Industria y Comercio

SUPERINTENDENCIA

05054176

Delegatura de propiedad Industrial

División de Nuevas Creaciones

P.C.T.

SOLICITUD

PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 05054176

54. **TÍTULO** DERIVADOS DE HIDROXIETILAMINA PARA EL TRATAMIENTO DE LA ENFERMEDAD DE ALZHEIMER.

51. **CLASIFICACIÓN INTERNACIONAL** A61K31/4015 A61P25/28.

71. **SOLICITANTE** GLAXO GROUP LIMITED.

DOMICILIO Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 ONN, Inglaterra.

74. **APODERADO** Carlos R. Olarte.

22. **BOGOTÁ, D. C.,** Junio 3 de 2005

(FORMA P-10)

(56)

OLARTERAISBECK

Industria y Comercio
SUPERINTENDENCIA

SUPERINDUSTRIA Y COMERCIO
Radicación : 05054175 [illegible]
Fecha (AMD): 2005-06-02 14:33:16 Folios: 557
Tramite : 811 PCT-PATENT 379 CASE HACI 411 PRESENTA
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL 05-07-05

(1) **SOLICITUD DE:**

[X] Patente de Invención. [ ] Patente de Modelo de Utilidad.

[ ] Capítulo I. [X] Capítulo II.

(2) **SOLICITANTE (71)**

Nombre: GLAXO GROUP LIMITED
Dirección: Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 ONN
Nacionalidad o Domicilio: BRITANICA
Lugar de Constitución: INGLATERRA
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
Teléfono: 601-7700 Fax: 601-7799
E-mail: office@olarteraisbeck.com

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/EP2003/013806 Fecha Diciembre 3, 2003
Publicación Internacional No. WO 2004/050619 Fecha Junio 17, 2004

(6) **Título (54)** **DERIVADOS DE HIDROXIETILAMINA PARA EL TRATAMIENTO DE LA ENFERMEDAD DE ALZHEIMER.**

(7) **Clasificación Internacional (51)** C07D 207/26 A61P25/28. A61K31/405

(8) **Prioridad** SI [X] N [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
GB	Diciembre 5, 2002	0228410.7

(9) **Comprobante de pago No.** 40,154 **Fecha** Junio 2, 2005

(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.
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [ ] 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

LISTA DE INVENTORES

EMMANUEL H DEMONT
New Frontiers Science Park South
Third Avenue, Harlow
Essex
CM19 5AW,
Gran Bretaña
Nacionalidad: Francesa

ANDREW FALLER
Erl Wood Manor
Sunninghill Road
Windlesham
Surrey, GU20 6PH,
Gran Bretaña
Nacionalidad: Británica

DAVID TIMOTHY MACPHERSON
New Frontiers Science Park South
Third Avenue, Harlow
Essex
CM19 5AW,
Gran Bretaña
Nacionalidad: Británica

PETER HENRY MILNER
New Frontiers Science Park South
Third Avenue, Harlow
Essex
CM19 5AW,
Gran Bretaña
Nacionalidad: Británica

ALAN NAYLOR
New Frontiers Science Park South
Third Avenue, Harlow
Essex
CM19 5AW,
Gran Bretaña
Nacionalidad: Británica

SALLY REDSHAW
New Frontiers Science Park South
Third Avenue, Harlow
Essex
CM19 5AW,
Gran Bretaña
Nacionalidad: Británica

STEVEN JAMES STANWAY
New Frontiers Science Park South
Third Avenue, Harlow
Essex
CM19 5AW,
Gran Bretaña
Nacionalidad: Británica

DAVID R VESEY
New Frontiers Science Park South
Third Avenue, Harlow
Essex
CM19 5AW,
Gran Bretaña
Nacionalidad: Británica

DARYL S. WALTER
New Frontiers Science Park South
Third Avenue, Harlow
Essex
CM19 5AW,
Gran Bretaña
Nacionalidad: Británica

5

SUPERINDUSTRIA Y COMERCIO
Radicacion : 03054176 00002000 Folios: 357
Fecha (AMD): 2005-06-03 17:33:16
Tramite : 911 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 05 - 40,154
FECHA : JUNIO 2 DE 2005

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEGR	CONSIGNACION	BANCO POPULAR	050-00110-6	36223409	02/06/2005	4,430,000.00

***** 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	443,000.00
			TOTAL : 1	443,000.00

SON: CUATROCIENTOS CUARENTA 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

GLAXO GROUP LIMITED

PODER DE REPRESENTACION

Bilingüe inglés- español otorgado en Brentford, Middlesex, Inglaterra el 13 de agosto de 2003 y firmado por Peter John Giddings, Apoderado y Funcionario autorizado.

Certificado de Notario De Pinna en español firmado por James Kerr Milligan

APOSTILLA

(Convención de la Haya del 5 de octubre de 1961)

1. País: Reino Unido de Gran Bretaña e Irlanda del Norte
   - Este documento Público
2. ha sido firmado por James Kerr Milligan
3. Quien ejerce funciones de Notario público
4. Lleva el sello del Notario público

CERTIFICADO

5. En Londres
6. El 14 agosto 2003
7. Por el Secretario de Estado Principal de su Majestad para Asuntos exteriores y de la Mancomunidad
8. No. G229474
9. Gran Sello de la Oficina de Asuntos exteriores y de la Mancomunidad
10. Firma legible de J. Garbrah- Por el Secretario de Estado

Si el documento se usa en un país que no pertenece a la Convención de la Haya del 5 de octubre de 1961 debe pasar por la sección consular de la Misión que representa el país.

Es traducción fiel del inglés, con copia archivo para confrontación. Bogotá 21 agosto-03.

Marlen Neira C

MARLEN NEIRA CASTRO
Traductor e Intérprete Ofi
Inglés - Español - Inglé
Resolución No. 2117 del 7 O

DE PINNA
NOTARIES

Yo, el infrascrito **JAMES KERR MILLIGAN**, Notario Público de la Ciudad de Londres, Inglaterra, por la Autoridad Real debidamente admitido y juramentado,

C E R T I F I C O:

QUE es auténtica la firma suscrita al pie del adjunto Poder, por ser del puño y letra del Señor Don **PETER JOHN GIDDINGS**, cuya identidad me consta, Apoderado de la Sociedad inglesa denominada **"GLAXO GROUP LIMITED"**, Sociedad legalmente constituída y existente de acuerdo con las leyes de Inglaterra, e inscrita en la Oficina de Registro de Sociedades bajo el número **305979**, con domicilio social en Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 ONN, Inglaterra;

QUE el citado Señor Don **PETER JOHN GIDDINGS** está debiday suficientemente autorizado para firmar documentos de esta clase en nombre y representación de dicha Sociedad en virtud de un Poder otorgado por la referida Sociedad fechado 3 de julio de 2002.

Y QUE los objetos para los cuales se otorgó dicho Poder se encuentran dentro de los objetos o actividades de la citada Sociedad, de acuerdo con la Escritura Constitutiva y los Estatutos Sociales, los cuales he tenido a la vista.

Y PARA QUE CONSTE donde y como convenga y fuere necesario expido el presente Certificado que firmo y sello en dicha Ciudad de Londres, el día de hoy diez de agosto del año dos mil tres.

