 mL) luego se agrega TFA (0.5 mL) gota a gota y se agita a temperatura ambiente durante 3 días. Se remueven los solventes *in vacuo* luego la base libre usando una columna SCX, eluyendo con amoniaco 7M en metanol. Se concentra *in vacuo*, luego se usa un método similar al Procedimiento

General 2-1 y se seca por congelado para dar el compuesto del título como un sólido (150 mg, 69%). EM (ER+) *m/z*: 347 $(M+H)^+$.

Ejemplo 661

Succinato de 7-cloro-6-(3-metilcarbamoil-propiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



3-*tert*-Butoxicarbonil-7-cloro-6-(3-carboxi-propiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina: Se agrega hidróxido de potasio (700 mg, 12.5 mmol) en una porción a una solución de 3-*tert*-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (150 mg, 0.39 mmol) en metanol (10 mL). Se calienta la reacción a reflujo bajo nitrógeno 4 h. Luego Se enfría a temperatura ambiente, se agrega ácido 4-bromo-butírico (65 mg, 0.39 mmol) y se agita durante 3 días. Se remueven los solventes *in vacuo*, se neutralizan con cloruro de amonio (200 mL) y se extraen en EtOAc (2 x 50 mL). Se secan sobre $MgSO_4$, se filtran y se concentran *in vacuo*

para dar un aceite claro (125 mg). Se disuelve el aceite en DMF anhidro (10 mL) y se agrega hidruro de sodio (30 mg, 0.78 mmol de dispersión 60% en aceite) bajo nitrógeno. Se agita durante 30 min. Se agrega ácido 4-bromo-butírico (65 mg, 0.39 mmol) y se agita durante 30 min. Se vacía en agua (50 mL) y se extrae con éter de dietilo (2 x 50 mL). Se lavan los extractos orgánicos combinados con salmuera (50 mL) y se secan sobre $MgSO_4$. Se concentra el filtrado *in vacuo* para dar el intermediario deseado como un sólido (146 mg, 94%). EM (ER+) *m/z*: 398 $(M+H)^+$.

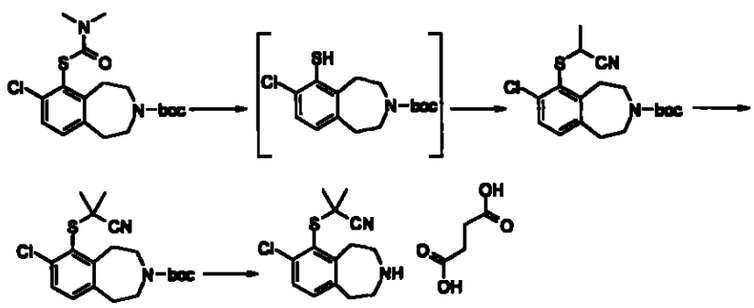
3-*tert*-Butoxicarbonil-7-cloro-6-(3-metilcarbamoil-propiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina: Se agrega tetrafluoroborato *de* *O*-benzotriazol-1-il-*N*,*N*,*N*',*N*'-tetrametiluronio (123 mg, 0383 mmol) en porciones a una solución de 3-*tert*-butoxicarbonil-7-cloro-6-(3-carboxi-propiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (146 mg, 0365 mmol) y metilamina (182 µL, 0.365 mmol) en DMF anhidro (5 mL) bajo nitrógeno a 0°C. Se agita durante 15 min luego se agrega diisopropiletilamina (127 µL, 0.73 mmol) en DMF anhidro (1 mL) y continua hasta agitar a 0°C durante 1 h. Se entibia a temperatura ambiente y continua hasta agitar durante la noche. Se vacía en agua (50 mL) y se extrae con EtOAc (3 x 20 mL). Se lavan los extractos orgánicos

combinados con $NaHCO_3$ acuoso saturado (50 mL) y salmuera (50 mL). Se secan sobre $MgSO_4$, se filtran y se concentran *in vacuo* para dar un aceite amarillo pálido (74 mg). EM (ER+) *m/z*: 398 $(M+H)^+$. Se purifica usando CLAR de fase inversa guiada por masa [columna Supelco Discovery C18 (21.2 x 100 mm, empacado 5µm), 25 mL/min relación de flujo, eluyendo con agua/acetonitrilo/ácido acético gradiente durante 12 min, colección de fracción accionada por Electrorocío EM]. Se concentra *in vacuo* para dar el intermediario deseado como un aceite incoloro (30 mg, 20%). EM (ER+) *m/z*: 435 $(M+Na)^+$.

Succinato de 7-cloro-6-(3-metilcarbamoil-propiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina: Se disuelve 3-*tert*-butoxicarbonil-7-cloro-6-(3-metilcarbamoil-propiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (30 mg, 0.07 mmol) en diclorometano (10 mL) luego se agrega TFA (0.5 mL) gota a gota y se agita a temperatura ambiente durante 3 días. Se remueven los solventes *in vacuo* luego la base libre usando una columna SCX, eluyendo con amoniaco 7M en metanol. Se concentra *in vacuo*, luego se usa un método similar al Procedimiento General 2-1 y se seca por congelado para dar el compuesto del título como un sólido (21 mg, 72%). EM (ER+) *m/z*: 313 $(M+H)^+$.

Ejemplo 662

Succinato de 7-cloro-6-(1-ciano-1-metil-etiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



3-tert-Butoxicarbonil-7-cloro-6-(1-ciano-etiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina: Se agrega hidróxido de potasio (10.8 g, 192 mmol) a una solución de 3-*tert*-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (3 g, 7.8 mmol) en metanol desgasificado (150 mL) bajo una atmósfera de nitrógeno. Se calienta la mezcla a 80°C durante 6 h. Se enfría la mezcla a temperatura ambiente, luego se concentra *in vacuo* a un aceite. Se disuelve el aceite en EtOAc (50 mL), se lava con cloruro de amonio saturado acuoso (30 mL). Se separa la capa orgánica y se extrae la capa acuosa con EtOAc (3 x 50 mL). Se secan los extractos orgánicos combinados sobre Na_2SO_4, se filtran y se concentran *in vacuo* a un aceite (2.4 g). Se disuelve el aceite en DMF anhidro (50 mL). Lentamente se agrega hidruro de sodio (470 mg, 11.7 mmol) en porciones durante 5 min seguido por 2-bromopropionitrilo (1 mL, 11.7 mmol). Se agita

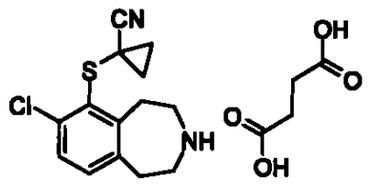
la mezcla bajo nitrógeno a temperatura ambiente durante 16 h. se diluye la mezcla lentamente con EtOAc (100 mL) y se lava con cloruro de amonio saturado acuoso frío (50 mL). Se separa la capa orgánica y se extrae la capa acuosa con EtOAc (3 x 50 mL). Se combinan los extractos orgánicos y se concentran *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con hexano/EtOAc (19:1 hasta 3:1 gradiente) para obtener el intermediario deseado (2.5 g, 89%). EM (ER+) *m/z*: 267.2 $(M-Boc)^+$.

3-*tert*-Butoxicarbonil-7-cloro-6-(1-ciano-1-metil-etiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina: Lentamente se agrega una solución de 3-*tert*-butoxicarbonil-7-cloro-6-(1-ciano-etiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (2.5 g, 6.8 mmol) en THF anhidro (20 mL) a una mezcla espesa de hidruro de sodio (1.4 g, 34 mmol) en THF anhidro (50 mL) a 0°C bajo una atmósfera de nitrógeno. Se agita la mezcla espesa durante 5 min, luego se agrega yodometano (12.7 mL, 204 mmol) a la mezcla espesa mientras se mantiene la temperatura bajo 30°C. Se agita la mezcla durante 3 h a temperatura ambiente luego se apaga con metanol (10 mL) y se concentra *in vacuo*. Se purifica la mezcla cruda por cromatografía en gel de sílice eluyendo con hexano/EtOAc (19:1 hasta 9:1 gradiente) para obtener el intermediario deseado (2 g, 79%). EM (ER+) *m/z*: 281.2 $(M+H-Boc)^+$.

Succinato de 7-cloro-6-(1-ciano-1-metil-etiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina: Se usa un método similar al Procedimiento General 1-5 para desproteger 3-*tert*-butoxicarbonil-7-cloro-6-(1-ciano-1-metil-etiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (1.4 g, 3.5 mmol). Se purifica por cromatografía en gel de sílice eluyendo con diclorometano/amoniaco 2M en metanol (99:1 hasta 90:10 gradiente) para dar la base libre del compuesto del título. Se usa un método similar al Procedimiento General 2-1 para obtener el compuesto del título (992 mg, 71%). EM (ER+) *m/z*: 281.2 $(M+H)^+$.

Ejemplo 663

Succinato de 7-cloro-6-(1-ciano-ciclopropiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



Se agrega hidróxido de potasio (5.4 g, 96.2 mmol) a una solución de 3-*tert*-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (1.5 g, 4.7 mmol) en metanol desgasificado (75 mL) bajo una atmósfera de nitrógeno. Se calienta la mezcla a 80°C durante 6 h. Se enfría la mezcla a temperatura ambiente, luego se

concentra *in vacuo* a un aceite. Se disuelve el aceite en EtOAc (50mL) y se lava con cloruro de amonio acuoso saturado (30 mL). Se separa la capa orgánica y se extrae la capa acuosa con EtOAc (3 x 50 mL). Se secan los extractos orgánicos combinados sobre Na_2SO_4, se filtran y se concentran *in vacuo* a un aceite (1.4 g). Se disuelve el aceite en DMF anhidro (25 mL), luego lentamente se agrega hidruro de sodio (282 mg, 7.1 mmol) y bromoacetonitrilo (470 µl, 7.1 mmol). Se agita la mezcla bajo nitrógeno a temperatura ambiente durante 16 h. se diluye la mezcla lentamente con EtOAc (100 mL) y se lava con cloruro de amonio saturado acuoso frío (40 mL). Se separa la capa orgánica y se extrae la capa acuosa con EtOAc (3 x 50 mL). Se combinan los extractos orgánicos y se concentran *in vacuo*. Se purifica el residuo por cromatografía en gel de sílice eluyendo con hexano/EtOAc (9:1 hasta 7:3 gradiente) para obtener 3-*tert*-butoxicarbonil-7-cloro-6-(1-ciano-metiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (1.34 g, 81%). EM (ER+) *m/z*: 253.2 $(M\text{-}Boc)^+$.

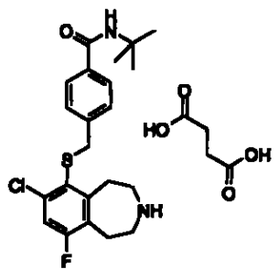
Se agrega bis(trimetilsilil)amida de sodio (5.4 mL, 5.4 mmol, solución 1M en THF) a temperatura ambiente bajo nitrógeno a una solución de 3-*tert*-butoxicarbonil-7-cloro-6-(1-ciano-metiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (380 mg, 1.1 mmol) en tolueno anhidro (4 mL). Se agita la solución durante 10 min, luego se agrega rapidamente 1,2-dibromoetano (2.8 mL, 32.4 mmol) seguido por DMF anhidro (4 mL). Una

reacción exotermica se observó y la temperatura de reacción se incrementa a 38°C. Se agita la mezcla durante 15 min a temperatura ambiente, luego se apaga con metanol (2 mL). Se concentra *in vacuo* y se purifica por cromatografía en gel de sílice eluyendo con hexano/EtOAc (9:1) para obtener 3-*tert*-butoxicarbonil-7-cloro-6-(1-ciano-ciclopropiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (259 mg).

Se usa un método similar al Procedimiento General 1-5 para desproteger 3-*tert*-butoxicarbonil-7-cloro-6-(1-ciano-ciclopropiltio)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina. Se purifica por cromatografía de fase inversa [Columna: Symmetry C18, 19 x 300 mm, relación de flujo 30 mL/min, eluyendo con agua con TFA 0.1%/acetonitrilo (gradiente 19:1 hasta 1:1)] seguido por cromatografía SCX para obtener la base libre del compuesto del título. Se usa un método similar al Procedimiento General 2-1 para obtener el compuesto del título (120 mg, 28% de rendimiento durante 3 etapas). EM (ER+) *m/z*: 279.2 $(M+H)^+$.

Ejemplo 664

Succinato de 6-(4-*tert*-Butilcarbamoil-benciltio)-7-cloro-9-fluoro-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina

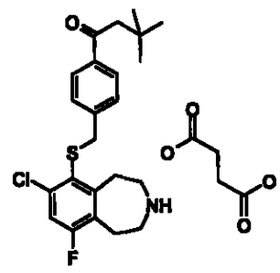


Se usa un método similar al Ejemplo 456 para reaccionar 3-*tert*-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-9-fluoro-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina con 4-clorometil-*N*-(*tert*-butil)-benzamida.

Se usan métodos similares a los Procedimientos Generales 1-5 y 2-1 para dar el compuesto del título como un sólido blanco. EM (ER+) *m/z*: 421 $(M+H)^+$.

Ejemplo 665

Succinato de 7-cloro-6-[4-(3,3-dimetilbutiril)-benciltio]-9-fluoro-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina

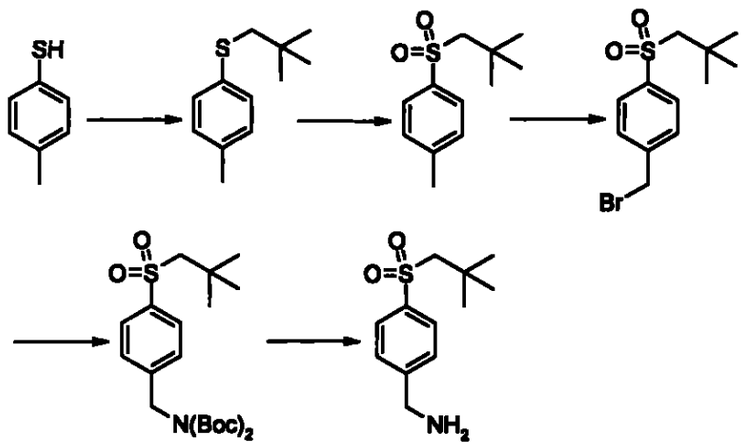


Se usa un método similar al Ejemplo 435 para reaccionar 3-*tert*-butoxicarbonil-7-cloro-6-dimetilcarbamoiltio-9-fluoro-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina con 1-(4-bromometilfenil)-3,3-dimetilbutan-1-ona.

Se usan métodos similares a los Procedimientos Generales 1-5 y 2-2 para dar el compuesto del título como un sólido blanco. EM (ER+) *m/z*: 420 $(M+H)^+$.

Preparación 346

4-(2,2-Dimetil-propano-1-sulfonil)-bencilamina



bencilamina

1-(2,2-Dimetil-propiltio)-4-metil-benceno: Se disuelve 4-metil-bencenotiol (1.5 g, 12.08 mmol) en DMF anhidro (6 mL). Se enfría la solución a 0°C, se agrega hidruro de sodio (435 mg, 17.21 mmol, 95%) y se agita la mezcla bajo atmósfera de nitrógeno durante 15 min. Se agrega 1-yodo-2,2-dimetilpropano (1.93 mL, 14.5 mmol), se agita la mezcla durante 1 h a 0°C, se entibia a temperatura ambiente y se agita durante la noche. Se agrega agua y se extrae la fase acuosa dos veces con EtOAc. Se lavan los extractos orgánicos combinados dos veces con agua con hielo, se secan sobre Na_2SO_4, se filtran y se concentran *in vacuo* para dar el intermediario deseado (1.476 g, 63% de rendimiento).

1-(2,2-Dimetil-propano-1-sulfonil)-4-metil-benceno: Se disuelve 1-(2,2-dimetil-propiltio)-4-metil-benceno (1.476 g, 7.6 mmol) en ácido trifluoroacético (9.5 mL). Se agrega gota

a gota peróxido de hidrógeno (9.9 mL, 30% en agua), Se enfría la mezcla a 0°C y se agita 15 min a esta temperatura y 45 min a temperatura ambiente. Se concentra la mezcla *in vacuo*, se diluye con $NaHCO_3$ acuoso saturado y se extrae la fase acuosa dos veces con EtOAc. Se secan los extractos orgánicos combinados sobre Na_2SO_4, se filtran y se concentran *in vacuo* para dar el intermediario deseado (1.548 g, 90%).

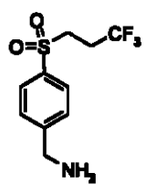
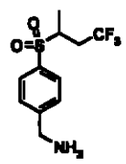
1-Bromometil-4-(2,2-dimetil-propano-1-sulfonil)-benceno: Se usa un método similar a la Preparación 213 (Etapa 2), usando 1-(2,2-dimetil-propano-1-sulfonil)-4-metil-benceno (560 mg, 2.47 mmol) para dar el intermediario deseado.

***N*-(di-*tert*-Butoxicarbonil)-4-(2,2-dimetil-propano-1-sulfonil)-bencilamina**: Se agrega hidruro de sodio (60 mg, 2.39 mmol) a una solución de di-*tert*-butil-iminodicarboxilato (519 mg, 2.39 mmol) en DMF anhidro (2mL) a temperatura ambiente bajo nitrógeno y se agita durante 15 min. Luego se agrega una solución de 1-bromometil-4-(2,2-dimetil-propano-1-sulfonil)-benceno (731 mg, 2.39 mmol) en DMF anhidro (3 mL) y se agita durante 1.5 h. Se agrega agua y se extrae la fase acuosa dos veces con EtOAc. Se lavan los extractos orgánicos combinados con agua con hielo. Se seca la capa orgánica sobre Na_2SO_4, se filtra y se concentra *in vacuo*. Se purifica por cromatografía en gel de sílice eluyendo con hexano/EtOAc

(88:12) para obtener el intermediario deseado (460 mg, 44% durante 2 etapas).

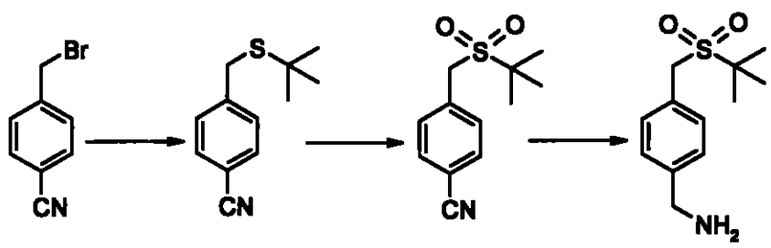
4-(2,2-Dimetil-propano-1-sulfonil)-bencilamina: Se agrega cloruro de hidrógeno 4N en dioxano (2 mL) a una solución de *N*-(di-*tert*-butoxicarbonil)-4-(2,2-dimetil-propano-1-sulfonil)-bencilamina (460 mg, 1.04 mmol) en diclorometano (20 mL) y se agita durante la noche. Se concentra *in vacuo*, se suspende el sólido obtenido en EtOAc, se agrega $NaHCO_3$ acuoso saturado y se agita hasta que ambas fases se limpian. Se extrae la fase acuosa tres veces con dichorometano EtOAc. Se secan los extractos orgánicos combinados sobre Na_2SO_4, se filtran y se concentran *in vacuo* para obtener el compuesto del título como un aceite que se usó sin ninguna purificación adicional (166 mg, 71% de rendimiento). EM (ER+) *m/z*: 242 $(M+H)^+$.

Los compuestos de las Preparaciones 347-348 se pueden preparar esencialmente como se describe en la Preparación 346 usando 1-yodo-3,3,3-trifluoropropano (Preparación 347) o 1,1,1-trifluoro-3-yodobutano (Preparación 348). Datos EM (ER+) se muestran en la Tabla a continuación.

Prep.	Estructura	Compuesto	EM (ER+) m/z
347		4-(3,3,3-Trifluoro-propano-1-sulfonil)-bencilamina	268 $(M+H)^+$
348		4-(4,4,4-Trifluoro-butano-2-sulfonil)-bencilamina	282 $(M+H)^+$

Preparación 349

4-(2-Metil-propano-2-sulfonilmetil)-bencilamina



4-*tert*-Butiltiometil-benzonitrilo: Se agrega hidruro de sodio (359 mg, 14.21 mmol) a una solución de 2-metil-2-propanotiol (900 mg, 9.98 mmol) en DMF anhidro (15 mL) bajo nitrógeno. Se agita la mezcla durante 15 min, se agrega 4-bromometil-benzonitrilo (2.348 g, 11.97 mmol) y se agita la mezcla

4526
1525

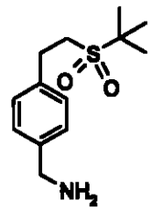
resultante durante la noche a temperatura ambiente. Se agrega agua y se extrae la fase acuosa dos veces con EtOAc. Se lavan los extractos orgánicos combinados dos veces con agua con hielo, se secan sobre Na_2SO_4, se filtran y se concentran *in vacuo*. Se purifica por cromatografía en gel de sílice eluyendo con hexano/EtOAc 92:8 para dar el intermediario deseado (1.42 g, 69% de rendimiento).

4-(2-Metil-propano-2-sulfonilmetil)-benzonitrilo: Se disuelve 4-*tert*-butiltiometil-benzonitrilo (1.42 g, 6.9 mmol) en ácido trifluoroacético (9 mL). Se agrega gota a gota peróxido de hidrógeno (9 mL, 30% en agua), Se enfría la mezcla a 0°C y se agita 15 min a esta temperatura y 45 min a temperatura ambiente. Se concentra la mezcla *in vacuo*, se diluye con $NaHCO_3$ acuoso saturado y se extrae la fase acuosa dos veces con EtOAc. Se secan los extractos orgánicos combinados sobre Na_2SO_4, se filtran y se concentran *in vacuo* para dar el intermediario deseado (1.46 g, 89%).

4-(2-Metil-propano-2-sulfonilmetil)-bencilamina: Se disuelve 4-(2-metil-propano-2-sulfonilmetil)-benzonitrilo (300 mg, 1.26 mmol) en metanol (50 mL). Se agrega HCl concentrado (10 gotas), Pd/C 10% (tipo Degussa E101, 60 mg) y se expone la mezcla a hidrogenación a presión atmosférica durante 1 h. Se filtra sobre Celite® y se lava con metanol. Se concentra el filtrado *in vacuo* para dar la sal de clorohidrato del

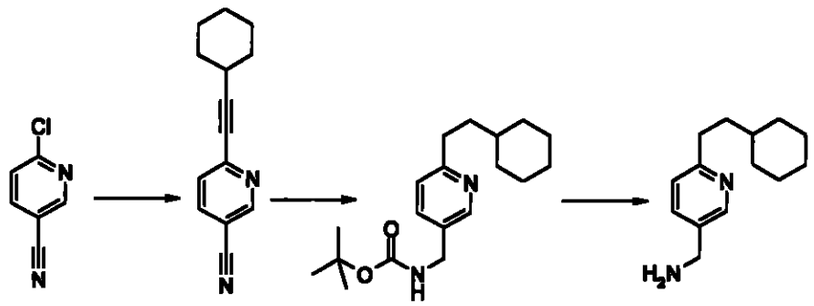
compuesto del título como un sólido que se lavó con éter de dietilo (366 mg, 87%). Se divide el sólido entre $NaHCO_3$ saturado y EtOAc y se extrae la fase acuosa dos veces con EtOAc. Se secan los extractos orgánicos combinados sobre Na_2SO_4, se filtran y se concentran *in vacuo* para dar el compuesto del título (195 mg, 74%). EM (ER+) *m/z*: 242 $(M+H)^+$.

El Compuesto de la Preparación 350 se puede preparar esencialmente como se describe en la Preparación 349 usando 4-(2-bromo-etil)-benzonitrilo. Datos EM (ER+) se muestran en la Tabla a continuación.

Prep.	**Estructura**	**Compuesto**	**EM (ER+) *m/z***
350		4-[2-(2-Metil-propano-2-sulfonil)-etil]-bencilamina	256 $(M+H)^+$

Preparación 351

3-Aminometil-6-(2-ciclohexil-etil)-piridina



6-Ciclohexiletinil-nicotinonitrilo: Se agrega ciclohexilacetileno (1.54 mL, 11.6 mmol), diclorobis(trifenilfosfina)paladio (200 mg, 0.28 mmol), yoduro de cobre (100 mg, 0.53 mmol), y trietilamina (2.0 mL, 14.3 mmol) a una solución de 6-cloronicotinonitrilo (1.38 g, 9.9 mmol) en DMF (4 mL). Se calienta la mezcla en un matraz sellado durante 3 h a 100°C. Se enfría la mezcla a temperatura ambiente, se diluye con 1:1 hexano/EtOAc (100 mL) y se lava con una solución de cloruro de sodio 10% acuoso (3 x 30 mL). Se colecta la capa orgánica, se concentra *in vacuo*, y se purifica el residuo por cromatografía en gel de sílice (90 g silica, hexano/EtOAc 95/5 hasta 85/15 gradiente) para obtener el intermediario deseado (1.75 g, 83%)

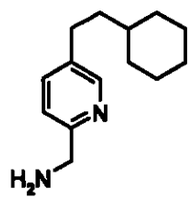
3-tert-Butoxicarbonil-aminometil-6-(2-ciclohexil-etil)-piridina: Se agrega 6-ciclohexiletinil-nicotinonitrilo (1.75 g, 8.3 mmol), Pd/C 10% (tipo Degussa E101, 50% agua por peso) (1.0 g), metanol (100 mL), y dicarbonato de di-*t*-butilo (2.3 g, 10.4 mmol) a un recipiente de presión bajo una atmósfera de nitrógeno. Se presuriza el recipiente a 30 psi (2.109 kg/cm^2) con hidrógeno, y se agita la mezcla durante 3 h (se observa la reacción por CCD). Se purga el recipiente con nitrógeno, se filtra la

mezcla a través de Celite y se lava la torta con diclorometano bajo una atmósfera de nitrógeno. Se concentra el filtrado *in vacuo*. Se purifica el residuo por cromatografía en gel de sílice (90 g silica, hexano/EtOAc, 95/5 hasta 50/50 gradiente) para obtener el intermediario deseado (1.05 mg, 40%). EM (ER+) *m/z*: 319.2 $(M+H)^+$.

3-Aminometil-6-(2-ciclohexil-etil)-piridina: Se agrega ácido trifluoroacético (2.0 mL) a una solución de 3-*tert*-butoxicarbonil-aminometil-6-(2-ciclohexil-etil)-piridina (1.05 g, 3.3 mmol) en metanol (20 mL). Se agita la solución durante 1 h a temperatura ambiente bajo una atmósfera de nitrógeno. Se concentra la solución *in vacuo* y se purifica el residuo por medio de cromatografía SCX para obtener el intermediario deseado (670 mg, 93%). EM (ER+) *m/z*: 219.2 $(M+H)^+$.

Preparación 352

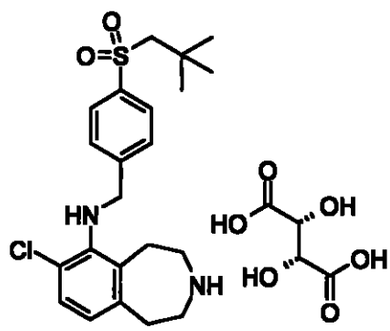
2-Aminometil-5-(2-ciclohexil-etil)-piridina



El compuesto del título se puede preparar esencialmente como se describe en la Preparación 351 al usar 5-cloro-piridina-2-carbonitrilo (24% de rendimiento, EM (ES) *m/z* 219.2 $(M+H)^+$.

Ejemplo 666

(*L*)-Tartrato de 7-cloro-6-[4-(2,2-dimetil-propano-1-sulfonil)-bencilamino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina



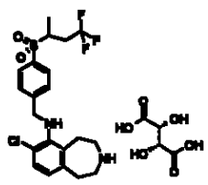
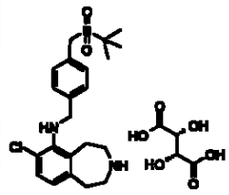
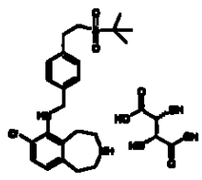
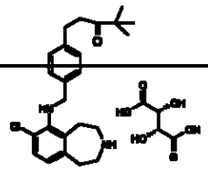
Se usa un método similar al Procedimiento General 5-2 para acoplar 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina (158 mg, 0.37 mmol) con 4-(2,2-dimetil-propano-1-sulfonil)-bencilamina (166 mg, 0.73 mmol) al usar tris(dibencilidenoacetona)dipaladio(0) (68 mg, 0.074 mmol), BINAP (92 mg, 0.148 mmol) y carbonato de cesio (169 mg, 0.518 mmol) en tolueno anhidro (15 mL). Se purifica por cromatografía en gel de sílice eluyendo con hexano/EtOAc (8:2) y luego por CLAR

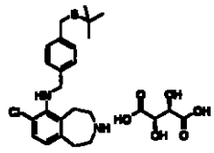
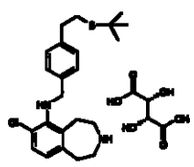
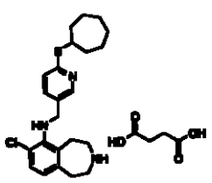
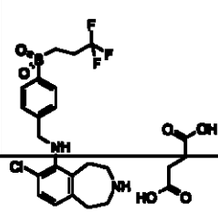
1530

inversa [Zorbax Bonus RP, 5 □M 21.2 x 100 mm, eluyendo con agua/acetonitrilo (TFA 0.05% en cada uno), detector UV (230 nm)] para dar 7-cloro-6-[4-(2,2-dimetil-propano-1-sulfonil)-bencilamino]-3-(2,2,2-trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina como un aceite (153 mg, 80%). EM (ER+) *m/z*: 517 $(M+H)^+$.

Se usan métodos similares a los Procedimientos Generales 1-2 y 2-6 para dar el compuesto del título como un sólido blanco. EM (ER+) *m/z*: 421 $(M+H)^+$.

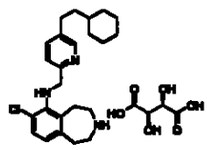
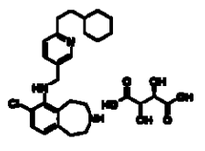
Los Ejemplos 667-672 se pueden preparar esencialmente como se describe en el Ejemplo 666 usando 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina y la amina apropiada. Los Ejemplos 673-674 se pueden preparar esencialmente como se describe en el Ejemplo 666 usando 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina y la amina apropiada pero la sal de succinato se preparó como se describe en el Procedimiento General 2-1. Datos EM (ER+) se muestran en la Tabla a continuación.

Ej.	Estructura	Compuesto	EM (ER+) m/z
667		(L)-Tartrato de 7-cloro-6-[4-(4,4,4-trifluorobutano-2-sulfonil)-bencilamino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	461 $(M+H)^+$
668		(L)-Tartrato de 7-cloro-6-[4-(2-metil-propano-2-sulfonilmetil)-bencilamino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	421 $(M+H)^+$
669		(L)-Tartrato de 7-cloro-6-[4-(2-metil-propano-2-sulfoniletil)-bencilamino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	435 $(M+H)^+$
670		(L)-Tartrato de 7-cloro-6-[4-(4,4-dimetil-3-oxo-pentil)-	399 $(M+H)^+$

		bencilamino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	
671		(L)-Tartrato de 7-cloro-6-[4-(t-butiltiometil-bencilamino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	389 $(M+H)^+$
672		(L)-Tartrato de 7-cloro-6-[4-(t-butiltioetil-bencilamino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	403 $(M+H)^+$
673		Succinato de 7-cloro-6-[(6-cicloheptiltio-piridin-3-ilmetil)-amino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	416 $(M+H)^+$
674		Succinato de 7-cloro-6-[4-(3,3,3-trifluoropropano-1-sulfonil)-bencilamino]-	447 $(M+H)^+$

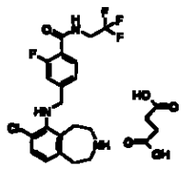
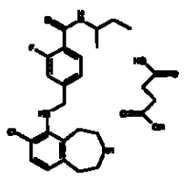
		2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	

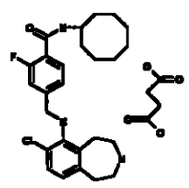
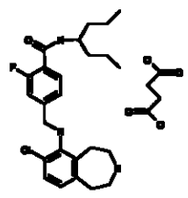
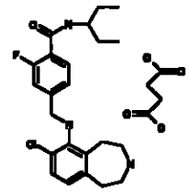
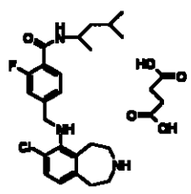
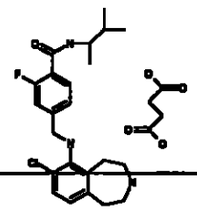
Los Ejemplos 675-676 se pueden preparar esencialmente como se describe en el Ejemplo 604 usando 7-cloro-3-(2,2,2-trifluoroacetil)-6-trifluorometansulfoniloxi-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina y la amina apropiada pero la sal de (L)-tartrato se preparó como se describe en el Procedimiento General 2-6. Los datos EM (ER+) se muestran en la Tabla a continuación.

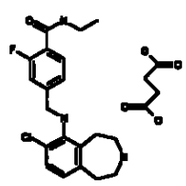
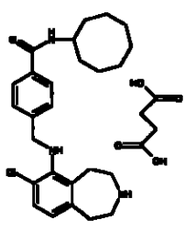
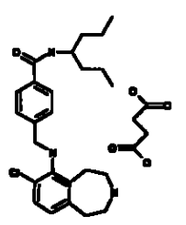
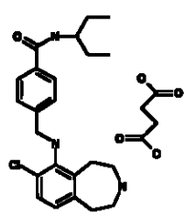
Ej.	Estructura	Compuesto	EM (ER+) m/z
675		(L)-Tartrato de 7-cloro-6-(5-ciclohexiletil-piridin-2-il-metilamino)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	398 $(M+H)^+$
676		(L)-Tartrato de 7-cloro-6-(6-ciclohexiletil-piridin-3-il-metilamino)-2,3,4,5-	398 $(M+H)^+$

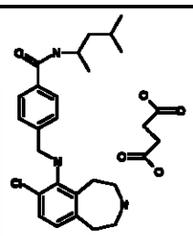
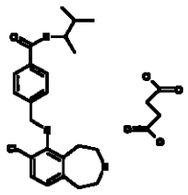
		tetrahidro-1*H*-benzo[*d*]azepina	

Los Ejemplos 677-684 se pueden preparar esencialmente como se describe en el Ejemplo 563 al usar 3-*tert*-butoxicarbonil-6-(4-carboxi-3-fluoro-bencilamino)-7-cloro-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina y la amina apropiada. Los Ejemplos 685-689 se pueden preparar esencialmente como se describe en el Ejemplo 563 al usar 3-*tert*-butoxicarbonil-6-(4-carboxi-bencilamino)-7-cloro-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina y la amina apropiada. Los datos EM (ER+) se muestran en la Tabla a continuación.

Ej.	**Estructura**	**Compuesto**	**EM (ER+) m/z**
677		Succinato de 7-cloro-6-[4-(2,2,2-trifluoroetilcarbamoil)-3-fluoro-bencilamino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	430 $(M+H)^+$
678		Succinato de 7-cloro-6-[4-(2-butilcarbamoil)-3-fluoro-bencilamino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	404 $(M+H)^+$
679		Succinato de 7-cloro-6-	458

		[4-(2-cicloheptilcarbamoil)-3-fluoro-bencilamino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	$(M+H)^+$
680		Succinato de 7-cloro-6-[4-(4-heptilcarbamoil)-3-fluoro-bencilamino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	446 $(M+H)^+$
681		Succinato de 7-cloro-6-[4-(3-pentilcarbamoil)-3-fluoro-bencilamino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	418 $(M+H)^+$
682		Succinato de 7-cloro-6-[4-(4-metil-2-pentilcarbamoil)-3-fluoro-bencilamino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	432 $(M+H)^+$
683		Succinato de 7-cloro-6-[4-(3-metil-2-butilcarbamoil)-3-fluoro-bencilamino]-	418 $(M+H)^+$

		2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	
684		Succinato de 7-cloro-6-[4-(etilcarbamoil)-3-fluoro-bencilamino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	376 $(M+H)^+$
685		Succinato de 7-cloro-6-[4-(2-cicloheptilcarbamoil)-bencilamino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	440 $(M+H)^+$
686		Succinato de 7-cloro-6-[4-(4-heptilcarbamoil)-bencilamino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	428 $(M+H)^+$
687		Succinato de 7-cloro-6-[4-(3-pentilcarbamoil)-bencilamino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	400 $(M+H)^+$
688		Succinato de 7-cloro-6-[4-(4-metil-2-	414 $(M+H)^+$

		pentilcarbamoil)-bencilamino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	
689		Succinato de 7-cloro-6-[4-(3-metil-2-butilcarbamoil)-bencilamino]-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepina	400 $(M+H)^+$

Los compuestos de la presente invención son relativamente selectivos para el receptor 5-HT_{2C}. Los compuestos de la presente invención son particularmente selectivos relativamente para el receptor 5-HT_{2C} en comparación con los otros subtipos del receptor 5-HT y especificamente los receptores 5-HT_{2A} y 5-HT_{2B}. Esta selectividad se demuestra en los siguientes ensayos de actividad agonista y ensayos de enlace de receptor.

Ensayos de Actividad Agonista (G alfa q-GTPγ[^{35}S] Ensayos de Enlace)

Los receptores 5-HT_2 se acoplan funcionalmente a las proteínas G específicas. La activación agonista de receptores acoplados a la proteína G 5-HT_2 resultan en la relación de

GDP desde la subunidad α (G alfa q o G alfa i) de la proteína G y el enlace posterior de GTP. El enlace de el análogo estable GTPγ[^{35}S] es un indicador de activación de receptor (esto es, actividad agonista).

El ensayo de enlace G alfa q-GTPγ[^{35}S] se usa para determinar la potencia in vitro (EC_{50}) y eficacia máxima (E_{max}, normalizada a la respuesta 5-HT) de un compuesto de prueba en los receptores 5-HT_{2A}, 5-HT_{2B}, y 5-HT_{2C}. El área bajo la curva de respuesta de dosis (AUC) se determina también para cada subtipo de receptor y se usa para medir la selectividad de compuestos de prueba para el receptor 5-HT_{2C} sobre los receptores 5-HT_{2A} y 5-HT_{2B}, expresados como relaciones de selectividad (AUC 2C/2A y AUC 2C/2B, respectivamente). Las relaciones de Selectividad permiten la evaluación de selectividad basada tanto en potencia como eficacia. Una medida de selectividad que incorpora ambas potencia y eficacia en el receptor 5-HT_{2C}, cuando se compara con los receptores 5-HT_{2A} y 5-HT_{2B}, se considera importante debido a los eventos adversos asociados con actividad agonista 5-HT_{2A} y 5-HT_{2B} (ver introducción). Preparación de membranas: Se hacen crecer células AV12 estables transfectadas con los receptores 5-HT_{2A}, 5-HT_{2B}, o 5-HT_{2C} humanos en suspensión, se cosechan por centrifugación, se lava el peletizado de célula con solución salina

amortiguada con fosfato, pH 7.4, se peletizan las células nuevamente, se remueve el sobrenadante, se congela el peletizado de células en hielo seco y se almacena a -70°C. Se descongela el peletizado de células de reserva y se vuelve a suspender en 50mM Tris, pH 7.4, se forman alícuotas en volúmenes de 1-2 mL y se vuelven a congelar a -70°C para ensayos posteriores. (Como se aprecia en la técnica, cantidades óptimas de la célula usadas por alícuota variarán con la línea celular transfectada individual usada. En una modalidad, las células transfectadas 5-HT_{2A} y 5-HT_{2C} se usan tipicamente en alrededor de 6 x 10^8 células por alícuota, mientras las células 5-HT_{2B} se usan tipicamente en alrededor de 7.5 x 10^8 células por alícuota).

El día del ensayo, se deshielan las membranas, se lavan las membranas con solución amortiguadora de ensayo (50 mM Tris-HCl (pH 7.4), 10 mM $MgCl_2$, 100 mM NaCl, y 0.2 mM EDTA), se vuelven a suspender en solución amortiguadora de ensayo y se incuban por 10 minutos a 37°C para hidrolizar cualquier 5-HT endógeno residual. Se lavan las membranas nuevamente con solución amortiguadora de ensayo y se vuelven a suspender en solución amortiguadora de ensayo a una concentración para proporcionar alícuotas de alrededor de 1-4x10^6 equivalente de células por pozo (típicamente alrededor de 1-2x10^6 equivalentes de células para ensayos con los ensayos del

receptor -HT_{2A} ó 5-HT_{2C} y alrededor de 3-4x10^6 equivalentes de células para ensayos con ensayos del receptor 5-HT_{2B}). Se homogenizan las células con un molino de tejidos y se usa el homogeneizado directamente en el ensayo como se describe a continuación.

Ensayos de enlace G alfa q-GTPγ[^{35}S]: El ensayo de proximidad de escintilación por inmunoadsorción (ISPA) del enlace de [^{35}S]-GTPγS a G alfa se modifica de las condiciones publicadas (DeLapp et al, JPET 289 (1999) 946-955). Se disuelven los compuestos de prueba en DMSO y se diluyen en solución amortiguadora de ensayo para suministrar un intervalo de concentraciones para generar una curva de respuesta a la concentración. En los pozos de una placa de micro titulación de 96 pozos, se mezcla el compuesto de prueba diluido, GDP (0.1 µM de concentración final), y [^{35}S]-GTPγS (entre 0.5 y 0.1 nM de concentración final). Se agrega una alícuota de membrana a la mezcla de incubación y se mezclan las placas para iniciar la estimulación del agonista del intercambio de nucleótidos (volumen final de 200 µl). Se incuban las placas de microtitulación durante 30 min. A temperatura ambiente. Se apaga la incubación con detergente IGEPAL® CA-630 (0.27% de concentración final). Se agrega el anticuerpo anti-G alfa de conejo policlonal purificado por afinidad (alrededor de 1-2 µg por pozo), y las perlas de

ensayo de proximidad de escintilación anticonejo Ig (Amersham; alrededor de 1.25 mg por pozo; 300 µl de volumen final). Se sellan las placas si se incuba la mezcla por 3 horas a temperatura ambiente. Se centrifugan las placas de micro titulación brevemente para paletizar las perlas. Se cuantifica el enlace de (GTPγ[^{35}S] por espectrometria de escintilación de placas de microtitulación ((Wallac Trilux MicroBeta™ contador de escintilación).

Análisis de Datos: Para cada curva de respuesta a la concentración para un compuesto de prueba a un receptor dado, se analizan los datos con el software GraphPad Prism™ (v3.02; GraphPad Software, San Diego, CA) que corre en una computadora personal con un MicroSoft Windows OS®, al usar una curva de análisis de regresión no lineal que se ajusta para determinar los EC_{50} y E_{max} (normalizados a las curvas de control 5-HT). Se determina el área bajo la curva de respuesta a la concentración del agonista (AUC) con GraphPad Prism™ por el método trapezoidal.