JAMES KERR MILLIGAN
Notario Público de Londres, Inglaterra

Notaría Veintiuno del Círculo de Santafé de Bogotá, Cuya Notaría Titularizo Hugo Gaitán Bohórquez, debidamente con Credencial Vigente, debidamente para su ejercicio en Colombia República de Colombia

JUN 2005

NOTARIA VEINTIUNO

SCRIVENER NOTARIES

APOSTILLE
(Hague Convention of 5 October 1961 / Convention de La Haye du 5 octobre 1961)

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

1. Country: United Kingdom of Great Britain and Northern Ireland
   Pays: Royaume-Uni de Grande-Bretagne et d'Irlande du Nord

   This public document / Le présent acte public

2. Has been signed by — James Kerr Milligan
   a été signé par

3. Acting in the capacity of — Notary Public
   agissant en qualité de

4. Bears the seal/stamp of — The Said Notary Public
   est revêtu du sceau/timbre de

Certified/Attesté

5. at London/à Londres — 6. the/le 14 August 2003

7. by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs /
   par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth.

8. Number/sous No **G229474**

9. Stamp:
   timbre:

10. Signature: J. Garbrah

For the Secretary of State / Pour le Secrétaire d'Etat

If this document is to be used in a country which is not party to the Hague Convention of 5 October 1961,
it should be presented to the consular section of the mission representing that country.

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

Power of Attorney

The undersigned,

Glaxo Group Limited

domiciled in

Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN, GB

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.

Poder

El suscrito,

Glaxo Group Limited

domiciliado en

Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN, GB

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: _____

Peter John GIDDINGS as Attorney and Authorised Official

Date/Fecha: 13 August 2003

City,Country/Ciudad,País: Brentford, Middlesex, England



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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 June 2004 (17.06.2004)

PCT

(10) International Publication Number
WO 2004/050619 A1

(51) International Patent Classification[7]: C07D 207/26, 279/02, 417/12, 405/12, 409/12, 403/12, 401/12, 275/02, 211/76, A61K 31/4015, 31/45, 31/415, 31/541, A61P 25/28

(21) International Application Number:
PCT/EP2003/013806

(22) International Filing Date: 3 December 2003 (03.12.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0228410.7 5 December 2002 (05.12.2002) GB

(71) Applicant (*for all designated States except US*): GLAXO GROUP LIMITED [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 ONN (GB).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): DEMONT, Emmanuel, H. [FR/GB]; GlaxoSmithKline, The Frythe, Welwyn, Hertfordshire AL6 9AR (GB). FALLER, Andrew [GB/GB]; Eli Lilly Research Centre, Erl Wood Manor, Sunninghill Road, Windlesham, Surrey GU20 6PH (GB). MACPHERSON, David, Timothy [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). MILNER, Peter, Henry [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). NAYLOR, Alan [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). REDSHAW, Sally [GB/GB]; GlaxoSmithKline, The Frythe, Welwyn, Hertfordshire AL6 9AR (GB). STANWAY, Steven, James [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). VESEY, David, R. [GB/GB]; GlaxoSmithKline, The Frythe, Welwyn, Hertfordshire AL6 9AR (GB). WALTER, Daryl, S. [GB/GB]; GlaxoSmithKline, The Frythe, Welwyn, Hertfordshire AL6 9AR (GB).

(74) Agent: VALENTINE, Jill, Barbara; GlaxoSmithKline, CN925.1 (CIP), 980 Great West Road, Brentford, Middlesex TW8 9GS (GB).

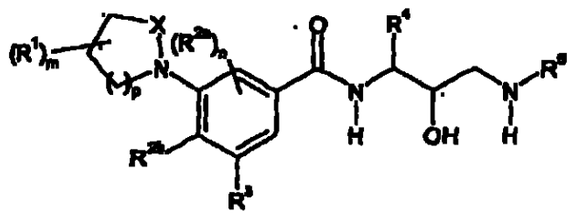
(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, 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, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: HYDROXYETHYLAMINE DERIVATIVES FOR THE TREATMENT OF ALZHEIMER'S DISEASE



(I)

(57) Abstract: The present invention relates to novel hydroxyethylamine compounds of formula (I): (I) having Asp2 (-secretase, BACE1 or Memapsin) inhibitory activity, processes for their preparation, to compositions containing them and to their use in the treatment of diseases characterised by elevated - amyloid levels or -amyloid deposits, particularly Alzheimer's disease.

WO 2004/050619 A1

HYDROXYETHYLAMINE DERIVATIVES FOR THE TREATMENT OF ALZHEIMER'S DISEASE

The present invention relates to novel hydroxyethylamine compounds having Asp2 (β-secretase, BACE1 or Memapsin) inhibitory activity, processes for their preparation, to compositions containing them and to their use in the treatment of diseases characterised by elevated β- amyloid levels or β-amyloid deposits, particularly Alzheimer's disease.

Alzheimer's disease is a degenerative brain disorder in which extracellular deposition of Aβ in the form of senile plaques represents a key pathological hallmark of the disease (Selkoe, D. J. (2001) Physiological Reviews 81: 741-766). The presence of senile plaques is accompanied by a prominent inflammatory response and neuronal loss. β-amyloid (Aβ) exists in soluble and insoluble, fibrillar forms and a specific fibrillar form has been identified as the predominant neurotoxic species (Vassar, R. and Citron, M. (2000) Neuron 27: 419-422). In addition it has been reported that dementia correlates more closely with the levels of soluble amyloid rather than plaque burden (Naslund, J. *et al.* (2000) J. Am. Med. Assoc. 12: 1571-1577; Younkin, S. (2001) Nat. Med. 1: 8-19). Aβ is known to be produced through the cleavage of the beta amyloid precursor protein (also known as APP) by an aspartyl protease enzyme known as Asp2 (also known as β-secretase, BACE1 or Memapsin) (De Strooper, B. and Konig, G. (1999) Nature 402: 471-472).

Therefore, it has been proposed that inhibition of the Asp2 enzyme would reduce the level of APP processing and consequently reduce the levels of Aβ peptides found within the brain. Therefore, it is also thought that inhibition of the Asp2 enzyme would be an effective therapeutic target in the treatment of Alzheimer's disease.

APP is cleaved by a variety of proteolytic enzymes (De Strooper, B. and Konig, G. (1999) Nature 402: 471-472). The key enzymes in the amyloidogenic pathway are Asp2 (β-secretase) and γ-secretase both of which are aspartic proteinases and cleavage of APP by these enzymes generates Aβ. The non-amyloidogenic, α-secretase pathway, which precludes Aβ formation, has been shown to be catalysed by a number of proteinases, the best candidate being ADAM10, a disintegrin and metalloproteinase. Asp1 has been claimed to show both α- and β-secretase activity *in vitro*. The pattern of expression of Asp1 and Asp2 are quite different, Asp2 is most highly expressed in the pancreas and brain while Asp1 expression occurs in many other peripheral tissues. The Asp2 knockout mouse indicates that lack of Asp2 abolished Aβ production and also shows that in this animal model endogenous Asp1 cannot substitute for the Asp2 deficiency (Luo, Y. *et al.* (2001) Nat Neurosci. 4: 231-232; Cai, H. *et. al.* (2001) Nat Neurosci. 4: 233-234; Roberds, S. L. *et al.* (2001) Hum. Mol. Genet. 10: 1317-1324).

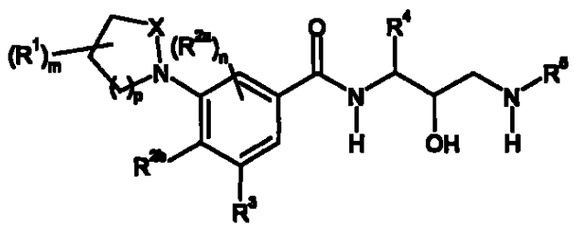
For an agent to be therapeutically useful in the treatment of Alzheimer's disease it is preferable that said agent is a potent inhibitor of the Asp2 enzyme, but should ideally also be selective for Asp2 over other enzymes of the aspartyl proteinase family, e.g Cathepsin D

(Connor, G. E. (1998) Cathepsin D In Handbook of Proteolytic Enzymes, Barrett, A. J., Rawlings, N. D., & Woessner, J. F. (Eds) Academic Press London. pp828-836).

WO 01/70672, WO 02/02512, WO 02/02505, WO 02/02506 and WO 03/040096 (Elan Pharmaceuticals Inc.) describe a series of hydroxyethylamine compounds having β-secretase activity which are implicated to be useful in the treatment of Alzheimer's disease.

We have found a novel series of compounds which are potent inhibitors of the Asp2 enzyme, thereby indicating the potential for these compounds to be effective in the treatment of Alzheimer's disease.

Thus, according to a first aspect of the present invention we provide a compound of formula (I):



(I)

wherein

R^1 represents C_{1-6} alkyl, C_{2-6} alkenyl, halogen, C_{1-6} alkoxy, amino, cyano, hydroxy, aryl, heteroaryl or heterocyclyl;

R^{2a} represents hydrogen, C_{1-3} alkyl, C_{1-3} alkoxy or halogen;

m and n independently represent 0, 1 or 2;

X represents CO, SO or SO_2;

p represents an integer from 1 to 3;

R^{2b} represents hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, halogen, C_{1-6} alkoxy, amino, cyano, hydroxy, aryl, heteroaryl or heterocyclyl;

R^3 represents halogen, C_{1-6} alkyl, C_{2-6} alkenyl, aryl, heteroaryl, heterocyclyl, -C_{1-6} alkyl-aryl, -C_{1-6} alkyl-heteroaryl, -C_{1-6} alkyl-heterocyclyl, -C_{2-6} alkenyl-aryl, -C_{2-6} alkenyl-heteroaryl, -C_{2-6} alkenyl-heterocyclyl, C_{3-6} cycloalkyl, -C_{1-6} alkyl-C_{3-6} cycloalkyl, cyano, azido, nitro, $-NR^7R^8$, -NR^9COR^{10}, -$NR^{11}SO_2R^{12}$, -OR^{13}, -SO_2R^{14}, -SR^{15}, -$C{=}CR^{16}$, -C_{1-6} alkyl-$(CF_2)_qCF_3$, -$CONR^{17}R^{18}$, $COOR^{19}$, -C_{1-6} alkyl-$NR^{20}R^{21}$ or -C_{1-6} alkyl-N_3, or R^3 and R^{2b} together with the phenyl group to which they are attached form a naphthyl or benzofused heterocyclic or heteroaryl ring optionally substituted by one or two C_{1-6} alkyl groups;

R^4 represents $-C_{2-6}$ alkynyl, -C_{1-6} alkyl-aryl, -C_{1-6} alkyl-heteroaryl or -C_{1-6} alkyl-heterocyclyl;

R^5 represents hydrogen, -C_{1-10} alkyl, -C_{3-10} cycloalkyl, -C_{3-10} cycloalkenyl, aryl, heteroaryl, heterocyclyl, -C_{1-6} alkyl-C_{3-10} cycloalkyl, -C_{3-10} cycloalkyl-C_{1-10} alkyl, -C_{3-10} cycloalkyl-C_{1-6} alkyl-aryl, -C_{3-10} cycloalkyl-aryl, -C_{1-6} alkyl-aryl-heteroaryl, -$C(R^aR^b)$-CONH-C_{1-6} alkyl, -$C(R^cR^d)$-CONH-C_{3-10} cycloalkyl, -C_{1-6} alkyl-S-C_{1-6} alkyl, -C_{1-6} alkyl-NR^eR^f, -C_{1-6} alkyl-aryl, -C_{1-6} alkyl-heteroaryl, -C_{1-6} alkyl-heterocyclyl -C_{1-6} alkyl-C_{1-6} alkoxy-aryl, -C_{1-6} alkyl-C_{1-6} alkoxy-heteroaryl or -C_{1-6} alkyl-C_{1-6} alkoxy-heterocyclyl;

R^7, R^8, R^9, R^{10}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20} and R^{21} independently represent hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl, aryl, heteroaryl, heterocyclyl, -C_{1-6} alkyl-C_{3-6} cycloalkyl, -C_{1-6} alkyl-aryl, -C_{1-6} alkyl-heteroaryl, -C_{1-6} alkyl-heterocyclyl or -CO-C_{1-6} alkyl;
R^{11}, R^{12}, R^a, R^c, R^e and R^f independently represent hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl;
R^b and R^d independently represent hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl or -C_{1-6} alkyl-SO_2-C_{1-6} alkyl;
q represents 1 to 3;
wherein said alkyl groups may be optionally substituted by one or more (eg. 1, 2 or 3) halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenoxy, C_{3-6} cycloalkyl, amino, cyano or hydroxy groups;
and wherein said cycloalkyl, aryl, heteroaryl or heterocyclyl groups may be optionally substituted by one or more (eg. 1, 2 or 3) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, haloC_{1-6} alkyl, -OCF_3, oxo, C_{1-6} alkoxy, -C_{1-6} alkoxy-CN, amino, cyano, nitro, -$NR^{22}COR^{23}$, -$CONR^{22}R^{23}$, -$COOR^{22}$, -SO_2R^{22}, -C_{1-6} alkyl-NR^{22} R^{23} (wherein R^{22} and R^{23} independently represent hydrogen or C_{1-6} alkyl), -C_{1-6} alkyl-C_{1-6} alkoxy, -C_{1-6} alkanol or hydroxy groups;
or a pharmaceutically acceptable salt or solvate thereof.

In one particular aspect of the present invention, there is provided a compound of formula (I) as defined above wherein:
X represents CO or SO_2; and
R^{2a} represents hydrogen, C_{1-3} alkyl or halogen; and
R^3 and R^{2b} together with the phenyl group which they are attached form an unsubstituted benzofused heterocyclic or heteroaryl ring; and
R^4 represents -C_{1-6} alkyl-aryl, -C_{1-6} alkyl-heteroaryl or -C_{1-6} alkyl-heterocyclyl; and
R^5 represents hydrogen, -C_{1-10} alkyl, -C_{3-6} cycloalkyl, -C_{3-6} cycloalkenyl, aryl, heteroaryl, heterocyclyl, -C_{1-6} alkyl-C_{3-6} cycloalkyl, -C_{1-6} alkyl-aryl-heteroaryl, -$C(R^aR^b)$-CONH-C_{1-6} alkyl, -$C(R^aR^b)$-CONH-C_{3-6} cycloalkyl, -C_{1-6} alkyl-S-C_{1-6} alkyl, -C_{1-6} alkyl-NR^eR^f, -C_{1-6} alkyl-aryl, -C_{1-6} alkyl-heteroaryl, -C_{1-6} alkyl-heterocyclyl -C_{1-6} alkyl-C_{1-6} alkoxy-aryl, -C_{1-6} alkyl-C_{1-6} alkoxy-heteroaryl or -C_{1-6} alkyl-C_{1-6} alkoxy-heterocyclyl; and
said alkyl groups may be optionally substituted by one or more (eg. 1, 2 or 3) halogen, C_{1-6} alkoxy, amino, cyano or hydroxy groups; and
wherein said aryl, heteroaryl or heterocyclyl groups may be optionally substituted by one or more (eg. 1, 2 or 3) C_{1-6} alkyl, halogen, -OCF_3, oxo, C_{1-6} alkoxy, amino, cyano, nitro, -$NR^{22}COR^{23}$, -C_{1-6} alkyl-NR^{22} R^{23} (wherein R^{22} and R^{23} independently represent hydrogen or C_{1-6} alkyl), -C_{1-6} alkyl-C_{1-6} alkoxy, -C_{1-6} alkanol or hydroxy groups.