Para calcular las relaciones de selectividad primero, determine el AUC para el compuesto de prueba para cada subtipo del receptor como se describe arriba. Segundo, normalizar los AUC en cada subtipo del receptor con relación al AUC determinado para 5-HT en ese receptor. El AUC normalizado para un compuesto de prueba a un receptor dado se

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expresa por lo tanto como un porcentaje del AUC determinado para 5-HT en ese receptor. Por ejemplo:

AUC Normalizado de $5HT_{2A}$=a=(AUC compuesto de prueba en receptor $5HT_{2A}$) X 100% (AUC 5-HT en receptor $5HT_{2A}$)

AUC Normalizado de $5HT_{2B}$=a=(AUC compuesto de prueba en receptor $5HT_{2B}$) X 100% (AUC 5-HT en receptor $5HT_{2B}$)

AUC Normalizado de $5HT_{2C}$=a=(AUC compuesto de prueba en receptor $5HT_{2C}$) X 100% (AUC 5-HT en receptor $5HT_{2C}$)

Tercero, calcular las relaciones de selectividad para el compuesto de prueba como sigue:

Relación de selectividad para el receptor 5-HT_{2C}/ receptor 5-HT_{2A} (AUC2C/2A)= c/a.

Relación de selectividad para el receptor 5-HT_{2C}/ receptor 5-HT_{2B} (AUC2C/2B)= c/b.

Para propósitos de referencia, del AUC 2C/2A y AUC 2C/2B para 5-HT son cada uno 1.0. Similarmente, las relaciones para mCPP (meta-clorofenilpiperazina) se prueban y se encuentran que son 2.1 y 201 respectivamente.

Los compuestos representativos de la presente invención se prueban en los ensayos G alfa q-GTPγ[^{35}S] para los receptores 5-HT_{2A}, 5-HT_{2B}, y 5-HT_{2C} esencialmente como se describen arriba y se encuentran que son agonistas selectivos

y altamente potentes del receptor 5-HT2C con las EC_{50} típicamente menores que o igual a 200 nM, y las relaciones de AUC 2C/2A y AUC 2C/2B mayores que 1.5. Los compuestos preferidos son aquellos con EC_{50} menores que o igual a 100 nM, y relaciones de AUC 2C/2A y AUC 2C/2B mayores que o igual a 2.0. Son más preferidos aquellas con EC_{50} menores que o igual a 50nM, y relaciones de AUC 2C/2A y AUC 2C/2B mayores que o igual a 3.0.

Ensayos de Enlace de Ligandos

La afinidad de enlace del ligando de los compuestos de la presente invención al subtipo del receptor 5 HT_{2C} se mide esencialmente como se describe por Wainscott (Wainscott, et al., Journal of Pharmacology and Experimental Therapeutics, 276:720-727 (1996)). Se analizan los datos por análisis de regresión no lineal en las curvas de respuesta a la concentración usando la ecuación logística de cuatro parámetros descrita por DeLean (DeLean, et al., Molecular Pharmacology, 21, 5-16 (1982)). Los valores IC_{50} se convierten a los valores K_i usando al ecuación Cheng-Prusoff (Cheng, et al., Biochem. Pharmacol., 22, 3099-3108 (1973)).

Los compuestos representativos de la presente invención se prueban esencialmente como se describen arriba y se encuentra que tienen una afinidad de

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excelente para el receptor 5-HT2C con K_i típicamente menores que o igual alrededor de 200 nM. Los compuestos preferidos con aquellos K_i menores que o igual alrededor de 100 nM. Son más preferidos aquellos con K_i menor que o igual a 50nM.

Las afinidades para otros subtipos del receptor se pueden determinar fácilmente por una modificación ligera del ensayo de enlace del receptor de radioligando antes descritas al usar células transfectadas con el receptor deseado en lugar de células transfectadas con el subtipo del receptor $5\text{-}HT_{2C}$ y usando un radioligando adecuado. Las afinidades de enlace para los compuestos representativos de la presente invención para una diversidad de receptores se determinan en tales ensayos y los compuestos se encuentra que tienen una afinidad sorprendentemente superior para el receptor $5\text{-}HT_{2c}$. La afinidad para el receptor $5\text{-}HT_{2c}$ se encuentra que es significativamente mayor para otros subtipos del receptor 5-HT y notablemente superior que los subtipos del receptor 5 HT_{2A} y $5\text{-}HT_{2B}$. Los compuestos preferidos son aquellos con una IC_{50}'s igual a o mayor que 300 nM para los receptores adrenérgicos alfa 1 y alfa2 e igual a o mayor que 500 nM para los receptores dopaminérgicos D_1 y D_2. Los compuestos más preferidos son aquellos con IC_{50} igual a o mayor que 1000 nM para los receptores adrenérgico alfa 1 y alfa 2 y los receptores

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dopaminérgicos D_1 y D_2. Son todavía más preferidos aquellos compuestos con IC_{50}'s igual a o mayor que 3000 nM para los receptores adrenérgicos alfa 1 y alfa 2 y los receptores dopaminérgicos D_1 y D_2.

Para los ensayos in Vitro anteriores, los compuestos ejemplificados se ensayan y se encuentran que tienen ya sea un EC_{50} o un valor Ki de igual a o menor que 50 nM y que tienen relaciones AUC 2C/2A y AUC 2C/2B mayores que o igual a 2.0. Los compuestos ejemplificados se ensayan y se encuentra que tienen los IC_{50}'s del receptor adrenérgico alfa 1 y alfa 2 igual a o mayor que 300 nM y los IC_{50}'s del receptor dopaminérgico D_1 y D_2 igual a o mayor que 500 nM.

Ensayos de Alimentación de Ratas

La capacidad de los compuestos de la presente invención para tratar la obesidad se demuestra por la prueba en ensayos de alimentación con ratas agudos y crónicos.

Animales: Se obtienen ratas macho Long-Evans (Harlan Sprague-Dawley, Indianapolis, IN) que tienen aproximadamente cien días de edad y se han mantenido en una dieta rica en calorías desde el destete (calorías de grasa; TD 95217, 40% Teklad, Madison, WI). Se alojan las ratas individualmente con un ciclo de luz:oscuridad de 12 h:12h (se encienden las luces desde 22:00 h hasta alrededor de 10:00 h)y se mantienen las ratas con la misma dieta (TD95217) con acceso libre al

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agua por alrededor de 1-2 semanas para aclimatar las ratas al ambiente. Se dosifican las ratas oralmente con vehículo (10% acacia con 0.15% de sacarina en agua) una vez al día por al menos 1 día (típicamente 1-2 día) para aclimatar las ratas a los procedimientos. Se seleccionan de forma aleatoria las ratas en grupos de manera que cada grupo tiene pesos corporales medios similares.

Ensayo de Alimentación Aguda Calorimétrico: A aproximadamente las 8:00 el día del ensayo, se pesa cada rata y se transfiere a las cámaras individuales de un sistema de calorimetría de circuito abierto (Oxymax, Columbus Instruments International Corporation; Columbus, OH) con acceso libre al alimento (pre-pesado) y agua y se comienza a medir VO_2 y VCO_2. A aproximadamente las 10:00 h, se dosifican las ratas oralmente con el vehículo o compuesto de prueba, se regresan a sus cámaras de calorimetría y se continúan midiendo VO_2 y VCO_2 en intervalos de tiempo regulares (aproximadamente cada hora). A aproximadamente 8:00 h el día siguiente, se mide el peso corporal de la rata y el alimento restante, suponiendo que la diferencia en peso del alimento es igual a la masa de alimento consumida. Se calcula el gasto de energía por 24 horas (EE) y el cociente respiratorio (RQ) esencialmente como se describe en Chen, Y. and Heiman, M. L., Regulatory Peptide, 92:113-119 (2000). El EE durante el fotoperiodo de luz es indicativo de la relación metabólica en

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reposo y RQ es indicativo de la fuente de combustible que utiliza el animal (el metabolismo de carbohidratos puro da un RQ de alrededor de 1.0, el metabolismo de grasa pura da un RQ de alrededor de 0.7 el metabolismo de grasa y carbohidratos mixtos da valores intermedios para RQ). Calcular EE como el producto de valor calorífico (CV) y VO_2 por peso corporal (kg); en donde CV = 3.815 + 1.232*RQ, y RQ es la relación de CO2 producido (VCO_2) al O_2 consumido (VO_2). La ingesta calórica se calcula como (masa de la ingesta alimenticia en 24 horas en gramos) x (valor del combustible fisiológico de la dieta en kilocalorías/g) por kg de peso corporal.

Ensayo de alimentación Agudo con un Antagonista del Receptor 5-HT2C Selectivo: El ensayo de alimentación aguda calorimétrico anterior se efectúa con las siguientes modificaciones. Los sistemas de calorimetría de circuito abierto no se usan y solamente se mide la ingesta alimenticia periódica en 24 horas si el peso corporal. Se usan tres grupos de ratas con el primer grupo que recibe una dosis subcutánea de solución salina (0.5 mL) alrededor de 15 minutos previos a la dosis oral de vehiculo el segundo grupo recibe una dosis subcutánea de solución salina (0.5mL) alrededor de 15 minutos previo a la dosis oral del compuesto de prueba en el vehiculo y el tercer grupo recibe una inyección subcutánea de un antagonista receptor selectivo 5-HT_{2C}, 6-cloro-5-metil-N-{2-[(2-metilpiridin-3-il-oxi)piridin-

5-il]aminocarbonil}-2,3-dihidroindol (3 mg/Kg, en 35% ciclodextrina, 0.5 mL) alrededor de 15 minutos previo a la dosis oral del compuesto de prueba en el vehiculo.

Ensayo de Alimentación Crónica: Entre aproximadamente las 8:00 h y 10:00 h el día 1 del ensayo, se pesan y dosifican oralmente cada rata con vehiculo o compuesto de prueba y se regresa el animal a su jaula de la casa con acceso libre al alimento (pre-pesado) y agua. Para cada uno de los días 2-15, a entre aproximadamente las 8:00 h y 10:00 h, se mide el peso corporal de la rata y el peso del alimento consumido en el último periodo de 24 horas y se administra diariamente la dosis oral del compuesto de prueba o vehiculo. En los días 2 y 15 se mide la masa de grasa total y la masa sin grasa o resonancia magnetica nuclear (NMR) usando un sistema a EchoMRI™ (Echo Medical Systems, Houston Texas). Ver Frank C. Tinsley, Gersh Z. Taicher, and Mark L. Heiman, "Evaluation of a New Quantitative Magnetic Resonance (QMR) Method for Mouse Whole Body Composition Analysis" Obesity Research, remitido el 1 de Mayo, 2003).

Los compuestos representativos de la presente invención se prueban en ensayos de alimentación de alimentación aguda y crónica esencialmente como se describe arriba. En los ensayos agudos, los compuestos se encuentra que reducen significativamente la ingesta de alimentos en 24 horas, cuyo efecto se bloquea por la preadministración del antagonista

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del receptor 5-HT_{2C}. Los compuestos también se encuentra que reducen dependiente de la dosis el RQ sin cambiar significativamente el gasto de energía durante el fotoperiodo de luz. Así, se encuentra que los compuestos reducen la ingesta calórica e incrementan la proporción del combustible que se derivan de la utilización de la grasa, sin cambiar significativamente la tasa metabólica en reposo. En el ensayo crónico, se encuentra que los compuestos disminuyen significativamente la ingesta alimenticia acumulativa y el cambio en peso corporal acumulativo en una forma dependiente de la dosis comparada con los animales de control. La disminución en el peso corporal se encuentra que se debe a la pérdida de tejido adiposo mientras que la masa corporal sin grasa no cambia.

La capacidad de los agonistas del receptor 5-HT_{2C} de la presente invención para tratar un trastorno obsesivo/compulsivo se demuestra por la prueba en una diversidad de ensayos in vivo como sigue:

Ensayo de Canicas Ocultas (Marble Burying)

Las canicas ocultas en ratones se han utilizado para modelar los trastornos de ansiedad que incluyen los trastornos obsesivos compulsivos (OCD) debido al estudio etológico del comportamiento (por ejemplo, Gyertyan I. "Analysis of the marble burying response: Marbles serve to

measure digging rather than evoke burying", Behavioural Pharmacology 6: 24-31, (1995)), y debido a los efectos farmacológicos de los estándares clínicos (c.f., Njung'E K. Handley SL. "Evaluation of marble-burying behavior as a model of anxiety", Pharmacology, Biochemistry & Behavior. 38: 63-67, (1991)); Borsini F., Podhorna J., and Marazziti, D. "Do animal models of anxiety predict anxiolytic effects of antidepressants?" Psychopharmacology 163: 121-141, (2002)). Así, los fármacos usados en el tratamiento de la ansiedad generalizada en humanos (por ejemplo benzodiazepinas) así como los compuestos usados para tratar OCD (por ejemplo, SSRI como la fluoxetina) disminuyen el ocultamiento.

Ratones NIH Swiss machos experimentalmente nuevos de laboratorio (Harlan Sprague-Dawley, Indianapolis, IN) que pesan entre 28-35 g en grupos de 12, por al menos tres días previo a la prueba en un vivarium con ciclos de 12 de luz y de oscuridad. Se efectuaron experimentos durante el ciclo de luz en un cuarto de prueba experimental con luz tenue. Se dosificaron los ratones con vehículo o el compuesto de prueba y después de un intervalo de pretratamiento específicos (generalmente 30 min), se coloca cada ratón individualmente en un rotorod (Ugo Basile 7650) que opera a una velocidad de 6 revoluciones por minuto y se observa la caída. Después de 2 minutos en el rotorod, se colocan los ratones individualmente en una tina de plástico alta de 17 x 28 x 12

cm con pedacearía de aserrín de 5 mm en el piso que se cubre con 20 canicas azules (1.5 cm de diámetro) colocadas en el centro. Después de 30 minutos, se cuenta el número de canicas ocultas (cubiertas en 2/3 con el aserrín). Se evalúa el efecto del compuesto de prueba en las canicas ocultas con la prueba de Dunnett y el efecto en el desempeño rotorod por la prueba exacta de Fisher.

Los compuestos estándar clínicamente efectivos suprimen el ocultamiento de canicas a dosis que están desprovistas de efectos debilitadores motores cuando se miden en el rotorod. La eficacia in vivo de los compuestos $5HT_{2C}$ en el receptor $5HT_{2C}$ se confirma por la prevención de efectos de los agonsitas $5HT_{2C}$ en el ocultamiento de canicas por la co-administración del antagonista del receptor $5HT_{2C}$ 6-cloro-5-metil-N-{2-[(2-metilpiridin-3-il-oxi)piridin-5-il]aminocarbonil}-2,3-dihidroindol.

Los compuestos representativos de la presente invención se ensayan en el ensayo de ocultamiento de canicas esencialmente como se describen y se encuentran sorprendentemente para reducir el comportamiento para ocultar en los ratones de prueba. La reducción del comportamiento para ocultar se encuentra que se bloquea por la co-administración del antagonista $5HT_{2C}$. En contraste a los compuestos de la presente invención, el compuesto ansiolítico clordiazepóxido y el compuesto antipsicótico clorpromazina

disminuyen el ocultamiento de canicas solamente la dosis que también alteran el desempeño del rotorod.

Desmenuzado del Nido (Nestlet Shredding)

Los ratones construirán naturalmente nidos del material disponible en su ambiente de vida. Ya que este comportamiento es obsesivo por naturaleza, se ha usado el modelo OCD (Xia Li, Denise Morrow and Jeffrey M. Witkin, "Decreases in nestlet shredding of mice by serotonin uptake inhibitors: comparison with marble burying", Psychopharmacology, remitida el 14 de Julio de 2003). Ratones NIH Swiss machos nuevos experimentalmente de laboratorio (Harlan Sprague-Dawley, Indianapolis, IN) que pesan entre 28-35 en grupos de 12 por al menos tres días previo a la prueba en un vivarium con un siclo de luz/oscuridad de 12 horas. Se efectúan experimentos durante el ciclo de luz en un cuarto experimental con alumbrado fluorescente en la parte superior normal. Se dosifican los ratones con vehículo o compuesto de prueba y después de un intervalo de pre-tratamiento específicos (generalmente 30 min.), se colocan los ratones individualmente en una tina alta de plástico de 17 x 28 x 12 cm con alrededor de fragmentos de aserrín de 5 mm en el piso junto con una almohadilla de gasa de capas múltiples previamente pesada (cuadrado de 51 mm). Después de 30 minutos, el peso del resto de la almohadilla de gasa no

retirada por el ratón. Se determina el peso de la gasa usada para la construcción del nido por sustracción. Se comparan los resultados para los ratones tratados con compuestos de prueba con los resultados para los ratones tratados con el control de vehiculo con la prueba de Dunnett.

Los compuestos estándar para el tratamiento de OCD clínicamente efectivo suprimen el triturado del nido a dosis que están desprovistas de los efectos debilitadores motores cuando se miden por la prueba de rotorod. La eficacia in vivo de los compuestos $5HT_{2C}$ en el receptor $5HT_{2C}$ se confirma por al prevención de los efectos de los agonistas $5HT_{2C}$ en el triturado del nido por la co-administración del antagonista del receptor $5HT_{2C}$ 6-cloro-5-metil-N-{2-[(2-metilpiridin-3-il-oxi)piridin-5-il]aminocarbonil}-2,3-dihidroindol.

Los compuestos representativos de la presente invención se ensayan esencialmente como se describe arriba y se encuentra sorprendentemente que suprimen el triturado del nido a dosis que están desprovistas de efectos debilitadores motores cuando se miden por la prueba de rotorod.

En contraste con los compuestos de la presente invención, el clordiazepóxido ansiolítico y el estimulante psicomotor de d-anfetamina disminuyen el triturado del nido solamente a dosis que producen efectos colaterales motores (depresión o estimulación respectivamente).

Polidipsia Inducida por Calendario

Ratas desprovistas de alimento expuestas a presentaciones intermitentes de alimento beberán cantidades de agua que están bastante en exceso de su ingesta y área normal y en exceso de su ingesta cuando se les da todo su alimento a la vez (Falk JL. "Production of polydipsia in normal rats by an intermittent food schedule", Science 133: 195-196, (1961)). Este comportamiento excesivo es persistente y se ha utilizado para modelar el OCD.

Se mantienen ratas Wistar en una dieta restringida de alimento (para mantener un 85% de peso de alimentación libre) pero con acceso libre al agua. Se entrenan las ratas en una cámara de prueba de comportamiento para oprimir una palanca para recibir un gránulo de alimento bajo un calendario de intervalos fijos de manera tal que las ratas se les recompense con un gránulo de alimento de 45 mg la primera vez que oprimen en una palanca después de que ha transcurrido un intervalo de 120 segundos. Luego se reestablece el intervalo fijo a los 120 segundos y se repite el proceso. Así durante una sesión de prueba de 90 minutos, las ratas pueden ganar un máximo de 45 gránulos. La cámara de comportamiento también está ocupada con una botella de agua que se pesa antes y después de la sesión para determinar la cantidad de agua consumida.

Se administran los compuestos de prueba los martes y los viernes. Se determinan los desempeños del día de control los jueves. Se administran los compuestos ya sea oralmente a los 60 minutos antes del comienzo de una sesión de prueba o subcutáneamente a los 20 minutos antes del comienzo de una sesión de pruebas. Se comparan las proporciones de la palanca que oprime y el consumo de agua para cada desempeño del animal durante la sesiones después del tratamiento con el compuesto de prueba con aquel desempeño del animal durante la sesiones de control expresado como un porcentaje de la relación de control. Se promedia el porcentaje individual de las relaciones de control para cada dosis y se calcula el error estándar de la media.

Los compuestos estándar para tratamiento de OCD clínicamente efectivo (por ejemplo, clomipramina, fluoxetina) suprimen la polidipsia inducida por calendario sin producir cambios notables en los patrones motores, la ingesta de alimento o el comportamiento al día siguiente. La eficacia in vivo de los compuestos $5HT_{2c}$ en el receptor $5HT_{2c}$ se confirma por la prevención de los efectos de los agonistas $5HT_{2c}$ con una bebida excesiva por la co-administración del antagonista del receptor $5HT_{2c}$, 6-cloro-5-metil-N-{2-[(2-metilpiridin-3-il-oxi)piridin-5-il]aminocarbonil}-2,3-dihidroindol.

Los compuestos representativos de la presente invención, se ensayan en un ensayo de polidipsia inducida por calendario

esencialmente como se describe arriba y se encuentra sorprendentemente que suprimen la polidipsia inducida por calendario sin producir cambios notables en los patrones motores, ingesta de alimento y comportamiento al día siguiente. La supresión del comportamiento se bloquea por la co-administración del antagonista $5HT_{2c}$.

En contraste con los compuestos de la presente invención, el estimulante psicomotor de d-anfetamina disminuye la bebida excesiva solamente a dosis que estimulan el comportamiento y estos efectos no se evitan por el antagonista del receptor $5HT_{2c}$.

Aunque es posible administrar los compuestos empleados en los métodos de esta invención directamente sin ninguna formulación, se administran usualmente los compuestos en forma de composiciones farmacéuticas que comprenden un excipiente farmacéuticamente aceptable y al menos un compuesto de fórmula I o una sal farmacéuticamente aceptable del mismo. Estas composiciones se pueden administrar por una diversidad de vías incluyendo oral, rectal, transdérmica, subcutánea, intravenosa, intramuscular e intranasal. Los compuestos empleados en los métodos de esta invención son efectivos tanto como composiciones inyectables como orales. Tales composiciones se preparan en una forma bien conocida en el arte farmacéutico ver por ejemplo, REMINGTON'S PHARMACEUTICAL SCIENCES, (16th ed. 1980).

En la elaboración de las composiciones empleadas en la presente invención, se mezcla usualmente el ingrediente activo con al menos un excipiente diluido por al menos un excipiente o encerrado dentro de tal portador el cual puede estar en forma de una cápsula, saquito, papel, u otro recipiente. Cuando el excipiente sirve como un diluyente puede ser un material sólido, semisólido o líquido el cual actúa como un vehículo portador o medio para el ingrediente activo. Así, las composiciones pueden estar en forma de tabletas, píldoras, polvos, grageas, saquitos, cápsulas, cápsulas amiláceas, elixires, suspensiones, emulsiones soluciones, jarabes, aerosoles, (como un medio sólido o en un medio líquido), ungüentos que contienen por ejemplo hasta el 10% en peso del compuesto activo, cápsulas de gelatina dura y suave, supositorios, soluciones inyectables estériles, y polvos empacados estériles.

En la preparación de una formulación, puede ser necesario moler el compuesto para suministrar el tamaño de partícula apropiado previo a la combinación con los otros ingredientes. Si el compuesto activo es substancialmente insoluble, se muele ordinariamente a un tamaño de partícula de menos de malla 200. Si el compuesto activo es substancialmente soluble en agua, el tamaño de partículas se ajusta normalmente al moler par proporcionar una distribución

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substancialmente uniforme en la formulación por ejemplo alrededor de malla 40.

Algunos ejemplos de excipientes adecuados incluyen lactosa, dextrosa, sacarosa, sorbitol, manitol, almidones, goma acacia, fosfato de calcio, alginatos, tragacanto, gelatina, silicato de calcio, celulosa microcristalina, polivinilpirrolidona, celulosa, agua, jarabe, y metil celulosa. Las formulaciones pueden incluir adicionalmente: agentes lubricantes tales como talco, estearato de magnesio, y aceite mineral; agentes humectantes; agentes emulsificantes y de suspensión, agentes conservadores tales como metil y propilhidroxibenzoatos; agentes edulcorantes y agentes saborizantes. Las composiciones de la invención se pueden formular de manera de proporcionar una liberación rápida sostenida o retrasada del ingrediente activo después de la administración al paciente al emplear procedimientos conocidos en el arte.

Las composiciones se formulan preferiblemente en una forma de dosis unitaria cada dosis contiene desde alrededor de 0.05 alrededor de 100 mg, más usualmente alrededor de 1.0 hasta alrededor de 30 mg., del ingrediente activo. El término forma de dosis unitaria se refiere a unidades físicamente discreta adecuadas como dosis unitarias para sujetos humanos y otros mamíferos, cada unidad contiene una cantidad predeterminada de material activo calculada para producir el

efecto terapéutico deseado en asociación con un excipiente farmacéutico adecuado.

Los compuestos son generalmente efectivos sobre un rango de dosis amplio. Por ejemplo, las dosis por día formalmente caen dentro del rango de alrededor de 0.01 alrededor de 30 mg/kg. En el tratamiento de humanos adultos el rango de alrededor de 0.1 alrededor de 15 mg/kg/día en dosis sencilla o dividida se prefiere especialmente. Sin embargo se entenderá que la cantidad del compuesto realmente administrado se determinará por un médico a la luz de la circunstancia relevante, incluyendo la condición a tratarse la vía elegida de administración el compuesto, compuestos actuales administrados la edad, peso y respuesta del paciente individual y la severidad de los síntomas del paciente y por lo tanto los rangos de dosificación anteriores no se pretende que limiten el alcance de la invención de ninguna manera. En algunos casos, los niveles de dosis debajo del límite inferior del rango anterior pueden ser más que adecuados mientras que en otros casos todavía dosis mayores que se puedan emplear.

Otra formulación preferida empleada en los métodos de la presente invención emplea dispositivo de suministro transdérmico ("parches"). Tales parches transdérmicos se pueden usar par proporcionar una infusión continua o discontinua de los compuestos de la presente invención en

cantidades controladas. La construcción y uso de los parches transdérmicos para el suministro de agentes farmacéuticos es bien conocido en el arte ver por ejemplo patentes de EUA 5,023,252, concedida el 11 Junio 1991, que se incorpora en la presente como referencia. Tales parches se pueden construir par el suministro continuo, de pulsos o el suministro a petición de agentes farmacéuticos.

Bajo algunas circunstancias, será deseable o necesario introducir la composición farmacéutica al cerebro ya sea directa o indirectamente. Las técnicas directas involucran usualmente la colocación de un catéter para suministro del fármaco en el sistema ventricular del huésped para desviar la barrera de sangre al cerebro. Uno de tales sistemas de suministro implantables usado por el transporte de factores biológicos a regiones anatómicas específicas del cuerpo, se describen en la patente de EUA 5,011,472 concedida el 30 de abril 1991, que se incorpora en la presente como referencia.

Las técnicas indirectas las cuales se prefieren generalmente, involucran usualmente formular las composiciones para proporcionar una latencia de fármaco por la conversión de fármacos hidrofílicos en fármacos solubles en lípidos o pro-fármacos. La latencia se logra generalmente a través del bloqueo de los grupos amina primaria, hidroxi, carbonilo y sulfato presentes en el fármaco para hacer al fármaco más soluble en lípidos y afín con el transporte a

través de la barrera de sangre al cerebro. Alternativamente, el suministro de fármacos hidrofílicos se puede potenciar por la infusión intra-arterial de soluciones hipertónicas las cuales pueden abrir transitoriamente la barrera de sangre al cerebro.

El tipo de formulación empleado para la administración de los compuestos empleados en los métodos de la presente invención puede estar dictado por el compuesto empleado en particular, el tipo de perfil farmacocinético deseado a partir de la vía de administración y el estado del paciente.

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PATENT CO PERATION TREATY

RECEIVED

MAY 30 2006

PCT ELI LILLY AND COMPANY Patent Division

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

TUCKER, R., Craig
P. O. Box 6288
Indianapolis, Indiana 46206-6288
ETATS-UNIS D'AMERIQUE

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	19.05.2006

Applicant's or agent's file reference	IMPORTANT NOTIFICATION
X-16115	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2005/005418	18.02.2005	25.02.2004

Applicant
ELI LILLY AND COMPANY

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Lafitte-de Jong, S Tel. +31 70 340-4827

Form PCT/IPEA/416 (January 2004)

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference X-16115	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/US2005/005418	International filing date *(day/month/year)* 18.02.2005	Priority date *(day/month/year)* 25.02.2004

International Patent Classification (IPC) or national classification and IPC

INV. C07D223/16 C07D401/12 C07D417/12 C07D413/12 C07D403/12 C07D409/12 C07D405/12 C07D413/14 C07D417/06 C07D403/06 A61K31/55 A61P25/22 A61P25/24 A61P25/30 A61P3/04

Applicant

ELI LILLY AND COMPANY

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 15 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20.12.2005	19.05.2006

Name and mailing address of the international preliminary examining authority:	Authorized officer
European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Seitner, I Telephone No. +31 70 340-2389

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2005/005418

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-574 as originally filed

   Claims, Numbers

   1-37 filed with telefax on 20.12.2005

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No. PCT/US2005/005418

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

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

☐ the entire international application,

☒ claims Nos. 18-25 (with respect to industrial applicability)

because:

☒ the said international application, or the said claims Nos. 18-25 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

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

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

☐ no international search report has been established for the said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REP RT ON PATENTABILITY

International application No.
PCT/US2005/005418

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-37
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-37
Industrial applicability (IA)	Yes:	Claims	1-17,26-37
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (SEPARATE SHEET)

International application No.
PCT/US2005/005418

Re Item III

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

Claims 18-25 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 93/04686 A (SMITHKLINE BEECHAM CORPORATION) 18 March 1993 (1993-03-18)

D2: US-A-4 265 890 (HOLDEN ET AL) 5 May 1981 (1981-05-05)

D3: WO 93/03015 A (SMITHKLINE BEECHAM CORPORATION) 18 February 1993 (1993-02-18)

D4: KILPATRICK, ANDREW T. ET AL: "The .alpha.2-adrenoceptor antagonist SK & F 104078 has high affinity for 5-HT1A and 5-HT2 receptors" EUROPEAN JOURNAL OF PHARMACOLOGY , 166(2), 315-18 CODEN: EJPHAZ; ISSN: 0014-2999, 1989, XP002328505

V.1. Novelty:

The compounds according to the general formula (I) of claim 1 have not been disclosed in the available prior art. Therefore, the subject-matter of claims 1-37 is novel (Article 33(2) PCT).

V.2. Inventive Step:

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-37, in as far as novel, does not involve an inventive step in the sense of Article 33(3) PCT:

Documents D1 and D3 disclose general formulae which overlap with the present formula I. The compounds of D1 and D3 are adrenergic antagonists and useful for the treatment of depression and obesity.

Even though the compounds of D1 and D3 are characterized as α-adrenoceptor antagonists, whereas the present compounds embody 5-HT_{2C} receptor agonists, it is known from D4 that the benzazepine derivative SK&F 104078 which is in principle an α_2-adrenoceptor antagonist, has high affinity for 5-HT_2 receptors.

In view of the teaching of the prior art, it would have been obvious to the skilled person to associate the formulae of D1 and D3 with a 5-HT_2 receptor activity, and to choose among said formulae when looking for further compounds for the treatment of obesity and neurological disorders such as depression.

Applicant argues that the present compounds are selective 5-HT_{2C} receptor agonists, particularly against adrenergic and dopaminergic receptors, thereby avoiding undesirable adverse events and cross reactivity associated with current therapies.

Such as selectivity can indeed be regarded as an indication for inventive step.

Hence, the technical problem underlying the present invention can be formulated as the provision of further compounds for the treatment of obesity, obsessive compulsive disorders, depression, anxiety, sleep disorders which are selective 5-HT_{2C} receptor agonists.

However, an inventive step relying on such an effect requires evidence to this effect, e.g. by means of comparative tests which convincingly show that the effect has its origin in the distinguishing feature of the invention over the prior art.

In absence of comparative tests with the prior art, the selectivity referred to by the applicant has therefore not been properly demonstrated in the description. Such alleged but unsupported advantages cannot be taken into consideration in respect of the determination of the problem underlying the application and hence the assessment of inventive step.

Consequently, the objective technical problem is merely to provide further compounds for the treatment of obesity, obsessive compulsive disorders, depression, anxiety, sleep disorders.

The arbitrary selection of substituents from the general formulae disclosed in D1 and D3 is one of several straightforward possibilities at which the skilled person would arrive without the exercise of inventive skill, in order to solve the problem posed.

Therefore, the subject-matter of claims 1-37 cannot be considered as involving an inventive step (Article 33(3) PCT).

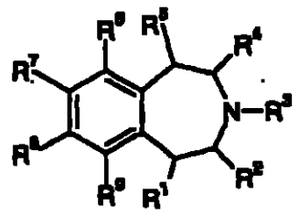
V.3. Industrial Applicability:

The present application relates to compounds which are useful for the treatment of obesity, obsessive compulsive disorder, depression and anxiety and the subject matter of claims 1-17, 26-37 is therefore considered as industrially applicable (Article 33(4) PCT).

For the assessment of the present claims 18-25 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

WE CLAIM:

1. A compound of Formula I:



I

where:

R^1 is hydrogen, fluoro, or (C_1-C_3)alkyl;

R^2, R^3, and R^4 are each independently hydrogen, methyl, or ethyl;

R^5 is hydrogen, fluoro, methyl, or ethyl;

R^6 is $-C\equiv C-R^{10}$, $-O-R^{12}$, $-S-R^{14}$, or $-NR^{24}R^{25}$;

R^7 is hydrogen, halo, cyano, (C_1-C_6)alkyl optionally substituted with 1 to 6 fluoro substituents, (C_2-C_6)alkenyl optionally substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl, (C_1-C_6)alkoxy optionally substituted with 1 to 6 fluoro substituents, (C_1-C_6)alkylthio optionally substituted with 1 to 6 fluoro substituents, Ph^1-(C_0-C_3)alkyl, Ph^1-(C_0-C_3)alkyl-O-, or Ph^1-(C_0-C_3)alkyl-S-;

R^8 is hydrogen, halo, cyano, or $-SCF_3$;

R^9 is hydrogen;

R^{10} is $-CF_3$, ethyl substituted with 1 to 5 fluoro substituents, (C_3-C_6) alkyl optionally substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, Ar^1-(C_0-C_3)alkyl, Ph^1-(C_0-C_3)alkyl, or 3-(C_1-C_4)alkyl-2-oxo-imidazolidin-1-yl-(C_1-C_3)alkyl;

R^{12} is Ph^2-(C_1-C_3)alkyl, Ar^2-(C_1-C_3)alkyl, (C_1-C_6)alkyl-S-(C_2-C_6)alkyl, (C_3-C_7)cycloalkyl-S-(C_2-C_6)alkyl, phenyl-S-(C_2-C_6)alkyl, Ph^2-S-(C_2-C_6)alkyl, phenylcarbonyl-(C_1-C_3)alkyl, Ph^2-C(O)-(C_1-C_3)alkyl, (C_1-C_6)alkoxycarbonyl(C_2-C_6)alkyl, (C_3-C_7)cycloalkyl-OC(O)-(C_2-C_6)alkyl,

phenyloxycarbonyl-(C_3-C_8)alkyl, Ph^2-OC(O)-(C_3-C_8)alkyl, Ar^2-OC(O)-(C_3-C_8)alkyl, (C_3-C_7)cycloalkyl-NH-C(O)-(C_2-C_4)alkyl-, Ph^1-NH-C(O)-(C_2-C_4)alkyl-, Ar^2-NH-C(O)-(C_2-C_4)alkyl-, or R^{13}-C(O)NH-(C_2-C_4)alkyl;

R^{13} is (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, Ph^1, Ar^2, or (C_1-C_3)alkoxy optionally substituted with 1 to 6 fluoro substituents, Ph^1-NH- or N-linked Het^1;

R^{14} is Ar^2 which is not N-linked to the sulfur atom, Ph^2, R^{15}-L-, tetrahydrofuranyl, tetrahydropyranyl, or phenyl-methyl substituted on the methyl moiety with a substituent selected from the group consisting of (C_1-C_3)-*n*-alkyl substituted with hydroxy, (C_1-C_3)alkyl-O-(C_1-C_2)-*n*-alkyl, (C_1-C_3)alkyl-C(O)-(C_0-C_2)-*n*-alkyl, and (C_1-C_3)alkyl-O-C(O)-(C_0-C_2)-*n*-alkyl,

wherein when R^{14} is Ph^2 or Ar^2, wherein Ar^2 is pyridyl, then R^{14} may also, optionally be substituted with phenyl-CH=CH- or phenyl-C≡C-,

said phenyl-CH=CH- or phenyl-C≡C- being optionally further substituted with 1 to 3 substituents independently selected from the group consisting of halo, cyano, $-SCF_3$, (C_1-C_4)alkyl optionally further substituted with 1 to 6 fluoro substituents, and (C_1-C_4)alkoxy optionally further substituted with 1 to 6 fluoro substituents, and

wherein when Ar^2 is pyridyl, the pyridyl may alternatively, optionally be substituted with $R^{28}R^{29}N$-C(O)-, and optionally further substituted with one methyl, $-CF_3$, cyano, or $-SCF_3$ substituent, or with 1 to 2 halo substituents, and

wherein the tetrahydrofuranyl and tetrahydropyranyl may optionally be substituted with an oxo substituent, or with one or two groups independently selected from methyl and $-CF_3$;

R^{15} is $-OR^{16}$, cyano, $-SCF_3$, Ph^2, Ar^2, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, phthalimido, benzothiophenyl optionally substituted at the 2-position with phenyl or benzyl, benzothiazolyl optionally substituted at the 2-position with phenyl or benzyl, benzothiadiazolyl optionally substituted with phenyl or benzyl, 2-oxo-dihydroindol-1-yl optionally substituted at the 3 position with gem dimethyl or (C_1-C_4)alkyl optionally further substituted with 1 to 6 fluoro substituents, 2-oxo-dihydroindol-5-yl

optionally substituted at the 3 position with gem dimethyl or (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, 2-oxo-imidazolidin-1-yl optionally substituted at the 3 position with gem dimethyl or (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, 2-oxo-tetrahydropyrimidinyl optionally substituted at the 3 or 4 position with gem dimethyl or (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, 2-oxo-tetrahydroquinolin-1-yl optionally substituted at the 3 position with gem dimethyl or (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, 2-oxo- dihydrobenzimidazol-1-yl optionally substituted at the 3 position with gem dimethyl or (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, $-NR^{17}R^{18}$, $-C(O)R^{22}$, or a saturated heterocycle selected from the group consisting of pyrrolidinyl, piperidinyl, morpholinyl, and thiomorpholinyl, tetrahydrofuranyl, and tetrahydropyranyl,

wherein Ph^2 and Ar^2 when Ar^2 is pyridyl, may also optionally be substituted with phenyl-CH=CH- or phenyl-C≡C-,

said phenyl-CH=CH- and phenyl-C≡C- being optionally further substituted on the phenyl moiety with 1 to 3 substituents independently selected from the group consisting of halo, cyano, $-SCF_5$, (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, and (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents, and

wherein Ar^2 may alternatively, optionally be substituted with a substituent selected from the group consisting of (C_3-C_7)cycloalkyl-(C_0-C_3)alkyl, Het^1-(C_0-C_3)alkyl, pyridyl-(C_0-C_3)alkyl, and phenyl-(C_0-C_3)alkyl, and optionally further substituted with one methyl, $-CF_3$, cyano, or $-SCF_3$ substituent, or with 1 to 2 halo substituents,

said pyridyl-(C_0-C_3)alkyl and phenyl-(C_0-C_3)alkyl optionally being further substituted with 1-3 substituents independently selected from halo, $-CH_3$, $-OCH_3$, $-CF_3$, $-OCF_3$, -CN, and $-SCF_3$, and

wherein when Ar^2 is pyridyl, the pyridyl may alternatively, optionally be substituted with $R^{24}R^{25}N$-C(O)-, or (C_1-C_6)alkyl-C(O)- optionally substituted with 1 to 6 fluoro substituents, and may be optionally further

substituted with one methyl, $-CF_3$, cyano, or $-SCF_3$ substituent, or with 1 to 2 halo substituents, and

wherein when Ar^2 is thiazolyl, the thiazolyl may alternatively, optionally be substituted with (C_3-C_7)cycloalkyl-(C_0-C_3)alkyl-NH-, and

wherein the pyrrolidinyl, piperidinyl, morpholinyl, and thiomorpholinyl is substituted with oxo- on a carbon atom adjacent to the ring nitrogen atom, or is N-substituted with a substituent selected from the group consisting of

(C_1-C_6)alkylcarbonyl, (C_1-C_6)alkylsulfonyl, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-C(O)-, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-$S(O)_2$-, Ph^1-(C_0-C_3)alkyl-C(O)-, and Ph^1-(C_0-C_3)alkyl-$S(O)_2$-, and

may optionally be further substituted with 1 or 2 methyl or $-CF_3$ substituents, and when oxo-substituted, may optionally be further N-substituted with a substituent selected from the group consisting of (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, and Ph^1-(C_0-C_3)alkyl, and

wherein tetrahydrofuranyl and tetrahydropyranyl may optionally be substituted with an oxo substituent, and/or with one or two groups independently selected from methyl and $-CF_3$;

L is branched or unbranched (C_1-C_6)alkylene, except when R^{15} is $-NR^{17}R^{18}$ or Ar^2-N-linked to L, in which case L is branched or unbranched (C_2-C_6)alkylene, and when L is methylene or ethylene, L may optionally be substituted with gem-ethano or with 1 to 2 fluoro substituents, and when R^{15} is Ph^2, Ar^2, or a saturated heterocycle, L may alternatively, optionally be substituted with a substituent selected from the group consisting of hydroxy, cyano, $-SCF_3$, (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents, (C_1-C_6)alkoxycarbonyl optionally further substituted with 1 to 6 fluoro substituents, (C_1-C_6)alkylcarbonyloxy optionally further substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl-(C_0-C_3)alkyl-O-, (C_3-C_7)cycloalkyl-(C_0-C_3)alkyl-O-C(O)-, and (C_3-C_7)cycloalkyl-(C_0-C_3)alkyl-C(O)-O-;

R^{16} is hydrogen, (C_1-C_6)alkyl optionally substituted with 1 to 6 fluoro substituents, (C_1-C_4)alkylcarbonyl, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-C(O)-, Ph^1-(C_0-C_3)alkyl, Ph^1-(C_0-C_3)alkyl-C(O)-, Ar^2-(C_0-C_3)alkyl, or Ar^2-(C_0-C_3)alkyl-C(O)-,

R^{17} is (C_1-C_4)alkyl optionally substituted with 1 to 6 fluoro substituents, *t*-butylsulfonyl, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-C(O)-, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-sulfonyl, Ph^1-(C_0-C_3)alkyl, Ph^1-(C_0-C_3)alkyl-C(O)-, Ph^1-(C_0-C_3)alkylsulfonyl, Ar^2-(C_0-C_3)alkyl, Ar^2-(C_0-C_3)alkyl-C(O)-, Ar^2-(C_0-C_3)alkylsulfonyl, $R^{19}OC(O)$-, or $R^{20}R^{21}NC(O)$-;

R^{18} is hydrogen or (C_1-C_4)alkyl optionally substituted with 1 to 6 fluoro substituents, or R^{17} and R^{18}, taken together with the nitrogen atom to which they are attached form Het^1 where Het^1 is substituted with oxo- on a carbon atom adjacent to the ring nitrogen atom, or

R^{17} and R^{18}, taken together with the nitrogen atom to which they are attached, form an aromatic heterocycle selected from the group consisting of pyrolyl, pyrazolyl, imidazolyl, 1,2,3-triazolyl, and 1,2,4-triazolyl,

said aromatic heterocycle optionally being substituted with 1 to 2 halo substituents, or substituted with 1 to 2 (C_1-C_4)alkyl substituents optionally further substituted with 1 to 3 fluoro substituents, or mono-substituted with fluoro, nitro, cyano, $-SCF_3$, or (C_1-C_4)alkoxy optionally further substituted with 1 to 3 fluoro substituents, and optionally further substituted with a (C_1-C_4)alkyl substituent optionally further substituted with 1 to 3 fluoro substituents;