References to alkyl include references to both straight chain and branched chain aliphatic isomers of the corresponding alkyl. It will be appreciated that references to alkenyl and alkenoxy shall be interpreted similarly. It will also be appreciated that when an alkenyl or alkenoxy group is attached to an O, N or S atom the double bond is not at the alpha position relative to said O, N or S atom.

References to cycloalkyl include references to all alicyclic (including branched) isomers of the corresponding alkyl. When a cycloalkyl group is substituted by two or more C_{1-6} alkyl groups,

said cycloalkyl groups together with any two alkyl groups may form a bridged cycloalkyl group which includes bicycloheptyl, adamantyl, bicyclo-octyl and the like.

References to 'aryl' include references to monocyclic carbocyclic aromatic rings (eg. phenyl) and bicyclic carbocyclic aromatic rings (e.g. naphthyl) or carbocyclic benzofused rings (eg. C_{5-8} cycloalkyl fused to a phenyl ring, such as dihydroindenyl or tetrahydronaphthalenyl).

References to 'heteroaryl' include references to mono- and bicyclic heterocyclic aromatic rings containing 1-4 hetero atoms selected from nitrogen, oxygen and sulphur. Examples of monocyclic heterocyclic aromatic rings include e.g. thienyl, furyl, pyrrolyl, triazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyrazolyl, pyrimidyl, pyridazinyl, pyrazinyl, pyridyl, tetrazolyl and the like. Examples of bicyclic heterocyclic aromatic rings include eg. quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, cinnolinyl, naphthyridinyl, indolyl, indazolyl, pyrrolopyridinyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzoxadiazolyl, benzothiadiazolyl and the like.

References to 'heterocyclyl' include references to a 5-7 membered non-aromatic monocyclic ring containing 1 to 3 heteroatoms selected from nitrogen, sulphur or oxygen. Examples of heterocyclic non-aromatic rings include e.g. morpholinyl, piperidinyl, piperazinyl, thiomorpholinyl, oxathianyl, dithianyl, dioxanyl, pyrrolidinyl, dioxolanyl, oxathiolanyl, imidazolidinyl, pyrazolidinyl and the like.

References to 'benzofused heterocyclyl or heteroaryl ring' include quinolinyl, isoquinolinyl, indolyl, indazolyl, dihydroindolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzoxadiazolyl, benzothiadiazolyl, dihydrochromene, benzotriazolyl, tetrahydroquinoxalinyl and the like.

Preferably, m is 0 or 1, preferably 0. When m represents 1, R^1 is preferably aryl (eg. phenyl).

Preferably, n is 0 or 1, more preferably 1.

When n represents 1, R^{2a} is preferably C_{1-3} alkoxy (eg. methoxy) or halogen (eg. fluorine), more preferably halogen (eg. fluorine).

When n represents 1, R^{2a} is preferably in the ortho position of the phenyl ring.

When X represents SO_2, p is preferably 2 or 3, more preferably 2 and when X represents CO, p is preferably 1 or 2, more preferably 1.

Preferably, R^{2b} is :

hydrogen;

halogen (eg. chlorine or fluorine);

C_{1-6} alkyl (eg. methyl);
C_{1-6} alkoxy (eg. methoxy); or
heterocyclyl (eg. pyrrolidinyl) optionally substituted by an oxo group (eg. 2-oxopyrrolidin-1-yl).

More preferably, R^{2b} is hydrogen or halogen (eg. fluorine), most preferably hydrogen.

Preferably, R^3 represents:
C_{1-6} alkyl (eg. methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl or t-butyl) optionally substituted by one or more (eg. 1, 2 or 3) hydroxy, halogen (eg. fluorine) or C_{1-6} alkoxy groups (eg. methoxy or ethoxy);
C_{2-6} alkenyl (eg. propenyl);
C_{3-6} cycloalkyl (eg. cyclopentyl or cyclohexyl);
cyano;
heterocyclyl (eg. piperidinyl, pyrrolidinyl or isothiazolidinyl) optionally substituted by one or two oxo groups;
$-NR^7R^8$;
$-OR^{13}$;
$-SR^{15}$; or
$-CONR^{17}R^{18}$.

Also preferably, R^3 and R^{2b} together with the phenyl group which they are attached represent indolyl, indazolyl, dihydroindolyl, benzofuranyl, dihydrochromenyl, benzotriazolyl, benzimidazolyl or tetrahydroquinoxalinyl, optionally substituted by one or two C_{1-6} alkyl (eg. methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, t-butyl or pentyl) groups. More preferably R^3 and R^{2b} together with the phenyl group which they are attached represent benzimidazolyl or indolyl substituted by a C_{1-6} alkyl group (eg. ethyl).

More preferably, R^3 represents:
C_{1-6} alkyl (eg. n-propyl);
$-NR^7R^8$;
C_{3-6} cycloalkyl (eg. cyclopentyl or cyclohexyl);
$-OR^{13}$; or
$-CONR^{17}R^{18}$.

Preferably, R^7 and R^8 independently represent:
hydrogen;
C_{1-6} alkyl (eg. methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, t-butyl, pentyl, i-propyl, i-butyl, $-CH_2C(CH_3)_3$, $-CH(CH_2CH_3)CH_2CH_3$ or $-(CH_2)_2CH(CH_3)_2$);
C_{3-6} cycloalkyl (eg. cyclopentyl or cyclohexyl);
aryl (eg. phenyl);
$-C_{1-6}$ alkyl-C_{3-6} cycloalkyl (eg. $-CH_2$-cyclopropyl);
$-C_{1-6}$ alkyl-aryl (eg. $-CH_2$-phenyl or $-(CH_2)_2$-phenyl); or

-CO-C_{1-6} alkyl (eg. –$COCH_3$).

More preferably, R^7 represents hydrogen and R^8 represents C_{1-6} alkyl (particularly ethyl or isopropyl, especially ethyl).

Preferably, R^{13} represents C_{1-6} alkyl (eg. methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl or t-butyl or pentyl) optionally substituted by a hydroxy or C_{1-6} alkoxy (eg. methoxy) group, more preferably R^{13} represents ethyl or i-propyl.

Preferably, R^{15} represents C_{1-6} alkyl (eg. methyl or ethyl).

Preferably, R^{17} and R^{18} both represent C_{1-6} alkyl (eg. both represent propyl or one represents propyl and the other represents methyl).

Preferably, R^4 represents -C_{1-6} alkyl-aryl (eg. benzyl) or -C_{1-6} alkyl-heteroaryl (eg. –CH_2-pyridinyl, –CH_2-thiazolyl, –CH_2-furanyl, –CH_2-thienyl or –CH_2-pyrazolyl) optionally substituted by one or two halogen atoms (eg. chlorine or fluorine). More preferably, R^4 represents -C_{1-6} alkyl-aryl (eg. benzyl) optionally substituted by one or two halogen atoms (eg. chlorine or fluorine), most preferably R^4 represents unsubstituted benzyl.