R^{19} is (C_1-C_6)alkyl optionally substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, Ar^2-(C_0-C_3)alkyl, or Ph^1-(C_0-C_3)alkyl,

R^{20} is (C_1-C_6)alkyl optionally substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, Ar^2-(C_0-C_3)alkyl, or Ph^1-(C_0-C_3)alkyl,

R^{21} is hydrogen or (C_1-C_4)alkyl optionally substituted with 1 to 6 fluoro substituents, or R^{20} and R^{21}, taken together with the nitrogen atom to which they are attached, form Het^1;

R^{22} is (C_1-C_6)alkyl optionally substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, R^{23}-O-, Ph^1-(C_0-C_3)alkyl, Ar^2-(C_0-C_3)alkyl, or $R^{24}R^{25}N$-;

R^{23} is (C_1-C_6)alkyl optionally substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, Ph^1-(C_0-C_3)alkyl, or Ar^2-(C_0-C_3)alkyl;

R^{24} is (C_1-C_6)alkoxy(C_2-C_3)alkyl optionally substituted with 1 to 6 fluoro substituents, (C_1-C_4)alkylthio(C_2-C_3)alkyl optionally substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl(C_0-C_1)alkyl-O-(C_1-C_2)alkyl, (C_3-C_7)cycloalkyl(C_0-C_1)alkyl-S-(C_1-C_2)alkyl, phenyl(C_1-C_3) *n*-alkyl, Ph^2-(C_1-C_3)-*n*-alkyl, Ar^2(C_0-C_3) *n*-alkyl, phenyl(C_0-C_1)alkyl-O-(C_1-C_2)alkyl, phenyl(C_0-C_1)alkyl-S-(C_1-C_2)alkyl, Ph^1-(C_0-C_1)alkyl-C(O)NH-(C_2-C_4)alkyl, Ph^1-(C_0-C_1)alkyl-NH-C(O)NH-(C_2-C_4)alkyl, pyridyl-(C_0-C_1)alkyl-C(O)NH-(C_2-C_4)alkyl, pyridyl-(C_0-C_1)alkyl-NH-C(O)NH-(C_2-C_4)alkyl, or Ar^3(C_1-C_2)alkyl,

where Ar^3 is a bi-cyclic moiety selected from a group consisting of indanyl, indolyl, dihydrobenzofuranyl, benzofuranyl, benzothiophenyl, benzoxazolyl, benzothiazolyl, benzo[1,3]dioxolyl, naphthyl, dihydrobenzopyranyl, quinolinyl, isoquinolinyl, and benzo[1,2,3]thiadiazolyl,

said Ar^3 optionally being substituted with (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, phenyl(C_0-C_1)alkyl optionally further substituted with 1 to 6 fluoro substituents, or substituted with (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, or substituted with 1-3 substituents independently selected from the group consisting of halo, oxo, methyl, and $-CF_3$,

said phenyl(C_1-C_3) *n*-alkyl, Ph^2-(C_1-C_3) *n*-alkyl, or Ar^2(C_0-C_3) *n*-alkyl optionally being substituted on the *n*-alkyl moiety when present with (C_1-C_3)alkyl, dimethyl, gem-ethano, 1 to 2 fluoro substituents, or (C_1-C_6)alkyl-C(O)-,

said Ar^3(C_0-C_3) *n*-alkyl being alternatively optionally substituted with a substituent selected from the group consisting of (C_3-C_7)cycloalkyl-(C_0-C_3)alkyl, Het^1-(C_0-C_3)alkyl, pyridyl-(C_0-C_3)alkyl, phenyl-

(C_0-C_3)alkyl, pyridyl-(C_0-C_3)alkyl-NH-, phenyl-(C_0-C_3)alkyl-NH-, (C_1-C_6)alkyl-S-, and (C_3-C_7)cycloalkyl-(C_0-C_3)alkyl-S-, and optionally further substituted with one methyl, $-CF_3$, cyano, or $-SCF_3$ substituent, or with 1 to 2 halo substituents,

said pyridyl-(C_0-C_3)alkyl and phenyl-(C_0-C_3)alkyl optionally being further substituted with 1-3 substituents independently selected from halo, $-CH_3$, $-OCH_3$, $-CF_3$, $-OCF_3$, -CN, and $-SCF_3$, and

said Ph^2-(C_1-C_3) *n*-alkyl and Ar^2(C_0-C_3) *n*-alkyl where Ar^2 is pyridyl, also optionally being substituted on the phenyl or Ar^2 moiety, respectively, with phenyl-CH=CH- or phenyl-C≡C-,

said phenyl-CH=CH- or phenyl-C≡C- being optionally further substituted with 1 to 3 substituents independently selected from the group consisting of halo, cyano, $-SCF_3$, (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, and (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents, and

said Ar^2(C_0-C_3) *n*-alkyl where Ar^2 is pyridyl, alternatively, optionally being substituted with (C_1-C_4)alkyl-C(O)- or $R^{28}R^{29}N$-C(O)-, and optionally further substituted with one methyl, $-CF_3$, cyano, or $-SCF_3$ substituent, or with 1 to 2 halo substituents,

said phenyl(C_0-C_1)alkyl-O-(C_1-C_3)alkyl, or phenyl(C_0-C_1)alkyl-S-(C_1-C_3)alkyl optionally being substituted on the phenyl moiety with (C_1-C_2)-$S(O)_2$-, or with 1 to 5 independently selected halo substituents, or with 1 to 3 substituents independently selected from the group consisting of halo, cyano, $-SCF_3$, (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, and (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents, and

said pyridyl-(C_0-C_1)alkyl-C(O)NH-(C_2-C_4)alkyl and pyridyl-(C_0-C_1)alkyl-NH-C(O)NH-(C_2-C_4)alkyl optionally being substituted on the pyridyl moiety with methyl, $-CF_3$, or 1 to 3 halo substituents;

R^{25} is hydrogen, (C_1-C_3)alkyl optionally substituted with 1 to 6 fluoro substituents, or allyl;

R^{26} is hydrogen, (C_1-C_4)alkyl optionally substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl;

R^{27} is hydrogen or (C_1-C_4)alkyl optionally substituted with 1 to 6 fluoro substituents, or R^{26} and R^{27}, taken together with the nitrogen atom to which they are attached, form Het^1;

R^{28} is (C_1-C_8)alkyl optionally substituted with 1 to 6 fluoro substituents, (C_3-C_8)cycloalkyl(C_0-C_3)alkyl, tetrahydropyran-3-yl(C_0-C_3)alkyl, tetrahydropyran-4-yl(C_0-C_3)alkyl, tetrahydrofuranyl(C_0-C_3)alkyl, Ph^1-(C_0-C_2) *n*-alkyl, or Ar^2-(C_0-C_2) *n*-alkyl,

said Ph^1-(C_0-C_2) *n*-alkyl and Ar^2-(C_0-C_2) *n*-alkyl optionally being substituted on the alkyl moiety when present with (C_1-C_3)alkyl, dimethyl, or gem-ethano;

R^{29} is hydrogen or (C_1-C_3)alkyl;

R^{30} is hydrogen, (C_1-C_8)alkyl optionally substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, Ph^1-(C_0-C_3)alkyl, or $Ar^2(C_0-C_3)$alkyl,

R^{31} is hydrogen or (C_1-C_6)alkyl optionally substituted with 1 to 6 fluoro substituents, or R^{30} and R^{31}, taken together with the nitrogen atom to which they are attached, form Het^1,

said Het^1 also optionally being substituted with phenyl optionally further substituted with 1 to 3 halo substituents;

R^{32} and R^{33} are each independently hydrogen or (C_1-C_6)alkyl optionally substituted with 1 to 6 fluoro substituents, or R^{32} and R^{33}, taken together with the nitrogen atom to which they are attached, form Het^1, or R^{32} is $Ph^1(C_0-C_1)$alkyl provided that R^{33} is hydrogen;

Ar^1 is an aromatic heterocycle substituent selected from the group consisting of furanyl, thiophenyl, thiazolyl, oxazolyl, isoxazolyl, pyridyl, and pyridazinyl, any of which may optionally be substituted with 1 to 3 substituents independently selected from the group consisting of halo, (C_1-C_3)alkyl, (C_1-C_3)alkoxy, $-CF_3$, $-O-CF_3$, nitro, cyano, and trifluoromethylthio;

Ar^2 is an aromatic heterocycle substituent selected from the group consisting of pyrrolyl, pyrazolyl, imidazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, furanyl, oxazolyl, isoxazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, thiophenyl, thiazolyl, isothiazolyl, 1,2,3-thiadiazolyl, 1,3,4-thiadiazolyl, pyridyl, pyridazinyl, and benzimidazolyl, any of which may optionally be substituted with 1 to 3 substituents independently selected from the group consisting of halo, cyano, $-SCF_3$, (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, and (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents, and wherein pyridyl and pyridazinyl may also optionally be substituted with (C_1-C_6)alkylamino optionally further substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, or (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-amino;

Het^1 is a saturated, nitrogen-containing heterocycle substituent selected from the group consisting of azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl, morpholinyl, thiomorpholinyl, homomorpholinyl, and homothiomorpholinyl, any of which may optionally be substituted with (C_1-C_6)alkyl or with 2 methyl substituents;

Het^2 is a saturated, oxygen-containing heterocycle substituent selected from the group consisting of tetrahydrofuranyl and tetrahydropyranyl, any of which may optionally be substituted with (C_1-C_6)alkyl or with 2 methyl substituents;

Ph^1 is phenyl optionally substituted with 1 to 5 independently selected halo substituents, or with 1 to 3 substituents independently selected from the group consisting of halo, cyano, $-SCF_3$, (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, and (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents;

Ph^2 is phenyl substituted with:

a) 1 to 5 independently selected halo substituents; or

b) 1 to 3 substituents independently selected from the group consisting of halo, cyano, $-SCF_3$, nitro, hydroxy, (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, and (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents; or

c) 0, 1, or 2 substituents independently selected from the group consisting of halo, cyano, $-SCF_3$, methyl, $-CF_3$, methoxy, $-OCF_3$, nitro, and hydroxy, together with one substituent selected from the group consisting of

i) (C_1-C_{10})alkyl optionally further substituted with 1 to 6 fluoro substituents or mono-substituted with hydroxy, (C_1-C_4)alkoxy, (C_3-C_7)cycloalkyl(C_0-C_3)alkyloxy, $Het^2-(C_0-C_3)$alkyloxy, $Ph^1-(C_0-C_3)$alkyloxy,

ii) (C_1-C_{10})alkoxy-(C_0-C_3)alkyl optionally further substituted with 1 to 6 fluoro substituents, and optionally further substituted with hydroxy,

iii) (C_1-C_4)alkyl-C(O)-(C_0-C_3)alkyl optionally further substituted with 1 to 6 fluoro substituents,

iv) carboxy,

v) (C_1-C_4)alkoxycarbonyl optionally further substituted with 1 to 6 fluoro substituents,

vi) (C_1-C_4)alkyl-C(O)-(C_0-C_3)-O- optionally further substituted with 1 to 6 fluoro substituents,

vii) (C_1-C_4)alkylthio-(C_0-C_3)alkyl optionally further substituted with 1 to 6 fluoro substituents,

viii) (C_1-C_4)alkylsulfinyl-(C_0-C_3)alkyl optionally further substituted with 1 to 6 fluoro substituents,

ix) (C_1-C_4)alkylsulfonyl-(C_0-C_3)alkyl optionally further substituted with 1 to 6 fluoro substituents,

x) (C_1-C_4)alkylsulfonyl-(C_0-C_3)alkyl-O- optionally further substituted with 1 to 6 fluoro substituents,

xi) (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, optionally further substituted on the cycloalkyl with 1 to 4 substituents selected from methyl and fluoro,

xii) (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-O-, optionally further substituted on the cycloalkyl with 1 to 4 substituents selected from methyl and fluoro,

xiii) (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-C(O)-,

xiv) (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-O-C(O)-,

xv) (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-S-,

xvi) (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-S(O)-,

xvii) (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-$S(O)_2$-,

xviii) Ph^1-(C_0-C_3)alkyl, optionally substituted on the alkyl moiety with 1 to 2 fluoro substituents,

xix) Ph^1-(C_0-C_3)alkyl-O-, optionally substituted on the alkyl moiety with 1 to 2 fluoro substituents

xx) Ph^1-(C_0-C_3)alkyl-C(O)-,

xxi) Ph^1-(C_0-C_3)alkyl-O-C(O)-,

xxii) Ph^1-(C_0-C_3)alkyl-C(O)-(C_0-C_3)alkyl-O-,

xxiii) Ph^1-(C_0-C_3)alkylthio,

xxiv) Ph^1-(C_0-C_3)alkylsulfinyl,

xxv) Ph^1-(C_0-C_3)alkylsulfonyl,

xxvi) $Ar^2(C_0-C_3)$alkyl,

xxvii) $Ar^2(C_0-C_3)$alkyl-O-

xxviii) Ar^2-(C_0-C_3)alkyl-S-,

xxix) $Ar^2(C_0-C_3)$alkyl-C(O)-,

xxx) $Ar^2(C_0-C_3)$alkyl-C(S)-,

xxxi) Ar^2-(C_0-C_3)alkylsulfinyl,

xxxii) Ar^2-(C_0-C_3)alkylsulfonyl,

xxxiii) $Het^1(C_0-C_3)$alkyl-C(O)- optionally substituted on the Het^1 moiety with Ph^1,

xxxiv) $Het^1(C_0-C_3)$alkyl-C(S)- optionally substituted on the Het^1 moiety with Ph^1,

xxxv) N-linked Het^1-C(O)-(C_0-C_3)alkyl-O-,

xxxvi) Het^2-(C_0-C_3)alkyloxy,

xxxvii) $R^{26}R^{27}N$-,

xxxviii) $R^{28}R^{29}$-N-(C_1-C_3)alkoxy,

xxxix) $R^{28}R^{29}N$-C(O)-,

xl) $R^{28}R^{29}N$-C(O)-(C_1-C_3)alkyl-O-,

xli) $R^{28}R^{29}N$-C(S)-,

xlii) $R^{30}R^{31}N\text{-}S(O)_2\text{-}$,

xliii) HON=C(CH_3)-, and

xliv) HON=C(Ph^1)-.

or a pharmaceutically acceptable salt thereof, subject to the following provisos:

a) no more than two of R^1, R^2, R^3, R^4, and R^5 may be other than hydrogen;

b) when R^2 is methyl, then R^1, R^3, R^4, and R^5 are each hydrogen; and

c) when R^3 is methyl, then R^2 and R^4 are each hydrogen.

2. A compound according to Claim 1 wherein R^7 is selected from halo, -CN, and CF_3.

3. A compound according to either Claim 1 or Claim 2 wherein R^7 is chloro.

4. A compound according to any one of Claims 1 to 3 wherein R^6 is -C≡C-R^{10}.

5. A compound according to any one of Claims 1 to 3 wherein R^6 is -O-R^{12}.

6. A compound according to any one of Claims 1 to 3 wherein R^6 is -S-R^{14}.

7. A compound according to Claim 6 wherein R^6 is -S-L-R^{15}.

8. A compound according to Claim 7 wherein R^{15} is Ph^2 or Ar^2.

9. A compound according to any one of Claims 1 to 3 wherein R^6 is -$NR^{24}R^{25}$.

10. A compound according to Claim 9 wherein R^{24} is Ph^2-(C_1-C_3) *n*-alkyl-.

11. A compound according to Claim 9 wherein R^{24} is Ar^2-(C_1-C_3) *n*-alkyl-.

12. A Compound according to any one of Claims 9 to 11 wherein R^{25} is hydrogen.

13. (Cancelled)

14. (Cancelled)

15. A compound according to any one of Claims 1 to 14 wherein R^1, R^2, R^3, R^4, R^5, and R^8, are each hydrogen.

16. A pharmaceutical composition comprising a compound according to any one of Claims 1 to 15 as an active ingredient in association with a pharmaceutically acceptable carrier, diluent or excipient.

17. A compound according to any one of Claims 1 to 15 for use in therapy.

18. A method for the treatment of obesity in mammals, comprising administering to a mammal in need of such treatment an effective amount of a compound according to Claim 1.

19. The method of Claim 18, where the mammal is human.

20. A method for the treatment of obsessive compulsive disorder in mammals, comprising administering to a mammal in need of such treatment an effective amount of a compound according to Claim 1.

21. The method of Claim 20, where the mammal is human.

22. A method for the treatment of depression in mammals, comprising administering to a mammal in need of such treatment an effective amount of a compound according to Claim 1.

23. The method of Claim 22, where the mammal is human.

24. A method for the treatment of anxiety in mammals, comprising administering to a mammal in need of such treatment an effective amount of a compound according to Claim 1.

25. The method of Claim 24, where the mammal is human.

26. A compound according to any one of Claims 1 to 15 for use as a pharmaceutical.

27. A compound according to any one of Claims 1 to 15 for use in the treatment of obesity in mammals.

28. A compound according to any one of Claims 1 to 15 for use in the treatment of obsessive/compulsive disorder in mammals.

29. A compound according to any one of Claims 1 to 15 for use in the treatment of depression in mammals.

30. A compound according to any one of Claims 1 to 15 for use in the treatment of anxiety in mammals.

31. A compound according to any one of Claims 27-30, where the mammal is a human.

32. The use of a compound according to any one of Claims 1 to 15 in the manufacture of a medicament for the treatment of a disorder selected from obesity, hyperphagia, obsessive/compulsive disorder, depression, anxiety, substance abuse, sleep disorder, hot flashes, and/or hypogonadism.

33. The use of a compound according to any one of Claims 1 to 15 in the manufacture of a medicament for the treatment of a disorder selected from obesity, obsessive/compulsive disorders, anxiety, or depression.

34. A pharmaceutical composition adapted for the treatment of obesity comprising a compound according to any one of Claims 1 to 15 in combination with one or more pharmaceutically acceptable excipients, carriers, or diluents therefore.

35. A pharmaceutical composition adapted for the treatment of obsessive/compulsive disorders comprising a compound according to any one of Claims 1 to 15 in combination with one or more pharmaceutically acceptable excipients, carriers, or diluents therefore.

36. A pharmaceutical composition adapted for the treatment of depression comprising a compound according to any one of Claims 1 to 15 in combination with one or more pharmaceutically acceptable excipients, carriers, or diluents therefore.

37. A pharmaceutical composition adapted for the treatment of anxiety comprising a compound according to any one of Claims 1 to 15 in combination with one or more pharmaceutically acceptable excipients, carriers, or diluents therefore.

PCT/US2005/005418

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

RECEIVED

AUG 14 2006

✓ TUCKER, R., Craig
P. O. Box 6288
Indianapolis, Indiana 46206-6288
United States of America

ELI LILLY AND COMPANY
Patent Division

Date of mailing (day/month/year)	
28 July 2006 (28.07.2006)	
Applicant's or agent's file reference	**IMPORTANT NOTIFICATION**
X-16115	
International application No.	**International filing date (day/month/year)**
PCT/US2005/005418 ✓	✓18 February 2005 (18.02.2005)

1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
	DE	GB
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[X] the person [ ] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
MAZANETZ, Michael, Philip Eli Lilly and Company Limited Kingsclere Road Basingstoke Hampshire RG21 6XA United Kingdom	DE	GB
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:
Person in box 2. is now recorded as inventor for all designations and inventor for the designation of the United States of America only.

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Laurence FAHY (Fax 338-71-30)
Facsimile No. (41-22) 338.71.30	Telephone No. (41-22) 338 9617

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IN THE EUROPEAN PATENT OFFICE ACTING AS PRELIMINARY EXAMINATION AUTHORITY UNDER THE PCT

Applicant Docket: X16115
International Application No.: PCT/US2005/005418
Applicant(s): ELI LILLY AND COMPANY
Earliest Priority Date: 25 February 2004 (25.02.2004)
International Filing Date: 18 February 2005 (18.02.2005)
Invention: 6-SUBSTITUTED 2,3,4,5-TETRAHYDRO-1H-BENZO[d]AZEPINES AS 5-HT$_{2C}$ RECEPTOR AGONISTS

AMENDMENTS UNDER ARTICLE 34(2)(B) AND REPLY TO WRITTEN OPINION

European Patent Office – P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk – Pays Bas

Attn: IPEA/EP

Dear Sir/Madam:

In response to the Written Opinion dated June 2, 2005, applicants submit amendments under Article 34 and note as follows.

Please substitute sheets 575-589, amending the claims. A clean and a marked up copy are attached. It is noted that Claim 1 is amended such that R^9 is now limited to hydrogen. This embodiment of the invention is supported on page 35, line 24 of the specification as filed. This limitation makes proviso e) extraneous in that R^9 is now always hydrogen. The Written Opinion also noted an error in proviso d) in that R^7 and previous R^8 could not be hydroxy, making proviso d) meaningless. Therefore proviso d) has also been deleted.

It is further noted that dependent Claims 13 and 14 are cancelled in that they do not further limit amended Claim 1, being drawn to embodiments wherein R^9 was selected to be hydrogen, to which it is now limited in Claim 1.

Regarding the Written Opinion's statements on novelty, the above mentioned amendments obviate references D1 and D2, in that disclosed compounds of D1 and example 19 of D2 all have a chloro group at position 9 of the tetrahydrobenzazepine core, which is not allowed in the presently claimed invention.

Regarding the Written Opinion's statements on inventive step, it is first noted that the present invention is drawn to selective 5-HT$_{2C}$ agonists, noting selectivity particularly against adrenergic and dopaminergic receptors among others. (See page 3, line 6

of the specification as published, as well as the discussion regarding detrimental side affects related to adrenergic and dopaminergic receptor cross reactivity on page 2, line 14 through page 3, line 4. See also selectivity discussion and summarized data on page 560, first paragraph through 565, line 7, demonstrating that the compounds solve the technical problem of 5-HT_{2C} selectivity along with high potency.) Therefore, the technical problem to be solved is not the provision of more random nerologically active compounds structurally similar to the referenced compounds, but rather to discover compounds that selectively activate the 5-HT_{2C} receptor, such that neither the adrenergic nor dopaminergic (as well as other 5-HT receptor subtypes) are modulated to a physiologically significant level, thus avoiding undesired cross reactivity. Thus, starting with the referenced compounds of D1-4, working toward the presently claimed invention would destroy the disclosed activity of the referenced compounds, in contradiction to any suggestion that those references would render the presently claimed invention obvious to one of ordinary skill in the art.

Regarding the Written Opinion's statement that D4 suggests that SK&F 104078, being an alpha-2-adrenergic antagonist which also has 5-HT_2 activity, gives motivation that other adrenergic antagonists will also have significant 5-HT_2 activity is unfounded and should be withdrawn. First, D4 does not disclose which structural features of SK&F 104078 are important for the disclosed serotonergic cross-reactivity. Nor does it guide the skilled artisan as to which structural features to modify to optimize the serotonergic activity while diminishing the adrenergic activity to below physiologically relevant levels. Secondly, the 5-HT_2 activity disclosed is not delineated between 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptors, all of which have very different physiological roles. No disclosure is given as to how the skilled artisan could modify the compound to gain selectivity between these receptors. Again, the technical problem to be solved is NOT to provide an agonist of all four of these serotonergic receptors (as well as alpha adrenergic receptor antagonism), but specifically selective agonists of the 5-HT_{2C} receptor.

It is believed all objections to the novelty and inventiveness of the claimed invention as amended are obviated or traversed. A positive opinion on these grounds is therefore requested.

Arguments and amendments regarding industrial applicability of the method of treatment type claims are reserved for national stage prosecution according to the various national laws regarding such claims.

Unless otherwise expressed herein, applicant disagrees with any statement in the Written Opinion to the effect that the invention as disclosed and claimed in the present application fails to possess novelty, inventive step, or industrial applicability,

or that is not useful or is obvious. Any arguments or amendments submitted herewith are for the purpose of obtaining a preliminary and non-binding opinion under the provisions of PCT Article 33 and should be considered without prejudice to any arguments or amendments which may be advanced in the national or regional phase examination of this application.

Applicant requests that this application receive a detailed, non-rationalized, examination under the new EPO preliminary examination guidelines. Applicant further requests the opportunity for an interview in the event that, after consideration of the foregoing amendments and arguments, the Examiner intends to issue an IPER which is not entirely positive.

Respectfully submitted,



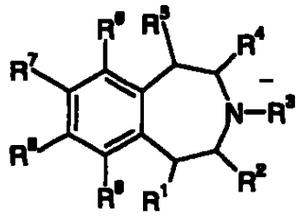
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20 December 2005

WE CLAIM:

1. A compound of Formula I:



I

where:

R^1 is hydrogen, fluoro, or (C_1-C_3)alkyl;

R^2, R^3, and R^4 are each independently hydrogen, methyl, or ethyl;

R^5 is hydrogen, fluoro, methyl, or ethyl;

R^6 is $-C{\equiv}C-R^{10}$, $-O-R^{12}$, $-S-R^{14}$, or $-NR^{24}R^{25}$;

R^7 is hydrogen, halo, cyano, (C_1-C_6)alkyl optionally substituted with 1 to 6 fluoro substituents, (C_2-C_6)alkenyl optionally substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl, (C_1-C_6)alkoxy optionally substituted with 1 to 6 fluoro substituents, (C_1-C_6)alkylthio optionally substituted with 1 to 6 fluoro substituents, Ph^1-(C_0-C_3)alkyl, Ph^1-(C_0-C_3)alkyl-O-, or Ph^1-(C_0-C_3)alkyl-S-;

R^8 is hydrogen, halo, cyano, or $-SCF_3$;

R^9 is hydrogen;

R^{10} is $-CF_3$, ethyl substituted with 1 to 5 fluoro substituents, (C_3-C_6) alkyl optionally substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, Ar^1-(C_0-C_3)alkyl, Ph^1-(C_0-C_3)alkyl, or 3-(C_1-C_4)alkyl-2-oxo-imidazolidin-1-yl-(C_1-C_3)alkyl;

R^{12} is Ph^2-(C_1-C_3)alkyl, Ar^2-(C_1-C_3)alkyl, (C_1-C_6)alkyl-S-(C_2-C_6)alkyl, (C_3-C_7)cycloalkyl-S-(C_2-C_6)alkyl, phenyl-S-(C_2-C_6)alkyl, Ph^2-S-(C_2-C_6)alkyl, phenylcarbonyl-(C_1-C_3)alkyl, Ph^2-C(O)-(C_1-C_3)alkyl, (C_1-C_6)alkoxycarbonyl(C_3-C_6)alkyl, (C_3-C_7)cycloalkyl-OC(O)-(C_3-C_6)alkyl,

phenyloxycarbonyl-(C_3-C_6)alkyl, Ph^2-OC(O)-(C_3-C_6)alkyl, Ar^2-OC(O)-(C_3-C_6)alkyl, (C_3-C_7)cycloalkyl-NH-C(O)-(C_2-C_4)alkyl-, Ph^1-NH-C(O)-(C_2-C_4)alkyl-, Ar^2-NH-C(O)-(C_2-C_4)alkyl-, or R^{13}-C(O)NH-(C_2-C_4)alkyl;

R^{13} is (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, Ph^1, Ar^2, or (C_1-C_3)alkoxy optionally substituted with 1 to 6 fluoro substituents, Ph^1-NH- or N-linked Het^1;

R^{14} is Ar^2 which is not N-linked to the sulfur atom, Ph^2, R^{15}-L-, tetrahydrofuranyl, tetrahydropyranyl, or phenyl-methyl substituted on the methyl moiety with a substituent selected from the group consisting of (C_1-C_3)-*n*-alkyl substituted with hydroxy, (C_1-C_3)alkyl-O-(C_1-C_2)-*n*-alkyl, (C_1-C_3)alkyl-C(O)-(C_0-C_2)-*n*-alkyl, and (C_1-C_3)alkyl-O-C(O)-(C_0-C_2)-*n*-alkyl,

wherein when R^{14} is Ph^2 or Ar^2, wherein Ar^2 is pyridyl, then R^{14} may also, optionally be substituted with phenyl-CH=CH- or phenyl-C≡C-, said phenyl-CH=CH- or phenyl-C≡C- being optionally further substituted with 1 to 3 substituents independently selected from the group consisting of halo, cyano, -SCF_3, (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, and (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents, and

wherein when Ar^2 is pyridyl, the pyridyl may alternatively, optionally be substituted with $R^{28}R^{29}$N-C(O)-, and optionally further substituted with one methyl, -CF_3, cyano, or -SCF_3 substituent, or with 1 to 2 halo substituents, and

wherein the tetrahydrofuranyl and tetrahydropyranyl may optionally be substituted with an oxo substituent, or with one or two groups independently selected from methyl and –CF_3;

R^{15} is -OR^{16}, cyano, –SCF_3, Ph^2, Ar^2, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, phthalimido, benzothiophenyl optionally substituted at the 2-position with phenyl or benzyl, benzothiazolyl optionally substituted at the 2-position with phenyl or benzyl, benzothiadiazolyl optionally substituted with phenyl or benzyl, 2-oxo-dihydroindol-1-yl optionally substituted at the 3 position with gem dimethyl or (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, 2-oxo-dihydroindol-5-yl

optionally substituted at the 3 position with gem dimethyl or (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, 2-oxo-imidazolidin-1-yl optionally substituted at the 3 position with gem dimethyl or (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, 2-oxo-tetrahydropyrimidinyl optionally substituted at the 3 or 4 position with gem dimethyl or (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, 2-oxo-tetrahydroquinolin-1-yl optionally substituted at the 3 position with gem dimethyl or (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, 2-oxo- dihydrobenzimidazol-1-yl optionally substituted at the 3 position with gem dimethyl or (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, $-NR^{17}R^{18}$, $-C(O)R^{22}$, or a saturated heterocycle selected from the group consisting of pyrrolidinyl, piperidinyl, morpholinyl, and thiomorpholinyl, tetrahydrofuranyl, and tetrahydropyranyl,

wherein Ph^2 and Ar^2 when Ar^2 is pyridyl, may also optionally be substituted with phenyl-CH=CH- or phenyl-C≡C-,

said phenyl-CH=CH- and phenyl-C≡C- being optionally further substituted on the phenyl moiety with 1 to 3 substituents independently selected from the group consisting of halo, cyano, $-SCF_3$, (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, and (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents, and

wherein Ar^2 may alternatively, optionally be substituted with a substituent selected from the group consisting of (C_3-C_7)cycloalkyl-(C_0-C_3)alkyl, Het^1-(C_0-C_3)alkyl, pyridyl-(C_0-C_3)alkyl, and phenyl-(C_0-C_3)alkyl, and optionally further substituted with one methyl, $-CF_3$, cyano, or $-SCF_3$ substituent, or with 1 to 2 halo substituents,

said pyridyl-(C_0-C_3)alkyl and phenyl-(C_0-C_3)alkyl optionally being further substituted with 1-3 substituents independently selected from halo, $-CH_3$, $-OCH_3$, $-CF_3$, $-OCF_3$, -CN, and $-SCF_3$, and

wherein when Ar^2 is pyridyl, the pyridyl may alternatively, optionally be substituted with $R^{28}R^{29}N$-C(O)-, or (C_1-C_6)alkyl-C(O)- optionally substituted with 1 to 6 fluoro substituents, and may be optionally further

substituted with one methyl, -CF_3, cyano, or -SCF_3 substituent, or with 1 to 2 halo substituents, and

wherein when Ar^2 is thiazolyl, the thiazolyl may alternatively, optionally be substituted with (C_3-C_7)cycloalkyl-(C_0-C_3)alkyl-NH-, and

wherein the pyrrolidinyl, piperidinyl, morpholinyl, and thiomorpholinyl is substituted with oxo- on a carbon atom adjacent to the ring nitrogen atom, or is N-substituted with a substituent selected from the group consisting of

(C_1-C_6)alkylcarbonyl, (C_1-C_6)alkylsulfonyl,

(C_3-C_7)cycloalkyl(C_0-C_3)alkyl-C(O)-,

(C_3-C_7)cycloalkyl(C_0-C_3)alkyl-S(O)$_2$-, Ph^1-(C_0-C_3)alkyl-C(O)-, and

Ph^1-(C_0-C_3)alkyl-S(O)$_2$-, and

may optionally be further substituted with 1 or 2 methyl or -CF_3 substituents, and when oxo-substituted, may optionally be further N-substituted with a substituent selected from the group consisting of

(C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, and Ph^1-(C_0-C_3)alkyl, and

wherein tetrahydrofuranyl and tetrahydropyranyl may optionally be substituted with an oxo substituent, and/or with one or two groups independently selected from methyl and –CF_3;

L is branched or unbranched (C_1-C_6)alkylene, except when R^{15} is -$NR^{17}R^{18}$ or Ar^2-N-linked to L, in which case L is branched or unbranched (C_2-C_6)alkylene, and when L is methylene or ethylene, L may optionally be substituted with gem-ethano or with 1 to 2 fluoro substituents, and when R^{15} is Ph^2, Ar^2, or a saturated heterocycle, L may alternatively, optionally be substituted with a substituent selected from the group consisting of hydroxy, cyano, -SCF_3, (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents, (C_1-C_6)alkoxycarbonyl optionally further substituted with 1 to 6 fluoro substituents, (C_1-C_6)alkylcarbonyloxy optionally further substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl-(C_0-C_3)alkyl-O-, (C_3-C_7)cycloalkyl-(C_0-C_3)alkyl-O-C(O)-, and (C_3-C_7)cycloalkyl-(C_0-C_3)alkyl-C(O)-O-;

R^{16} is hydrogen, (C_1-C_6)alkyl optionally substituted with 1 to 6 fluoro substituents, (C_1-C_6)alkylcarbonyl, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-C(O)-, Ph^1-(C_0-C_3)alkyl, Ph^1-(C_0-C_3)alkyl-C(O)-, Ar^2-(C_0-C_3)alkyl, or Ar^2-(C_0-C_3)alkyl-C(O)-,

R^{17} is (C_1-C_4)alkyl optionally substituted with 1 to 6 fluoro substituents, *t*-butylsulfonyl, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-C(O)-, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-sulfonyl, Ph^1-(C_0-C_3)alkyl, Ph^1-(C_0-C_3)alkyl-C(O)-, Ph^1-(C_0-C_3)alkylsulfonyl, Ar^2-(C_0-C_3)alkyl, Ar^2-(C_0-C_3)alkyl-C(O)-, Ar^2-(C_0-C_3)alkylsulfonyl, $R^{19}OC(O)$-, or $R^{20}R^{21}NC(O)$-;

R^{18} is hydrogen or (C_1-C_4)alkyl optionally substituted with 1 to 6 fluoro substituents, or R^{17} and R^{18}, taken together with the nitrogen atom to which they are attached form Het^1 where Het^1 is substituted with oxo- on a carbon atom adjacent to the ring nitrogen atom, or

R^{17} and R^{18}, taken together with the nitrogen atom to which they are attached, form an aromatic heterocycle selected from the group consisting of pyrolyl, pyrazolyl, imidazolyl, 1,2,3-triazolyl, and 1,2,4-triazolyl,

said aromatic heterocycle optionally being substituted with 1 to 2 halo substituents, or substituted with 1 to 2 (C_1-C_4)alkyl substituents optionally further substituted with 1 to 3 fluoro substituents, or mono-substituted with fluoro, nitro, cyano, $-SCF_3$, or (C_1-C_4)alkoxy optionally further substituted with 1 to 3 fluoro substituents, and optionally further substituted with a (C_1-C_4)alkyl substituent optionally further substituted with 1 to 3 fluoro substituents;

R^{19} is (C_1-C_6)alkyl optionally substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, Ar^2-(C_0-C_3)alkyl, or Ph^1-(C_0-C_3)alkyl,

R^{20} is (C_1-C_6)alkyl optionally substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, Ar^2-(C_0-C_3)alkyl, or Ph^1-(C_0-C_3)alkyl,

R^{21} is hydrogen or (C_1-C_4)alkyl optionally substituted with 1 to 6 fluoro substituents, or R^{20} and R^{21}, taken together with the nitrogen atom to which they are attached, form Het^1;

R^{22} is (C_1-C_6)alkyl optionally substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, R^{23}-O-, Ph^1-(C_0-C_3)alkyl, Ar^2-(C_0-C_3)alkyl, or $R^{32}R^{33}N$-;

R^{23} is (C_1-C_6)alkyl optionally substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, Ph^1-(C_0-C_3)alkyl, or Ar^2-(C_0-C_3)alkyl;

R^{24} is (C_1-C_6)alkoxy(C_2-C_5)alkyl optionally substituted with 1 to 6 fluoro substituents, (C_1-C_6)alkylthio(C_2-C_5)alkyl optionally substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl(C_0-C_1)alkyl-O-(C_1-C_5)alkyl, (C_3-C_7)cycloalkyl(C_0-C_1)alkyl-S-(C_1-C_5)alkyl, phenyl(C_1-C_3) *n*-alkyl, Ph^2-(C_1-C_3)-*n*-alkyl, $Ar^2(C_0-C_3)$ *n*-alkyl, phenyl(C_0-C_1)alkyl-O-(C_1-C_5)alkyl, phenyl(C_0-C_1)alkyl-S-(C_1-C_5)alkyl, Ph^1-(C_0-C_1)alkyl-C(O)NH-(C_2-C_4)alkyl, Ph^1-(C_0-C_1)alkyl-NH-C(O)NH-(C_2-C_4)alkyl, pyridyl-(C_0-C_1)alkyl-C(O)NH-(C_2-C_4)alkyl, pyridyl-(C_0-C_1)alkyl-NH-C(O)NH-(C_2-C_4)alkyl, or $Ar^3(C_1-C_2)$alkyl,

where Ar^3 is a bi-cyclic moiety selected from a group consisting of indanyl, indolyl, dihydrobenzofuranyl, benzofuranyl, benzothiophenyl, benzoxazolyl, benzothiazolyl, benzo[1,3]dioxolyl, naphthyl, dihydrobenzopyranyl, quinolinyl, isoquinolinyl, and benzo[1,2,3]thiadiazolyl,

said Ar^3 optionally being substituted with (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, phenyl(C_0-C_1)alkyl optionally further substituted with 1 to 6 fluoro substituents, or substituted with (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, or substituted with 1-3 substituents independently selected from the group consisting of halo, oxo, methyl, and $-CF_3$,

said phenyl(C_1-C_3) *n*-alkyl, Ph^2-(C_1-C_3) *n*-alkyl, or $Ar^2(C_0-C_3)$ *n*-alkyl optionally being substituted on the *n*-alkyl moiety when present with (C_1-C_3)alkyl, dimethyl, gem-ethano, 1 to 2 fluoro substituents, or (C_1-C_6)alkyl-C(O)-,

said $Ar^2(C_0-C_3)$ *n*-alkyl being alternatively optionally substituted with a substituent selected from the group consisting of (C_3-C_7)cycloalkyl-(C_0-C_3)alkyl, Het^1-(C_0-C_3)alkyl, pyridyl-(C_0-C_3)alkyl, phenyl-

(C_0-C_3)alkyl, pyridyl-(C_0-C_3)alkyl-NH-, phenyl-(C_0-C_3)alkyl-NH-, (C_1-C_6)alkyl-S-, and (C_3-C_7)cycloalkyl-(C_0-C_3)alkyl-S-, and optionally further substituted with one methyl, -CF_3, cyano, or -SCF_3 substituent, or with 1 to 2 halo substituents,

said pyridyl-(C_0-C_3)alkyl and phenyl-(C_0-C_3)alkyl optionally being further substituted with 1-3 substituents independently selected from halo, -CH_3, -OCH_3, -CF_3, -OCF_3, -CN, and -SCF_3, and

said Ph^2-(C_1-C_3) *n*-alkyl and Ar^2(C_0-C_3) *n*-alkyl where Ar^2 is pyridyl, also optionally being substituted on the phenyl or Ar^2 moiety, respectively, with phenyl-CH=CH- or phenyl-C≡C-,

said phenyl-CH=CH- or phenyl-C≡C- being optionally further substituted with 1 to 3 substituents independently selected from the group consisting of halo, cyano, -SCF_3, (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, and (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents, and

said Ar^2(C_0-C_3) *n*-alkyl where Ar^2 is pyridyl, alternatively, optionally being substituted with (C_1-C_6)alkyl-C(O)- or $R^{28}R^{29}$N-C(O)-, and optionally further substituted with one methyl, -CF_3, cyano, or -SCF_3 substituent, or with 1 to 2 halo substituents,

said phenyl(C_0-C_1)alkyl-O-(C_1-C_5)alkyl, or phenyl(C_0-C_1)alkyl-S-(C_1-C_5)alkyl optionally being substituted on the phenyl moiety with (C_1-C_2)-$S(O)_2$-, or with 1 to 5 independently selected halo substituents, or with 1 to 3 substituents independently selected from the group consisting of halo, cyano, –SCF_3, (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, and (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents, and

said pyridyl-(C_0-C_1)alkyl-C(O)NH-(C_2-C_4)alkyl and pyridyl-(C_0-C_1)alkyl-NH-C(O)NH-(C_2-C_4)alkyl optionally being substituted on the pyridyl moiety with methyl, -CF_3, or 1 to 3 halo substituents;

R^{25} is hydrogen, $(C_1\text{-}C_3)$alkyl optionally substituted with 1 to 6 fluoro substituents, or allyl;

R^{26} is hydrogen, $(C_1\text{-}C_6)$alkyl optionally substituted with 1 to 6 fluoro substituents, $(C_3\text{-}C_7)$cycloalkyl$(C_0\text{-}C_3)$alkyl;

R^{27} is hydrogen or $(C_1\text{-}C_4)$alkyl optionally substituted with 1 to 6 fluoro substituents, or R^{26} and R^{27}, taken together with the nitrogen atom to which they are attached, form Het^1;

R^{28} is $(C_1\text{-}C_8)$alkyl optionally substituted with 1 to 6 fluoro substituents, $(C_3\text{-}C_8)$cycloalkyl$(C_0\text{-}C_3)$alkyl, tetrahydropyran-3-yl$(C_0\text{-}C_3)$alkyl, tetrahydropyran-4-yl$(C_0\text{-}C_3)$alkyl, tetrahydrofuranyl$(C_0\text{-}C_3)$alkyl, Ph^1-$(C_0\text{-}C_2)$ *n*-alkyl, or Ar^2-$(C_0\text{-}C_2)$ *n*-alkyl,

said Ph^1-$(C_0\text{-}C_2)$ *n*-alkyl and Ar^2-$(C_0\text{-}C_2)$ *n*-alkyl optionally being substituted on the alkyl moiety when present with $(C_1\text{-}C_3)$alkyl, dimethyl, or gem-ethano;

R^{29} is hydrogen or $(C_1\text{-}C_3)$alkyl;

R^{30} is hydrogen, $(C_1\text{-}C_6)$alkyl optionally substituted with 1 to 6 fluoro substituents, $(C_3\text{-}C_7)$cycloalkyl$(C_0\text{-}C_3)$alkyl, Ph^1-$(C_0\text{-}C_3)$alkyl, or $Ar^2(C_0\text{-}C_3)$alkyl,