Preferably, R^5 represents

-C_{1-10} alkyl (eg. methyl, ethyl, n-propyl, n-butyl, n-pentyl or n-hexyl) optionally substituted by one or more C_{1-6} alkyl (eg. methyl), C_{1-6} alkoxy (eg. methoxy or –$OCH_2CH(CH_3)_2$) or C_{2-6} alkenoxy (eg.-$OCH_2C(CH_3)=CH_2$) groups;

-C_{3-10} cycloalkyl (eg. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicycloheptyl, adamantyl or bicyclo-octyl) optionally substituted by one or more C_{1-6} alkyl (eg. methyl, ethyl or propyl) or halogen (eg. fluorine) groups;

-C_{1-6} alkyl-C_{3-10} cycloalkyl (eg. –CH_2-cyclohexyl or –CH_2-cyclopropyl);

-aryl (eg. phenyl, dihydroindenyl or tetrahydronaphthalenyl) optionally substituted by one or more hydroxy or C_{1-6} alkoxy (eg. methoxy) groups;

-C_{1-6} alkyl-aryl (eg. benzyl, -ethyl-phenyl, -ethyl-naphthyl, -propyl-phenyl, -C(H)(Me)-phenyl, -C(H)(Et)-phenyl –C(Me)(Me)-benzyl or –C(Me)(Me)-phenyl) optionally substituted by one or more halogen (eg. chlorine, bromine or fluorine), hydroxy, -OCF_3, haloC_{1-6} alkyl (eg. -CH_2CF_3 or -CF_3), C_{1-6} alkyl (eg. methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl or t-butyl), C_{2-6} alkenyl (eg. ethenyl), C_{2-6} alkynyl, C_{1-6} alkoxy (eg. methoxy, ethoxy, propoxy, isopropoxy or methylethoxy), cyano, nitro, -$COOR^{22}$ (eg. COOH or COOMe), -SO_2R^{22} (eg. –SO_2Me), -$NR^{22}COR^{23}$ (eg.-$NHCOCH_3$), -C_{1-6} alkyl-$NR^{22}R^{23}$ (eg. –$CH_2N(CH_3)_2$), -C_{1-6} alkyl-C_{1-6} alkoxy (eg. -$CH_2OC(CH_3)_3$), -C_{1-6} alkanol (eg. -CH_2OH) or -C_{1-6} alkoxy-CN (eg. OCH_2CN) groups;

-C_{1-6} alkyl-heteroaryl (eg. –CH_2-furanyl, –CH_2-quinolinyl, –CH_2-thiophenyl, –CH_2-indolyl, –CH_2-benzoimidazolyl, –CH_2-imidazolyl, –CH_2-benzofuranyl, –CH_2-thiazolyl, –CH_2-pyridinyl, –CH_2-benzothiazolyl, –CH_2-pyrazolyl, –CH_2-isoxazolyl, –CH_2-oxazolyl, –CH_2-pyrrolyl, –CH_2-dihydrobenzofuranyl, –CH_2-dihydrobenzodioxinyl or –CH_2-dihydrochromenyl) optionally

substituted by one or more C_{1-6} alkyl (eg. methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl or t-butyl), C_{2-6} alkenyl (eg. ethenyl or propenyl), C_{2-6} alkynyl, halogen (eg. bromine or chlorine), haloC_{1-6} alkyl (eg. fluoroethyl or trifluoroethyl), cyano, C_{1-6} alkoxy (eg. methoxy), -$CONR^{22}R^{23}$ (eg. –CONHMe) or -$COOR^{22}$ (eg. –COOMe) groups;

-heterocyclyl (eg. tetrahydropyranyl or tetrahydrothiopyranyl);

-C_{1-6} alkyl-heterocyclyl (eg. –CH_2-tetrahydropyranyl);

-C_{3-10} cycloalkyl-C_{1-10} alkyl (eg. –cyclobutyl-isopropyl, -cyclobutyl-ethyl, -cyclobutyl-propyl, -cyclopropyl-ethyl, -cyclopropyl-propyl, -cyclopropyl-isopropyl, -cyclopropyl-t-butyl, -cyclopropyl-$CH_2CH(CH_3)_2$, -cyclopropyl-$(CH_2)_2CH(CH_3)_2$, –cyclopropyl-$(CH_2)_2CH(CH_3)_2$ or –cyclopropyl-$(CH_2)_3CH(CH_3)_2$);

-C_{3-10} cycloalkyl-C_{1-6} alkyl-aryl (eg. –cyclopropyl-CH_2-phenyl) optionally substituted by one or more halogen (eg. chlorine) atoms;

-C_{3-10} cycloalkyl-aryl (eg. –cyclopropyl-phenyl) optionally substituted by one or more halogen (eg. chlorine, bromine or fluorine), hydroxy, -OCF_3, haloC_{1-6} alkyl (eg. -CH_2CF_3 or -CF_3), C_{1-6} alkyl (eg. methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl or t-butyl), C_{2-6} alkenyl (eg. ethenyl), C_{2-6} alkynyl, C_{1-6} alkoxy (eg. methoxy, ethoxy, propoxy, isopropoxy or methylethoxy), cyano, nitro, -$COOR^{22}$ (eg. COOH or COOMe), -SO_2R^{22} (eg. –SO_2Me), -$NR^{22}COR^{23}$ (eg. $NHCOCH_3$), -C_{1-6} alkyl-$NR^{22}R^{23}$ (eg. –$CH_2N(CH_3)_2$), -C_{1-6} alkyl-C_{1-6} alkoxy (eg. -$CH_2OC(CH_3)_3$), -C_{1-6} alkanol (eg. -CH_2OH) or -C_{1-6} alkoxy-CN (eg. OCH_2CN) groups;

-$C(R^aR^b)$-CONH-C_{1-6} alkyl (eg. -$C(R^aR^b)$-CONH-t-butyl);

-$C(R^cR^d)$-CONH-C_{3-10} cycloalkyl (eg. $C(R^cR^d)$-CONH-cyclohexyl);

-C_{1-6} alkyl-S-C_{1-6} alkyl (eg. -propyl-S-methyl or –dimethylethyl-S-isobutyl); or

-C_{1-6} alkyl-NR^eR^f (eg. -dimethylpropyl-NR^eR^f).

More preferably R^5 represents:

-C_{3-10} cycloalkyl (eg. cyclohexyl);

-C_{1-6} alkyl-aryl (eg. benzyl) optionally substituted by one or more halogen (eg. chlorine, bromine or fluorine), -OCF_3 or haloC_{1-6} alkyl (eg. -CF_3) groups;

-C_{1-6} alkyl-heteroaryl (eg. -CH_2-thienyl, –CH_2-pyrazolyl or –CH_2-isoxazolyl) optionally substituted by one or more C_{1-6} alkyl (eg. methyl, ethyl, isopropyl, propyl or butyl) or haloC_{1-6} alkyl (eg. CH_2CF_3) groups; or

-heterocyclyl (eg. tetrahydropyranyl).

Preferably, q represents 1 or 2.

Preferably, R^a represents hydrogen or C_{1-6} alkyl (methyl).

Preferably, R^b and R^d independently represent C_{1-6} alkyl (eg. methyl, ethyl, propyl or butyl) or -C_{1-6} alkyl-SO_2-C_{1-6} alkyl (eg. -$CH_2CH_2SO_2CH_3$) optionally substituted by one or more hydroxy groups.

Preferably, R^c represents hydrogen or C_{1-6} alkyl (methyl).

Preferably, R^e and R^f both represent C_{1-6} alkyl (eg. methyl).

Preferred compounds according to the invention includes examples E1-E744 as shown below, or a pharmaceutically acceptable salt thereof.

More preferred compounds according to the invention include:
formic acid - 5-cyclopentyl-3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-*N*-[(1*S*,2*R*)-3-[[(1-ethyl-1*H*-pyrazol-4-yl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-2-fluorobenzamide (1:1);
formic acid - 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluoro-*N*-[(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl]methyl}amino)propyl]-5-[(1-methylethyl)amino]benzamide (1:1);
formic acid - 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-*N*-[(1*S*,2*R*)-3-[[(1-ethyl-1*H*-pyrazol-4-yl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-2-fluoro-5-[(1-methylethyl)amino]benzamide (1:1);
formic acid - 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluoro-*N*-{(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-[({3-[(trifluoromethyl)oxy]phenyl}methyl)amino]propyl}-5-[(1-methylethyl)amino]benzamide (1:1);
formic acid - N-((1S,2R)-1-benzyl-3-[[4-fluoro-3-(trifluoromethyl)benzyl] amino}-2-hydroxypropyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)-2-fluorobenzamide (1:1);
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-2-fluoro-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl] benzamide;
formic acid – 3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-3-[[(5-ethyl-3-thienyl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl] benzamide (1:1); and
formic acid - 3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-2-fluoro-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[({3-[(trifluoromethyl)oxy] phenyl}methyl)amino] propyl}benzamide (1:1)
or a pharmaceutically acceptable salt thereof.