R^{31} is hydrogen or $(C_1\text{-}C_6)$alkyl optionally substituted with 1 to 6 fluoro substituents, or R^{30} and R^{31}, taken together with the nitrogen atom to which they are attached, form Het^1,

said Het^1 also optionally being substituted with phenyl optionally further substituted with 1 to 3 halo substituents;

R^{32} and R^{33} are each independently hydrogen or $(C_1\text{-}C_6)$alkyl optionally substituted with 1 to 6 fluoro substituents, or R^{32} and R^{33}, taken together with the nitrogen atom to which they are attached, form Het^1, or R^{32} is $Ph^1(C_0\text{-}C_1)$alkyl provided that R^{33} is hydrogen;

Ar^1 is an aromatic heterocycle substituent selected from the group consisting of furanyl, thiophenyl, thiazolyl, oxazolyl, isoxazolyl, pyridyl, and pyridazinyl, any of which may optionally be substituted with 1 to 3 substituents independently selected from the group consisting of halo, $(C_1\text{-}C_3)$alkyl, $(C_1\text{-}C_3)$alkoxy, $-CF_3$, $-O\text{-}CF_3$, nitro, cyano, and trifluoromethylthio;

Ar^2 is an aromatic heterocycle substituent selected from the group consisting of pyrrolyl, pyrazolyl, imidazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, furanyl, oxazolyl, isoxazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, thiophenyl, thiazolyl; isothiazolyl, 1,2,3-thiadiazolyl, 1,3,4-thiadiazolyl, pyridyl, pyridazinyl, and benzimidazolyl, any of which may optionally be substituted with 1 to 3 substituents independently selected from the group consisting of halo, cyano, $-SCF_3$, (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, and (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents, and wherein pyridyl and pyridazinyl may also optionally be substituted with (C_1-C_6)alkylamino optionally further substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, or (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-amino;

Het^1 is a saturated, nitrogen-containing heterocycle substituent selected from the group consisting of azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl, morpholinyl, thiomorpholinyl, homomorpholinyl, and homothiomorpholinyl, any of which may optionally be substituted with (C_1-C_6)alkyl or with 2 methyl substituents;

Het^2 is a saturated, oxygen-containing heterocycle substituent selected from the group consisting of tetrahydrofuranyl and tetrahydropyranyl, any of which may optionally be substituted with (C_1-C_6)alkyl or with 2 methyl substituents;

Ph^1 is phenyl optionally substituted with 1 to 5 independently selected halo substituents, or with 1 to 3 substituents independently selected from the group consisting of halo, cyano, $-SCF_3$, (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, and (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents;

Ph^2 is phenyl substituted with:

a) 1 to 5 independently selected halo substituents; or

b) 1 to 3 substituents independently selected from the group consisting of halo, cyano, $-SCF_3$, nitro, hydroxy, (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, and (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents; or

c) 0, 1, or 2 substituents independently selected from the group consisting of halo, cyano, $-SCF_3$, methyl, $-CF_3$, methoxy, $-OCF_3$, nitro, and hydroxy, together with one substituent selected from the group consisting of

i) (C_1-C_{10})alkyl optionally further substituted with 1 to 6 fluoro substituents or mono-substituted with hydroxy, (C_1-C_6)alkoxy, (C_3-C_7)cycloalkyl(C_0-C_3)alkyloxy, $Het^2-(C_0-C_3)$alkyloxy, $Ph^1-(C_0-C_3)$alkyloxy,

ii) (C_1-C_{10})alkoxy-(C_0-C_3)alkyl optionally further substituted with 1 to 6 fluoro substituents, and optionally further substituted with hydroxy,

iii) (C_1-C_6)alkyl-C(O)-(C_0-C_5)alkyl optionally further substituted with 1 to 6 fluoro substituents,

iv) carboxy,

v) (C_1-C_6)alkoxycarbonyl optionally further substituted with 1 to 6 fluoro substituents,

vi) (C_1-C_6)alkyl-C(O)-(C_0-C_3)-O- optionally further substituted with 1 to 6 fluoro substituents,

vii) (C_1-C_6)alkylthio-(C_0-C_5)alkyl optionally further substituted with 1 to 6 fluoro substituents,

viii) (C_1-C_6)alkylsulfinyl-(C_0-C_5)alkyl optionally further substituted with 1 to 6 fluoro substituents,

ix) (C_1-C_6)alkylsulfonyl-(C_0-C_5)alkyl optionally further substituted with 1 to 6 fluoro substituents,

x) (C_1-C_6)alkylsulfonyl-(C_0-C_3)alkyl-O- optionally further substituted with 1 to 6 fluoro substituents,

xi) (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, optionally further substituted on the cycloalkyl with 1 to 4 substituents selected from methyl and fluoro,

xii) (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-O-, optionally further substituted on the cycloalkyl with 1 to 4 substituents selected from methyl and fluoro,

xiii) (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-C(O)-,

xiv) (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-O-C(O)-,

xv) (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-S-,

xvi) (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-S(O)-,

xvii) (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-$S(O)_2$-,

xviii) Ph^1-(C_0-C_3)alkyl, optionally substituted on the alkyl moiety with 1 to 2 fluoro substituents,

xix) Ph^1-(C_0-C_3)alkyl-O-, optionally substituted on the alkyl moiety with 1 to 2 fluoro substituents

xx) Ph^1-(C_0-C_3)alkyl-C(O)-,

xxi) Ph^1-(C_0-C_3)alkyl-O-C(O)-,

xxii) Ph^1-(C_0-C_3)alkyl-C(O)-(C_0-C_3)alkyl-O-,

xxiii) Ph^1-(C_0-C_3)alkylthio,

xxiv) Ph^1-(C_0-C_3)alkylsulfinyl,

xxv) Ph^1-(C_0-C_3)alkylsulfonyl,

xxvi) $Ar^2(C_0-C_3)$alkyl,

xxvii) $Ar^2(C_0-C_3)$alkyl-O-

xxviii) Ar^2-(C_0-C_3)alkyl-S-,

xxix) $Ar^2(C_0-C_3)$alkyl-C(O)-,

xxx) $Ar^2(C_0-C_3)$alkyl-C(S)-,

xxxi) Ar^2-(C_0-C_3)alkylsulfinyl,

xxxii) Ar^2-(C_0-C_3)alkylsulfonyl,

xxxiii) $Het^1(C_0-C_3)$alkyl-C(O)- optionally substituted on the Het^1 moiety with Ph^1,

xxxiv) $Het^1(C_0-C_3)$alkyl-C(S)- optionally substituted on the Het^1 moiety with Ph^1,

xxxv) N-linked Het^1-C(O)-(C_0-C_3)alkyl-O-,

xxxvi) Het^2-(C_0-C_3)alkyloxy,

xxxvii) $R^{26}R^{27}N$-,

xxxviii) $R^{28}R^{29}$-N-(C_1-C_3)alkoxy,

xxxix) $R^{28}R^{29}N$-C(O)-,

xl) $R^{28}R^{29}N$-C(O)-(C_1-C_3)alkyl-O-,

xli) $R^{28}R^{29}N$-C(S)-,

xlii) $R^{30}R^{31}N\text{-}S(O)_2\text{-}$,

xliii) $HON{=}C(CH_3)\text{-}$, and

xliv) $HON{=}C(Ph^1)\text{-}$,

or a pharmaceutically acceptable salt thereof, subject to the following provisos:

a) no more than two of R^1, R^2, R^3, R^4, and R^5 may be other than hydrogen;

b) when R^2 is methyl, then R^1, R^3, R^4, and R^5 are each hydrogen; and

c) when R^3 is methyl, then R^2 and R^4 are each hydrogen.

2. A compound according to Claim 1 wherein R^7 is selected from halo, -CN, and CF_3.

3. A compound according to either Claim 1 or Claim 2 wherein R^7 is chloro.

4. A compound according to any one of Claims 1 to 3 wherein R^6 is $-C{\equiv}C\text{-}R^{10}$.

5. A compound according to any one of Claims 1 to 3 wherein R^6 is $-O\text{-}R^{12}$.

6. A compound according to any one of Claims 1 to 3 wherein R^6 is $-S\text{-}R^{14}$.

7. A compound according to Claim 6 wherein R^6 is $-S\text{-}L\text{-}R^{15}$.

8. A compound according to Claim 7 wherein R^{15} is Ph^2 or Ar^2.

9. A compound according to any one of Claims 1 to 3 wherein R^6 is $-NR^{24}R^{25}$.

10. A compound according to Claim 9 wherein R^{24} is Ph^2-(C_1-C_3) *n*-alkyl-.

11. A compound according to Claim 9 wherein R^{24} is Ar^2-(C_1-C_3) *n*-alkyl-.

12. A Compound according to any one of Claims 9 to 11 wherein R^{25} is hydrogen.

13. (Cancelled)

14. (Cancelled)

15. A compound according to any one of Claims 1 to 14 wherein R^1, R^2, R^3, R^4, R^5, and R^8, are each hydrogen.

16. A pharmaceutical composition comprising a compound according to any one of Claims 1 to 15 as an active ingredient in association with a pharmaceutically acceptable carrier, diluent or excipient.

17. A compound according to any one of Claims 1 to 15 for use in therapy.

18. A method for the treatment of obesity in mammals, comprising administering to a mammal in need of such treatment an effective amount of a compound according to Claim 1.

19. The method of Claim 18, where the mammal is human.

20. A method for the treatment of obsessive compulsive disorder in mammals, comprising administering to a mammal in need of such treatment an effective amount of a compound according to Claim 1.

21. The method of Claim 20, where the mammal is human.

22. A method for the treatment of depression in mammals, comprising administering to a mammal in need of such treatment an effective amount of a compound according to Claim 1.

23. The method of Claim 22, where the mammal is human.

24. A method for the treatment of anxiety in mammals, comprising administering to a mammal in need of such treatment an effective amount of a compound according to Claim 1.

25. The method of Claim 24, where the mammal is human.

26. A compound according to any one of Claims 1 to 15 for use as a pharmaceutical.

27. A compound according to any one of Claims 1 to 15 for use in the treatment of obesity in mammals.

28. A compound according to any one of Claims 1 to 15 for use in the treatment of obsessive/compulsive disorder in mammals.

29. A compound according to any one of Claims 1 to 15 for use in the treatment of depression in mammals.

30. A compound according to any one of Claims 1 to 15 for use in the treatment of anxiety in mammals.

31. A compound according to any one of Claims 27-30, where the mammal is a human.

32. The use of a compound according to any one of Claims 1 to 15 in the manufacture of a medicament for the treatment of a disorder selected from obesity, hyperphagia, obsessive/compulsive disorder, depression, anxiety, substance abuse, sleep disorder, hot flashes, and/or hypogonadism.

33. The use of a compound according to any one of Claims 1 to 15 in the manufacture of a medicament for the treatment of a disorder selected from obesity, obsessive/compulsive disorders, anxiety, or depression.

34. A pharmaceutical composition adapted for the treatment of obesity comprising a compound according to any one of Claims 1 to 15 in combination with one or more pharmaceutically acceptable excipients, carriers, or diluents therefore.

35. A pharmaceutical composition adapted for the treatment of obsessive/compulsive disorders comprising a compound according to any one of Claims 1 to 15 in combination with one or more pharmaceutically acceptable excipients, carriers, or diluents therefore.

36. A pharmaceutical composition adapted for the treatment of depression comprising a compound according to any one of Claims 1 to 15 in combination with one or more pharmaceutically acceptable excipients, carriers, or diluents therefore.

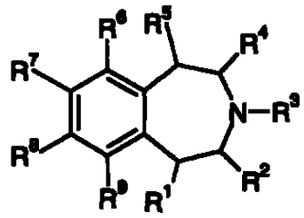
37. A pharmaceutical composition adapted for the treatment of anxiety comprising a compound according to any one of Claims 1 to 15 in combination with one or more pharmaceutically acceptable excipients, carriers, or diluents therefore.

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WE CLAIM:

1. A compound of Formula I:



I

where:

R^1 is hydrogen, fluoro, or $(C_1$-$C_3)$alkyl;

R^2, R^3, and R^4 are each independently hydrogen, methyl, or ethyl;

R^5 is hydrogen, fluoro, methyl, or ethyl;

R^6 is -C≡C-R^{10}, -O-R^{12}, -S-R^{14}, or -$NR^{24}R^{25}$;

R^7 is hydrogen, halo, cyano, $(C_1$-$C_6)$alkyl optionally substituted with 1 to 6 fluoro substituents, $(C_2$-$C_6)$alkenyl optionally substituted with 1 to 6 fluoro substituents, $(C_3$-$C_7)$cycloalkyl, $(C_1$-$C_6)$alkoxy optionally substituted with 1 to 6 fluoro substituents, $(C_1$-$C_6)$alkylthio optionally substituted with 1 to 6 fluoro substituents, Ph^1-$(C_0$-$C_3)$alkyl, Ph^1-$(C_0$-$C_3)$alkyl-O-, or Ph^1-$(C_0$-$C_3)$alkyl-S-;

R^8 is hydrogen, halo, cyano, or $-SCF_3$;

R^9 is hydrogen~~, halo, cyano, $-CF_3$, $-SCF_3$, or $(C_1$-$C_2)$alkoxy optionally substituted with 1 to 6 fluoro substituents~~;

R^{10} is $-CF_3$, ethyl substituted with 1 to 5 fluoro substituents, $(C_3$-$C_6)$ alkyl optionally substituted with 1 to 6 fluoro substituents, $(C_3$-$C_7)$cycloalkyl$(C_0$-$C_3)$alkyl, Ar^1-$(C_0$-$C_3)$alkyl, Ph^1-$(C_0$-$C_3)$alkyl, or 3-$(C_1$-$C_4)$alkyl-2-oxo-imidazolidin-1-yl-$(C_1$-$C_3)$alkyl;

R^{12} is Ph^2-$(C_1$-$C_3)$alkyl, Ar^2-$(C_1$-$C_3)$alkyl, $(C_1$-$C_6)$alkyl-S-$(C_2$-$C_6)$alkyl, $(C_3$-$C_7)$cycloalkyl-S-$(C_2$-$C_6)$alkyl, phenyl-S-$(C_2$-$C_6)$alkyl, Ph^2-S-$(C_2$-$C_6)$alkyl, phenylcarbonyl-$(C_1$-$C_3)$alkyl, Ph^2-C(O)-$(C_1$-$C_3)$alkyl, $(C_1$-$C_6)$alkoxycarbonyl$(C_3$-$C_6)$alkyl, $(C_3$-$C_7)$cycloalkyl-OC(O)-$(C_3$-$C_6)$alkyl,

phenyloxycarbonyl-(C_3-C_6)alkyl, Ph^2-OC(O)-(C_3-C_6)alkyl, Ar^2-OC(O)-(C_3-C_6)alkyl, (C_3-C_7)cycloalkyl-NH-C(O)-(C_2-C_4)alkyl-, Ph^1-NH-C(O)-(C_2-C_4)alkyl-, Ar^2-NH-C(O)-(C_2-C_4)alkyl-, or R^{13}-C(O)NH-(C_2-C_4)alkyl;

R^{13} is (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, Ph^1, Ar^2, or (C_1-C_3)alkoxy optionally substituted with 1 to 6 fluoro substituents, Ph^1-NH- or N-linked Het^1;

R^{14} is Ar^2 which is not N-linked to the sulfur atom, Ph^2, R^{15}-L-, tetrahydrofuranyl, tetrahydropyranyl, or phenyl-methyl substituted on the methyl moiety with a substituent selected from the group consisting of (C_1-C_3)-*n*-alkyl substituted with hydroxy, (C_1-C_3)alkyl-O-(C_1-C_2)-*n*-alkyl, (C_1-C_3)alkyl-C(O)-(C_0-C_2)-*n*-alkyl, and (C_1-C_3)alkyl-O-C(O)-(C_0-C_2)-*n*-alkyl,

wherein when R^{14} is Ph^2 or Ar^2, wherein Ar^2 is pyridyl, then R^{14} may also, optionally be substituted with phenyl-CH=CH- or phenyl-C≡C-, said phenyl-CH=CH- or phenyl-C≡C- being optionally further substituted with 1 to 3 substituents independently selected from the group consisting of halo, cyano, -SCF_3, (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, and (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents, and

wherein when Ar^2 is pyridyl, the pyridyl may alternatively, optionally be substituted with $R^{28}R^{29}$N-C(O)-, and optionally further substituted with one methyl, -CF_3, cyano, or -SCF_3 substituent, or with 1 to 2 halo substituents, and

wherein the tetrahydrofuranyl and tetrahydropyranyl may optionally be substituted with an oxo substituent, or with one or two groups independently selected from methyl and –CF_3;

R^{15} is -OR^{16}, cyano, –SCF_3, Ph^2, Ar^2, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, phthalimido, benzothiophenyl optionally substituted at the 2-position with phenyl or benzyl, benzothiazolyl optionally substituted at the 2-position with phenyl or benzyl, benzothiadiazolyl optionally substituted with phenyl or benzyl, 2-oxo-dihydroindol-1-yl optionally substituted at the 3 position with gem dimethyl or (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, 2-oxo-dihydroindol-5-yl

optionally substituted at the 3 position with gem dimethyl or (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, 2-oxo-imidazolidin-1-yl optionally substituted at the 3 position with gem dimethyl or (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, 2-oxo-tetrahydropyrimidinyl optionally substituted at the 3 or 4 position with gem dimethyl or (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, 2-oxo-tetrahydroquinolin-1-yl optionally substituted at the 3 position with gem dimethyl or (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, 2-oxo- dihydrobenzimidazol-1-yl optionally substituted at the 3 position with gem dimethyl or (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, $-NR^{17}R^{18}$, $-C(O)R^{22}$, or a saturated heterocycle selected from the group consisting of pyrrolidinyl, piperidinyl, morpholinyl, and thiomorpholinyl, tetrahydrofuranyl, and tetrahydropyranyl,

wherein Ph^2 and Ar^2 when Ar^2 is pyridyl, may also optionally be substituted with phenyl-CH=CH- or phenyl-C≡C-,

said phenyl-CH=CH- and phenyl-C≡C- being optionally further substituted on the phenyl moiety with 1 to 3 substituents independently selected from the group consisting of halo, cyano, $-SCF_3$, (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, and (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents, and

wherein Ar^2 may alternatively, optionally be substituted with a substituent selected from the group consisting of (C_3-C_7)cycloalkyl-(C_0-C_3)alkyl, Het^1-(C_0-C_3)alkyl, pyridyl-(C_0-C_3)alkyl, and phenyl-(C_0-C_3)alkyl, and optionally further substituted with one methyl, $-CF_3$, cyano, or $-SCF_3$ substituent, or with 1 to 2 halo substituents,

said pyridyl-(C_0-C_3)alkyl and phenyl-(C_0-C_3)alkyl optionally being further substituted with 1-3 substituents independently selected from halo, $-CH_3$, $-OCH_3$, $-CF_3$, $-OCF_3$, -CN, and $-SCF_3$, and

wherein when Ar^2 is pyridyl, the pyridyl may alternatively, optionally be substituted with $R^{28}R^{29}N$-C(O)-, or (C_1-C_6)alkyl-C(O)- optionally substituted with 1 to 6 fluoro substituents, and may be optionally further

substituted with one methyl, $-CF_3$, cyano, or $-SCF_3$ substituent, or with 1 to 2 halo substituents, and

wherein when Ar^2 is thiazolyl, the thiazolyl may alternatively, optionally be substituted with (C_3-C_7)cycloalkyl-(C_0-C_3)alkyl-NH-, and

wherein the pyrrolidinyl, piperidinyl, morpholinyl, and thiomorpholinyl is substituted with oxo- on a carbon atom adjacent to the ring nitrogen atom, or is N-substituted with a substituent selected from the group consisting of

(C_1-C_6)alkylcarbonyl, (C_1-C_6)alkylsulfonyl,

(C_3-C_7)cycloalkyl(C_0-C_3)alkyl-C(O)-,

(C_3-C_7)cycloalkyl(C_0-C_3)alkyl-$S(O)_2$-, Ph^1-(C_0-C_3)alkyl-C(O)-, and

Ph^1-(C_0-C_3)alkyl-$S(O)_2$-, and

may optionally be further substituted with 1 or 2 methyl or $-CF_3$ substituents, and when oxo-substituted, may optionally be further N-substituted with a substituent selected from the group consisting of

(C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, and Ph^1-(C_0-C_3)alkyl, and

wherein tetrahydrofuranyl and tetrahydropyranyl may optionally be substituted with an oxo substituent, and/or with one or two groups independently selected from methyl and $-CF_3$;

L is branched or unbranched (C_1-C_6)alkylene, except when R^{15} is $-NR^{17}R^{18}$ or Ar^2-N-linked to L, in which case L is branched or unbranched (C_2-C_6)alkylene, and when L is methylene or ethylene, L may optionally be substituted with gem-ethano or with 1 to 2 fluoro substituents, and when R^{15} is Ph^2, Ar^2, or a saturated heterocycle, L may alternatively, optionally be substituted with a substituent selected from the group consisting of hydroxy, cyano, $-SCF_3$, (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents, (C_1-C_6)alkoxycarbonyl optionally further substituted with 1 to 6 fluoro substituents, (C_1-C_6)alkylcarbonyloxy optionally further substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl-(C_0-C_3)alkyl-O-, (C_3-C_7)cycloalkyl-(C_0-C_3)alkyl-O-C(O)-, and (C_3-C_7)cycloalkyl-(C_0-C_3)alkyl-C(O)-O-;