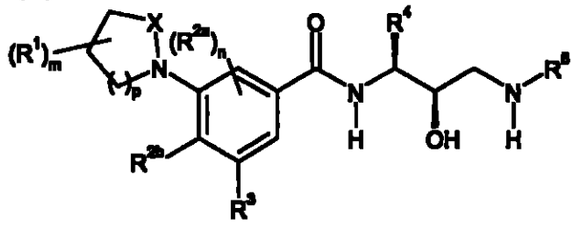
The compounds of formula (I) can form acid addition salts thereof. It will be appreciated that for use in medicine the salts of the compounds of formula (I) should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art and include those described in J. Pharm. Sci., 1977, 66, 1-19, such as acid addition salts formed with inorganic or organic acids e.g. hydrochlorides, hydrobromides, sulphates, phosphates, acetates, benzoates, citrates, nitrates, succinates, lactates, tartrates, fumarates, maleates, 1-hydroxy-2-naphthoates, palmoates, methanesulphonates, p-toluenesulphonates, naphthalenesulphonates, formates or trifluoroacetates. The present invention includes within its scope all possible stoichiometric and non-stoichiometric forms.

The present invention also includes within its scope prodrugs of compounds of formula (I). As used herein, the term "prodrug" means a compound which is converted within the body, e.g. by hydrolysis in the blood, into its active form that has medical effects. Pharmaceutically acceptable prodrugs are described in T. Higuchi and V. Stella, Prodrugs as Novel Delivery

Systems, Vol. 14 of the A.C.S. Symposium Series, Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, and in D. Fleisher, S. Ramon and H. Barbra "Improved oral drug delivery: solubility limitations overcome by the use of prodrugs", Advanced Drug Delivery Reviews (1996) 19(2) 115-130, each of which are incorporated herein by reference. Esters may be active in their own right and /or be hydrolysable under *in vivo* conditions in the human body. Suitable pharmaceutically acceptable *in vivo* hydrolysable ester groups include those which break down readily in the human body to leave the parent acid or its salt.

The compounds of formula (I) may be prepared in crystalline or non-crystalline form, and, if crystalline, may optionally be solvated, eg. as the hydrate. This invention includes within its scope stoichiometric solvates (eg. hydrates) as well as compounds containing variable amounts of solvent (eg. water).

Certain compounds of formula (I) are capable of existing in stereoisomeric forms (e.g. diastereomers and enantiomers) and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be separated one from the other by the usual methods, or any given isomer may be obtained by stereospecific or asymmetric synthesis. The invention also extends to any tautomeric forms and mixtures thereof. Preferably, compounds of formula (I) are in the form of a single enantiomer of formula (Ia):

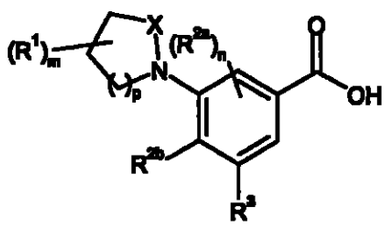


(Ia)

The compounds of formula (I) and salts and solvates thereof may be prepared by the methodology described hereinafter, constituting a further aspect of this invention.

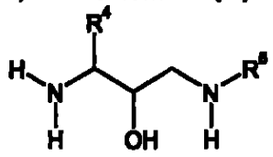
A process according to the invention for preparing a compound of formula (I) which comprises:

(a) reacting a compound of formula (II)



(II)

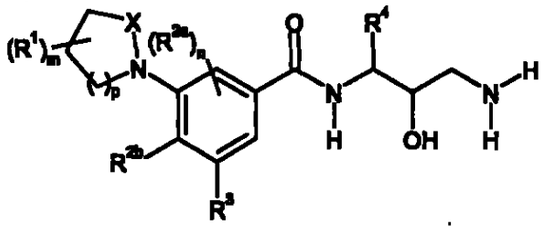
or an activated and optionally protected derivative thereof wherein R^1, m, X, p, R^{2a}, n, R^{2b} and R^3 are as defined above, with a compound of formula (III)



(III)

wherein R^4 and R^5 are as defined above; or

(b) preparing a compound of formula (I) which comprises reductive amination of a compound of formula (IV)



(IV)

wherein R^1, m, X, p, R^{2a}, n, R^{2b}, R^3 and R^4 are as defined above, with an appropriate aldehyde or ketone; or

(c) deprotecting a compound of formula (I) which is protected; and optionally thereafter

(d) interconversion of compounds of formula (I) to other compounds of formula (I).

Process (a) typically comprises the use of water soluble carbodiimide, HOBT and a suitable base such as tertiary alkylamine or pyridine in a suitable solvent such as DMF and at a suitable temperature, eg. between 0°C and room temperature.

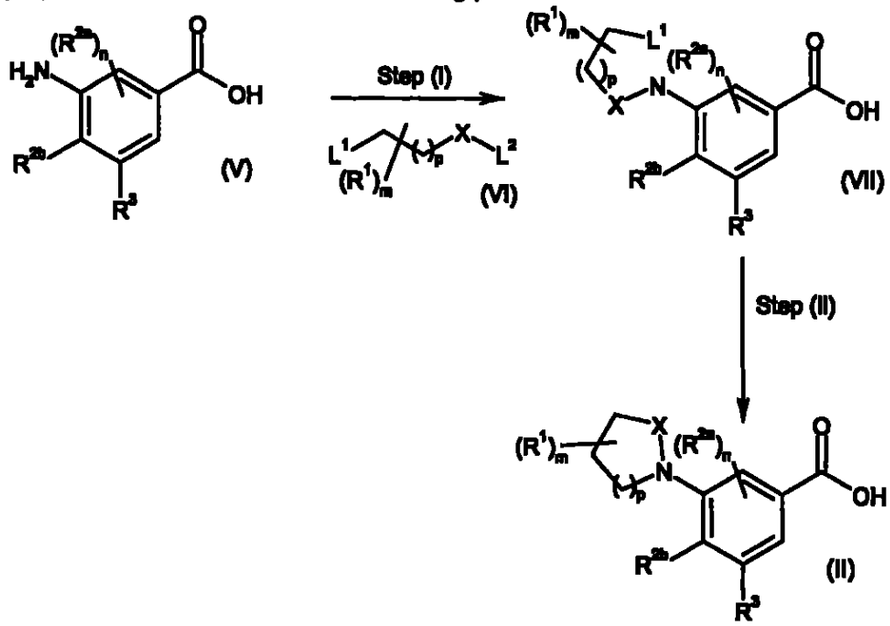
Process (b) typically comprises the use of sodium borohydride triacetate in the presence of a suitable solvent, such as ethanol and dichloromethane and at a suitable temperature, e.g. between 0°C and room temperature.

In process (c), examples of protecting groups and the means for their removal can be found in T. W. Greene and P.G.M. Wuts 'Protective Groups in Organic Synthesis' (J. Wiley and Sons, 3rd Ed. 1999). Suitable amine protecting groups include aryl sulphonyl (e.g. tosyl), acyl (e.g. acetyl), carbamoyl (e.g. benzyloxycarbonyl or t-butoxycarbonyl) and arylalkyl (e.g. benzyl), which may be removed by hydrolysis or hydrogenolysis as appropriate. Other suitable amine protecting groups include trifluoroacetyl (-$COCF_3$) which may be removed by base catalysed hydrolysis. Suitable hydroxy protecting groups would be silyl based groups such as t-butyldimethylsilyl, which may be removed using standard methods, for example use of an acid

such as trifluoroacetic or hydrochloric acid or a fluoride source such as tetra n-butylammonium fluoride.

Process (d) may be performed using conventional interconversion procedures such as epimerisation, oxidation, reduction, alkylation, aromatic substitution, ester hydrolysis, amide bond formation or removal and sulphonylation. An example of such an interconversion reaction may include interconversion of a compound of formula (I) wherein R^3 represents a C_{2-6} alkenyl containing group to a corresponding compound of formula (I) wherein R^3 represents a C_{1-6} alkyl containing group, using standard hydrogenation or reductive conditions. A further example of such an interconversion reaction may include interconversion of a compound of formula (I) wherein R^3 represents - C_{1-6} alkyl-N_3 to a corresponding compound of formula (I) wherein R^3 represents -C_{1-6} alkyl-NH_2, using standard hydrogenation or reductive conditions. A yet further example of such an interconversion reaction may include interconversion of a compound of formula (I) wherein R^3 represents a nitro group to a corresponding compound of formula (I) wherein R^3 represents NH_2, using standard hydrogenation or reductive conditions.

Compounds of formula (II) or activated and optionally protected derivatives thereof may be prepared in accordance with the following process:



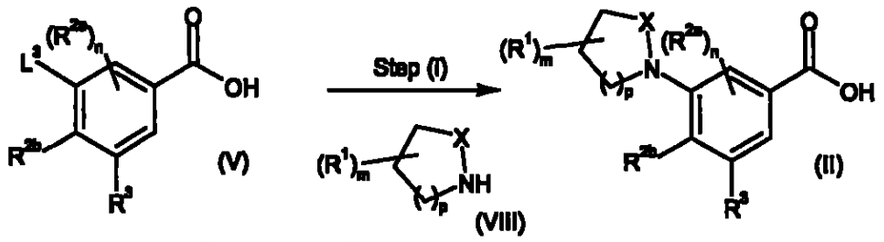
wherein R^{2a}, n, R^{2b}, R^3, p, X, R^1 and m are as defined above and L^1 and L^2 independently represent a suitable leaving group such as a halogen atom (eg. iodine, chlorine or bromine).

Step (I) typically comprises the use of a suitable solvent such as dichloromethane and a suitable base such as triethylamine.

Step (II) typically comprises the use of sodium hydride in the presence of a suitable solvent such as tetrahydrofuran under nitrogen.

2L

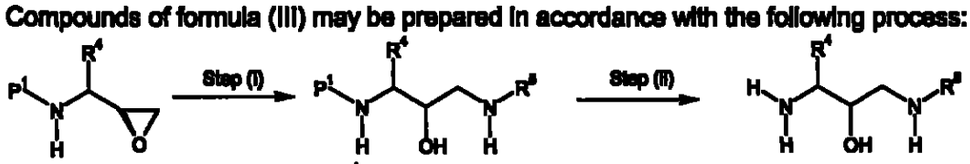
Compounds of formula (II) or activated and optionally protected derivatives thereof may also be prepared in accordance with the following process:



wherein R^{2a}, n, R^{2b}, R^3, p, X, R^1 and m are as defined above and L^3 represents a suitable leaving group such as a halogen atom (eg. iodine, chlorine or bromine).

Step (i) typically comprises the use of caesium carbonate, 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene and a suitable catalyst such as tris(dibenzylideneacetone)dipalladium(0) under suitable conditions such as reflux under argon in the presence of a suitable solvent such as dioxan.

Compounds of formula (III) may be prepared in accordance with the following process:

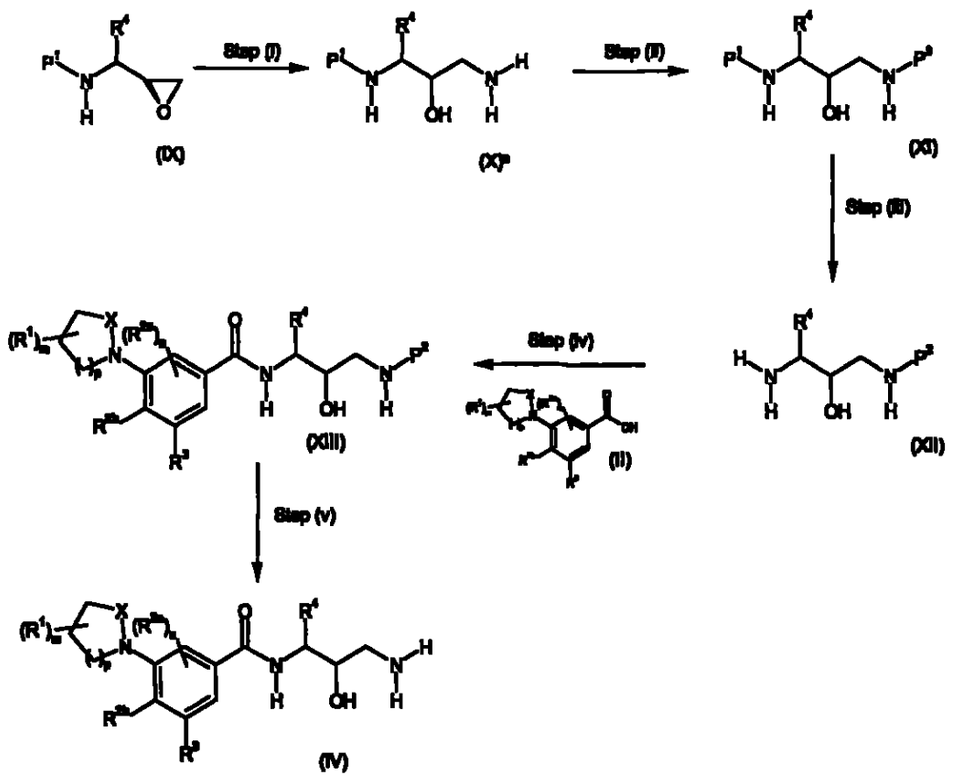


wherein R^4 and R^5 are as defined above and P^1 represents a suitable amine protecting group, such as t-butoxycarbonyl.

Step (i) typically comprises the reaction of a compound of formula (IX) with a compound of formula NH_2R^5 in the presence of a suitable solvent, e.g. ethanol at a suitable temperature, e.g. reflux.

Step (ii) typically comprises the use of suitable deprotection reactions as described above for process (c), eg. when P^1 represents t-butoxycarbonyl, deprotection typically comprises the use of trifluoroacetic acid in the presence of a suitable solvent, such as dichloromethane at a suitable temperature, e.g. between 0°C and room temperature.

Compounds of formula (IV) may be prepared in accordance with the following process:



wherein R^1, m, X, p, R^{2a}, n, R^{2b}, R^3, R^4 and P^1 are as defined above and P^2 represents a suitable amine protecting group different to P^1, such as -$COOCH_2$-phenyl.

Step (i) typically comprises the reaction of a compound of formula (IX) in aqueous ammonia in the presence of a suitable solvent, e.g. ethanol at a suitable temperature, e.g. reflux.

When P^2 represents -$COOCH_2$-phenyl, step (ii) typically comprises the use of $ClCOOCH_2$-phenyl in the presence of a suitable base, e.g. triethylamine, a suitable solvent, e.g. dimethylformamide at a suitable temperature, e.g. between 0°C and room temperature.

Step (iii) typically comprises the use of suitable deprotection reactions as described above for process (c), eg. when P^1 represents t-butoxycarbonyl, deprotection typically comprises the use of trifluoroacetic acid in the presence of a suitable solvent, such as dichloromethane at a suitable temperature, e.g. between 0°C and room temperature.