R^{16} is hydrogen, (C_1-C_6)alkyl optionally substituted with 1 to 6 fluoro substituents, (C_1-C_6)alkylcarbonyl, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-C(O)-, Ph^1-(C_0-C_3)alkyl, Ph^1-(C_0-C_3)alkyl-C(O)-, Ar^2-(C_0-C_3)alkyl, or Ar^2-(C_0-C_3)alkyl-C(O)-,

R^{17} is (C_1-C_4)alkyl optionally substituted with 1 to 6 fluoro substituents, *t*-butylsulfonyl, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-C(O)-, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-sulfonyl, Ph^1-(C_0-C_3)alkyl, Ph^1-(C_0-C_3)alkyl-C(O)-, Ph^1-(C_0-C_3)alkylsulfonyl, Ar^2-(C_0-C_3)alkyl, Ar^2-(C_0-C_3)alkyl-C(O)-, Ar^2-(C_0-C_3)alkylsulfonyl, $R^{19}OC(O)$-, or $R^{20}R^{21}NC(O)$-;

R^{18} is hydrogen or (C_1-C_4)alkyl optionally substituted with 1 to 6 fluoro substituents, or R^{17} and R^{18}, taken together with the nitrogen atom to which they are attached form Het^1 where Het^1 is substituted with oxo- on a carbon atom adjacent to the ring nitrogen atom, or

R^{17} and R^{18}, taken together with the nitrogen atom to which they are attached, form an aromatic heterocycle selected from the group consisting of pyrolyl, pyrazolyl, imidazolyl, 1,2,3-triazolyl, and 1,2,4-triazolyl,

said aromatic heterocycle optionally being substituted with 1 to 2 halo substituents, or substituted with 1 to 2 (C_1-C_4)alkyl substituents optionally further substituted with 1 to 3 fluoro substituents, or mono-substituted with fluoro, nitro, cyano, $-SCF_3$, or (C_1-C_4)alkoxy optionally further substituted with 1 to 3 fluoro substituents, and optionally further substituted with a (C_1-C_4)alkyl substituent optionally further substituted with 1 to 3 fluoro substituents;

R^{19} is (C_1-C_6)alkyl optionally substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, Ar^2-(C_0-C_3)alkyl, or Ph^1-(C_0-C_3)alkyl,

R^{20} is (C_1-C_6)alkyl optionally substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, Ar^2-(C_0-C_3)alkyl, or Ph^1-(C_0-C_3)alkyl,

R^{21} is hydrogen or (C_1-C_4)alkyl optionally substituted with 1 to 6 fluoro substituents, or R^{20} and R^{21}, taken together with the nitrogen atom to which they are attached, form Het^1;

R^{22} is (C_1-C_6)alkyl optionally substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, R^{23}-O-, Ph^1-(C_0-C_3)alkyl, Ar^2-(C_0-C_3)alkyl, or $R^{32}R^{33}N$-;

R^{23} is (C_1-C_6)alkyl optionally substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, Ph^1-(C_0-C_3)alkyl, or Ar^2-(C_0-C_3)alkyl;

R^{24} is (C_1-C_6)alkoxy(C_2-C_5)alkyl optionally substituted with 1 to 6 fluoro substituents, (C_1-C_6)alkylthio(C_2-C_5)alkyl optionally substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl(C_0-C_1)alkyl-O-(C_1-C_5)alkyl, (C_3-C_7)cycloalkyl(C_0-C_1)alkyl-S-(C_1-C_5)alkyl, phenyl(C_1-C_3) *n*-alkyl, Ph^2-(C_1-C_3)-*n*-alkyl, $Ar^2(C_0-C_3)$ *n*-alkyl, phenyl(C_0-C_1)alkyl-O-(C_1-C_5)alkyl, phenyl(C_0-C_1)alkyl-S-(C_1-C_5)alkyl, Ph^1-(C_0-C_1)alkyl-C(O)NH-(C_2-C_4)alkyl, Ph^1-(C_0-C_1)alkyl-NH-C(O)NH-(C_2-C_4)alkyl, pyridyl-(C_0-C_1)alkyl-C(O)NH-(C_2-C_4)alkyl, pyridyl-(C_0-C_1)alkyl-NH-C(O)NH-(C_2-C_4)alkyl, or $Ar^3(C_1-C_2)$alkyl,

where Ar^3 is a bi-cyclic moiety selected from a group consisting of indanyl, indolyl, dihydrobenzofuranyl, benzofuranyl, benzothiophenyl, benzoxazolyl, benzothiazolyl, benzo[1,3]dioxolyl, naphthyl, dihydrobenzopyranyl, quinolinyl, isoquinolinyl, and benzo[1,2,3]thiadiazolyl,

said Ar^3 optionally being substituted with (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, phenyl(C_0-C_1)alkyl optionally further substituted with 1 to 6 fluoro substituents, or substituted with (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, or substituted with 1-3 substituents independently selected from the group consisting of halo, oxo, methyl, and $-CF_3$,

said phenyl(C_1-C_3) *n*-alkyl, Ph^2-(C_1-C_3) *n*-alkyl, or $Ar^2(C_0-C_3)$ *n*-alkyl optionally being substituted on the *n*-alkyl moiety when present with (C_1-C_3)alkyl, dimethyl, gem-ethano, 1 to 2 fluoro substituents, or (C_1-C_6)alkyl-C(O)-,

said $Ar^2(C_0-C_3)$ *n*-alkyl being alternatively optionally substituted with a substituent selected from the group consisting of (C_3-C_7)cycloalkyl-(C_0-C_3)alkyl, Het^1-(C_0-C_3)alkyl, pyridyl-(C_0-C_3)alkyl, phenyl-

(C_0-C_3)alkyl, pyridyl-(C_0-C_3)alkyl-NH-, phenyl-(C_0-C_3)alkyl-NH-, (C_1-C_6)alkyl-S-, and (C_3-C_7)cycloalkyl-(C_0-C_3)alkyl-S-, and optionally further substituted with one methyl, -CF_3, cyano, or -SCF_3 substituent, or with 1 to 2 halo substituents,

said pyridyl-(C_0-C_3)alkyl and phenyl-(C_0-C_3)alkyl optionally being further substituted with 1-3 substituents independently selected from halo, -CH_3, -OCH_3, -CF_3, -OCF_3, -CN, and -SCF_3, and

said Ph^2-(C_1-C_3) *n*-alkyl and Ar^2(C_0-C_3) *n*-alkyl where Ar^2 is pyridyl, also optionally being substituted on the phenyl or Ar^2 moiety, respectively, with phenyl-CH=CH- or phenyl-C≡C-,

said phenyl-CH=CH- or phenyl-C≡C- being optionally further substituted with 1 to 3 substituents independently selected from the group consisting of halo, cyano, -SCF_3, (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, and (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents, and

said Ar^2(C_0-C_3) *n*-alkyl where Ar^2 is pyridyl, alternatively, optionally being substituted with (C_1-C_6)alkyl-C(O)- or $R^{28}R^{29}$N-C(O)-, and optionally further substituted with one methyl, -CF_3, cyano, or -SCF_3 substituent, or with 1 to 2 halo substituents,

said phenyl(C_0-C_1)alkyl-O-(C_1-C_5)alkyl, or phenyl(C_0-C_1)alkyl-S-(C_1-C_3)alkyl optionally being substituted on the phenyl moiety with (C_1-C_2)-$S(O)_2$-, or with 1 to 5 independently selected halo substituents, or with 1 to 3 substituents independently selected from the group consisting of halo, cyano, –SCF_3, (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, and (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents, and

said pyridyl-(C_0-C_1)alkyl-C(O)NH-(C_2-C_4)alkyl and pyridyl-(C_0-C_1)alkyl-NH-C(O)NH-(C_2-C_4)alkyl optionally being substituted on the pyridyl moiety with methyl, -CF_3, or 1 to 3 halo substituents;

R^{25} is hydrogen, $(C_1\text{-}C_3)$alkyl optionally substituted with 1 to 6 fluoro substituents, or allyl;

R^{26} is hydrogen, $(C_1\text{-}C_6)$alkyl optionally substituted with 1 to 6 fluoro substituents, $(C_3\text{-}C_7)$cycloalkyl$(C_0\text{-}C_3)$alkyl;

R^{27} is hydrogen or $(C_1\text{-}C_4)$alkyl optionally substituted with 1 to 6 fluoro substituents, or R^{26} and R^{27}, taken together with the nitrogen atom to which they are attached, form Het^1;

R^{28} is $(C_1\text{-}C_8)$alkyl optionally substituted with 1 to 6 fluoro substituents, $(C_3\text{-}C_8)$cycloalkyl$(C_0\text{-}C_3)$alkyl, tetrahydropyran-3-yl$(C_0\text{-}C_3)$alkyl, tetrahydropyran-4-yl$(C_0\text{-}C_3)$alkyl, tetrahydrofuranyl$(C_0\text{-}C_3)$alkyl, Ph^1-$(C_0\text{-}C_2)$ *n*-alkyl, or Ar^2-$(C_0\text{-}C_2)$ *n*-alkyl,

said Ph^1-$(C_0\text{-}C_2)$ *n*-alkyl and Ar^2-$(C_0\text{-}C_2)$ *n*-alkyl optionally being substituted on the alkyl moiety when present with $(C_1\text{-}C_3)$alkyl, dimethyl, or gem-ethano;

R^{29} is hydrogen or $(C_1\text{-}C_3)$alkyl;

R^{30} is hydrogen, $(C_1\text{-}C_6)$alkyl optionally substituted with 1 to 6 fluoro substituents, $(C_3\text{-}C_7)$cycloalkyl$(C_0\text{-}C_3)$alkyl, Ph^1-$(C_0\text{-}C_3)$alkyl, or $Ar^2(C_0\text{-}C_3)$alkyl,

R^{31} is hydrogen or $(C_1\text{-}C_6)$alkyl optionally substituted with 1 to 6 fluoro substituents, or R^{30} and R^{31}, taken together with the nitrogen atom to which they are attached, form Het^1,

said Het^1 also optionally being substituted with phenyl optionally further substituted with 1 to 3 halo substituents;

R^{32} and R^{33} are each independently hydrogen or $(C_1\text{-}C_6)$alkyl optionally substituted with 1 to 6 fluoro substituents, or R^{32} and R^{33}, taken together with the nitrogen atom to which they are attached, form Het^1, or R^{32} is $Ph^1(C_0\text{-}C_1)$alkyl provided that R^{33} is hydrogen;

Ar^1 is an aromatic heterocycle substituent selected from the group consisting of furanyl, thiophenyl, thiazolyl, oxazolyl, isoxazolyl, pyridyl, and pyridazinyl, any of which may optionally be substituted with 1 to 3 substituents independently selected from the group consisting of halo, $(C_1\text{-}C_3)$alkyl, $(C_1\text{-}C_3)$alkoxy, $-CF_3$, $-O-CF_3$, nitro, cyano, and trifluoromethylthio;

Ar^2 is an aromatic heterocycle substituent selected from the group consisting of pyrrolyl, pyrazolyl, imidazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, furanyl, oxazolyl, isoxazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, thiophenyl, thiazolyl, isothiazolyl, 1,2,3-thiadiazolyl, 1,3,4-thiadiazolyl, pyridyl, pyridazinyl, and benzimidazolyl, any of which may optionally be substituted with 1 to 3 substituents independently selected from the group consisting of halo, cyano, $-SCF_3$, (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, and (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents, and wherein pyridyl and pyridazinyl may also optionally be substituted with (C_1-C_6)alkylamino optionally further substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, or (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-amino;

Het^1 is a saturated, nitrogen-containing heterocycle substituent selected from the group consisting of azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl, morpholinyl, thiomorpholinyl, homomorpholinyl, and homothiomorpholinyl, any of which may optionally be substituted with (C_1-C_6)alkyl or with 2 methyl substituents;

Het^2 is a saturated, oxygen-containing heterocycle substituent selected from the group consisting of tetrahydrofuranyl and tetrahydropyranyl, any of which may optionally be substituted with (C_1-C_6)alkyl or with 2 methyl substituents;

Ph^1 is phenyl optionally substituted with 1 to 5 independently selected halo substituents, or with 1 to 3 substituents independently selected from the group consisting of halo, cyano, $-SCF_3$, (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, and (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents;

Ph^2 is phenyl substituted with:

a) 1 to 5 independently selected halo substituents; or

b) 1 to 3 substituents independently selected from the group consisting of halo, cyano, $-SCF_3$, nitro, hydroxy, (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, and (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents; or

c) 0, 1, or 2 substituents independently selected from the group consisting of halo, cyano, -SCF_3, methyl, -CF_3, methoxy, -OCF_3, nitro, and hydroxy, together with one substituent selected from the group consisting of

i) (C_1-C_{10})alkyl optionally further substituted with 1 to 6 fluoro substituents or mono-substituted with hydroxy, (C_1-C_6)alkoxy, (C_3-C_7)cycloalkyl(C_0-C_3)alkyloxy, Het^2-(C_0-C_3)alkyloxy, Ph^1-(C_0-C_3)alkyloxy,

ii) (C_1-C_{10})alkoxy-(C_0-C_3)alkyl optionally further substituted with 1 to 6 fluoro substituents, and optionally further substituted with hydroxy,

iii) (C_1-C_6)alkyl-C(O)-(C_0-C_5)alkyl optionally further substituted with 1 to 6 fluoro substituents,

iv) carboxy,

v) (C_1-C_6)alkoxycarbonyl optionally further substituted with 1 to 6 fluoro substituents,

vi) (C_1-C_6)alkyl-C(O)-(C_0-C_3)-O- optionally further substituted with 1 to 6 fluoro substituents,

vii) (C_1-C_6)alkylthio-(C_0-C_5)alkyl optionally further substituted with 1 to 6 fluoro substituents,

viii) (C_1-C_6)alkylsulfinyl-(C_0-C_5)alkyl optionally further substituted with 1 to 6 fluoro substituents,

ix) (C_1-C_6)alkylsulfonyl-(C_0-C_5)alkyl optionally further substituted with 1 to 6 fluoro substituents,

x) (C_1-C_6)alkylsulfonyl-(C_0-C_3)alkyl-O- optionally further substituted with 1 to 6 fluoro substituents,

xi) (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, optionally further substituted on the cycloalkyl with 1 to 4 substituents selected from methyl and fluoro,

xii) (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-O-, optionally further substituted on the cycloalkyl with 1 to 4 substituents selected from methyl and fluoro,

xiii) (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-C(O)-,

xiv) (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-O-C(O)-,

xv) (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-S-,

xvi) (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-S(O)-,

xvii) (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-S$(O)_2$-,

xviii) Ph^1-(C_0-C_3)alkyl, optionally substituted on the alkyl moiety with 1 to 2 fluoro substituents,

xix) Ph^1-(C_0-C_3)alkyl-O-, optionally substituted on the alkyl moiety with 1 to 2 fluoro substituents

xx) Ph^1-(C_0-C_3)alkyl-C(O)-,

xxi) Ph^1-(C_0-C_3)alkyl-O-C(O)-,

xxii) Ph^1-(C_0-C_3)alkyl-C(O)-(C_0-C_3)alkyl-O-,

xxiii) Ph^1-(C_0-C_3)alkylthio,

xxiv) Ph^1-(C_0-C_3)alkylsulfinyl,

xxv) Ph^1-(C_0-C_3)alkylsulfonyl,

xxvi) $Ar^2(C_0-C_3)$alkyl,

xxvii) $Ar^2(C_0-C_3)$alkyl-O-

xxviii) Ar^2-(C_0-C_3)alkyl-S-,

xxix) $Ar^2(C_0-C_3)$alkyl-C(O)-,

xxx) $Ar^2(C_0-C_3)$alkyl-C(S)-,

xxxi) Ar^2-(C_0-C_3)alkylsulfinyl,

xxxii) Ar^2-(C_0-C_3)alkylsulfonyl,

xxxiii) $Het^1(C_0-C_3)$alkyl-C(O)- optionally substituted on the Het^1 moiety with Ph^1,

xxxiv) $Het^1(C_0-C_3)$alkyl-C(S)- optionally substituted on the Het^1 moiety with Ph^1,

xxxv) N-linked Het^1-C(O)-(C_0-C_3)alkyl-O-,

xxxvi) Het^2-(C_0-C_3)alkyloxy,

xxxvii) $R^{26}R^{27}N$-,

xxxviii) $R^{28}R^{29}$-N-(C_1-C_3)alkoxy,

xxxix) $R^{28}R^{29}N$-C(O)-,

xl) $R^{28}R^{29}N$-C(O)-(C_1-C_3)alkyl-O-,

xli) $R^{28}R^{29}N$-C(S)-,

xlii) $R^{30}R^{31}N\text{-}S(O)_2\text{-}$,

xliii) $HON{=}C(CH_3)\text{-}$, and

xliv) $HON{=}C(Ph^1)\text{-}$,

or a pharmaceutically acceptable salt thereof, subject to the following provisos:

a) no more than two of R^1, R^2, R^3, R^4, and R^5 may be other than hydrogen;

b) when R^2 is methyl, then R^1, R^3, R^4, and R^5 are each hydrogen; and

c) when R^3 is methyl, then R^2 and R^4 are each hydrogen;

~~d) when R^3 is methyl, R^7 and R^8 are each -OH, and R^1, R^2, R^4, R^5, and R^9 are each hydrogen, then R^6 is other than cyclohexylthio, furanylthio, or phenylthio; and~~

~~e) When R^{13} is Ar^2-(C_1-C_2)alkyl, then R^2 is other than hydrogen or R^8 is other than chloro.~~

2. A compound according to Claim 1 wherein R^7 is selected from halo, -CN, and CF_3.

3. A compound according to either Claim 1 or Claim 2 wherein R^7 is chloro.

4. A compound according to any one of Claims 1 to 3 wherein R^6 is -C≡C-R^{10}.

5. A compound according to any one of Claims 1 to 3 wherein R^6 is -O-R^{12}.

6. A compound according to any one of Claims 1 to 3 wherein R^6 is -S-R^{14}.

7. A compound according to Claim 6 wherein R^6 is -S-L-R^{15}.

8. A compound according to Claim 7 wherein R^{15} is Ph^2 or Ar^2.

9. A compound according to any one of Claims 1 to 3 wherein R^6 is -$NR^{24}R^{25}$.

10. A compound according to Claim 9 wherein R^{24} is Ph^2-(C_1-C_3) *n*-alkyl-.

11. A compound according to Claim 9 wherein R^{24} is Ar^2-(C_1-C_3) *n*-alkyl-.

12. A Compound according to any one of Claims 9 to 11 wherein R^{25} is hydrogen.

13. (Cancelled) ~~A compound according to any one of Claims 1 to 12 wherein R^6 is hydrogen, halo or (C_1-C_2)alkoxy.~~

14. (Cancelled) ~~A compound according to any one of Claims 1 to 12 wherein R^8 is hydrogen.~~

15. A compound according to any one of Claims 1 to 14 wherein R^1, R^2, R^3, R^4, R^5, and R^8, are each hydrogen.

16. A pharmaceutical composition comprising a compound according to any one of Claims 1 to 15 as an active ingredient in association with a pharmaceutically acceptable carrier, diluent or excipient.

17. A compound according to any one of Claims 1 to 15 for use in therapy.

18. A method for the treatment of obesity in mammals, comprising administering to a mammal in need of such treatment an effective amount of a compound according to Claim 1.

19. The method of Claim 18, where the mammal is human.

20. A method for the treatment of obsessive compulsive disorder in mammals, comprising administering to a mammal in need of such treatment an effective amount of a compound according to Claim 1.

21. The method of Claim 20, where the mammal is human.

22. A method for the treatment of depression in mammals, comprising administering to a mammal in need of such treatment an effective amount of a compound according to Claim 1.

23. The method of Claim 22, where the mammal is human.

24. A method for the treatment of anxiety in mammals, comprising administering to a mammal in need of such treatment an effective amount of a compound according to Claim 1.

25. The method of Claim 24, where the mammal is human.

26. A compound according to any one of Claims 1 to 15 for use as a pharmaceutical.

27. A compound according to any one of Claims 1 to 15 for use in the treatment of obesity in mammals.

28. A compound according to any one of Claims 1 to 15 for use in the treatment of obsessive/compulsive disorder in mammals.

29. A compound according to any one of Claims 1 to 15 for use in the treatment of depression in mammals.

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30. A compound according to any one of Claims 1 to 15 for use in the treatment of anxiety in mammals.

31. A compound according to any one of Claims 27-30, where the mammal is a human.

32. The use of a compound according to any one of Claims 1 to 15 in the manufacture of a medicament for the treatment of a disorder selected from obesity, hyperphagia, obsessive/compulsive disorder, depression, anxiety, substance abuse, sleep disorder, hot flashes, and/or hypogonadism.

33. The use of a compound according to any one of Claims 1 to 15 in the manufacture of a medicament for the treatment of a disorder selected from obesity, obsessive/compulsive disorders, anxiety, or depression.

34. A pharmaceutical composition adapted for the treatment of obesity comprising a compound according to any one of Claims 1 to 15 in combination with one or more pharmaceutically acceptable excipients, carriers, or diluents therefore.

35. A pharmaceutical composition adapted for the treatment of obsessive/compulsive disorders comprising a compound according to any one of Claims 1 to 15 in combination with one or more pharmaceutically acceptable excipients, carriers, or diluents therefore.

36. A pharmaceutical composition adapted for the treatment of depression comprising a compound according to any one of Claims 1 to 15 in combination with one or more pharmaceutically acceptable excipients, carriers, or diluents therefore.

37. A pharmaceutical composition adapted for the treatment of anxiety comprising a compound according to any one of Claims 1 to 15 in combination with one or more pharmaceutically acceptable excipients, carriers, or diluents therefore.

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REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT

PATENTE DE INVENCION [ ] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Descripción de la invención [ ]
- Dibujos de ser estos pertinentes [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
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