Step (iv) typically comprises reacting a compound of formula (XII) with a compound of formula (II) in the presence of water soluble carbodiimide and HOBT.

Step (iv) typically comprises the use of suitable deprotection reactions as described above for process (c), eg. when P^2 represents -$COOCH_2$-phenyl, deprotection typically comprises the use of a suitable catalyst, eg. palladium in the presence of a suitable solvent, e.g. water and

ethanol and in the presence of a suitable hydrogen source, e.g. ammonium formate at a suitable temperature, eg. 60°C.

Compounds of formula (V) are either commercially available or may be prepared by interconversion of commercially available compounds of formula (V).

Compounds of formula (VI), (VIII) and (IX) are either known or may be prepared in accordance with known procedures.

As a further aspect of the invention there is thus provided a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof for use as a pharmaceutical, particularly in the treatment of patients with diseases characterised by elevated β-amyloid levels or β-amyloid deposits.

According to another aspect of the invention, there is provided the use of a compound of formula (I) or a physiologically acceptable salt or solvate thereof for the manufacture of a medicament for the treatment of patients with diseases characterised by elevated β-amyloid levels or β-amyloid deposits.

In a further or alternative aspect there is provided a method for the treatment of a human or animal subject with diseases characterised by elevated β-amyloid levels or β-amyloid deposits, which method comprises administering to said human or animal subject an effective amount of a compound of formula (I) or a physiologically acceptable salt or solvate thereof.

As a further aspect of the invention there is thus provided a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof for use in the treatment of diseases characterised by elevated β-amyloid levels or β-amyloid deposits.

It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of diseases characterised by elevated β-amyloid levels or β-amyloid deposits.

The compounds according to the invention may be formulated for administration in any convenient way, and the invention therefore also includes within its scope pharmaceutical compositions for use in the therapy of diseases characterised by elevated β-amyloid levels or β-amyloid deposits, comprising a compound of formula (I) or a physiologically acceptable salt or solvate thereof together, if desirable, with one or more physiologically acceptable diluents or carriers.

It will be appreciated that diseases characterised by elevated β-amyloid levels or β-amyloid deposits include Alzheimer's disease, mild cognitive impairment, Down's syndrome, hereditary cerebral haemorrhage with β-amyloidosis of the Dutch type, cerebral β-amyloid angiopathy

and various types of degenerative dementias, such as those associated with Parkinson's disease, progressive supranuclear palsy, cortical basal degeneration and diffuse Lewis body type of Alzheimer's disease.

Most preferably, the disease characterised by elevated β-amyloid levels or β-amyloid deposits is Alzheimer's disease.

There is also provided a process for preparing such a pharmaceutical formulation which comprises mixing the ingredients.

Compounds of formula (I) may be used in combination with other therapeutic agents. Suitable examples of such other therapeutic agents may be acetylcholine esterase inhibitors (such as tetrahydroaminoacridine, donepezil hydrochloride and rivastigmine), gamma secretase inhibitors, anti-inflammatory agents (such as cyclooxygenase II inhibitors), antioxidants (such as Vitamin E and ginkolidesor), statins or p-glycoprotein (P-gp) inhibitors (such as cyclosporin A, verapamil, tamoxifen, quinidine, Vitamin E-TGPS, ritonavir, megestrol acetate, progesterone, rapamycin, 10,11-methanodibenzosuberane, phenothiazines, acridine derivatives such as GF120918, FK506, VX-710, LY335979, PSC-833, GF-102 and 918).

When the compounds are used in combination with other therapeutic agents, the compounds may be administered either sequentially or simultaneously by any convenient route.

The compounds according to the invention may, for example, be formulated for oral, inhaled, intranasal, buccal, enteral, parenteral, topical, sublingual, intrathecal or rectal administration, preferably for oral administration.

Tablets and capsules for oral administration may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch, cellulose or polyvinyl pyrrolidone; fillers, for example, lactose, microcrystalline cellulose, sugar, maize- starch, calcium phosphate or sorbitol; lubricants, for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica; disintegrants, for example, potato starch, croscarmellose sodium or sodium starch glycollate; or wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxymethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example, lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; or preservatives, for example, methyl or propyl p- hydroxybenzoates or sorbic acid. The

preparations may also contain buffer salts, flavouring, colouring and/or sweetening agents (e.g. mannitol) as appropriate.
For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds may also be formulated as suppositories, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

The compounds according to the invention may also be formulated for parenteral administration by bolus injection or continuous infusion and may be presented in unit dose form, for instance as ampoules, vials, small volume infusions or pre-filled syringes, or in multi-dose containers with an added preservative. The compositions may take such forms as solutions, suspensions, or emulsions in aqueous or non-aqueous vehicles, and may contain formulatory agents such as anti-oxidants, buffers, antimicrobial agents and/or tonicity adjusting agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use. The dry solid presentation may be prepared by filling a sterile powder aseptically into individual sterile containers or by filling a sterile solution aseptically into each container and freeze-drying.

When the compounds of the invention are administered topically they may be presented as a cream, ointment or patch.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 3000 mg; and such unit doses may be administered more than once a day, for example one, two, three or four times per day (preferably once or twice); and such therapy may extend for a number of weeks, months or years.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

Examples

Preparation of intermediates

Description 1

3-Amino-5-nitro-benzoic acid methyl ester (D1)

To a solution of 3-amino-5-nitro-benzoic acid (65 g, 357 mmol, 1 equiv) in MeOH (650 ml) at 0°C was added $SOCl_2$ dropwise (39 ml, 536 mmol, 1.5 equiv). The resulting solution was

allowed to warm to room temperature and stirred for 16 h. A further portion of $SOCl_2$ (10 ml, 137 mmol, 0.4 equiv) was added dropwise and the solution was stirred at room temperature for 5 h, at 50°C for 2 h and then cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in AcOEt and the organic phase washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo*. The solid residue was triturated with AcOEt/*iso*-hexane to give 3-amino-5-nitro-benzoic acid methyl ester (D1) (55 g, 78%) as a pale yellow solid.

Description 2

3-(4-Chloro-butanoylamino)-5-nitro-benzoic acid methyl ester (D2)

To a solution of 3-amino-5-nitro-benzoic acid methyl ester (D1) (38 g, 194 mmol, 1 equiv) in CH_2Cl_2 (350 ml) was added NEt_3 (32 ml , 230 mmol, 1.2 equiv) followed by 4-chlorobutyryl chloride (24.7 ml, 220 mmol, 1.13 equiv) dropwise over 20 mn. The resulting mixture was allowed to warm to room temperature and stirred for 30 min. The organic phase was then washed with 2N aqueous HCl solution, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with *iso*-hexane and Et_2O to give 3-(4-chloro-butanoylamino)-5-nitro-benzoic acid methyl ester D2 (56 g, 96%) as a brown solid.

Description 3

3-(5-Chloro-pentanoylamino)-5-nitro-benzoic acid methyl ester (D3)

5-Chlorovaleryl chloride (2.64 g, 17 mmol, 1.1 equiv) in CH_2Cl_2 (5 ml) was added over 2 min to a stirred solution of 3-amino-5-nitro-benzoic acid methyl ester (D1) (3 g, 15.3 mmol, 1 equiv) and NEt_3 (2.6 ml, 18 mmol, 1.2 equiv) in CH_2Cl_2 (30 ml). The resulting mixture was stirred for 1 h at room temperature then washed with 2N aqueous HCl solution, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with CH_2Cl_2 to give 3-(5-Chloro-pentanoylamino)-5-nitro-benzoic acid methyl ester D3 (6g, 112%) as a brown oil.

Description 4a

3-Amino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D4a)

A flask was charged with 3-nitro-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B27) (5 g, 19 mmol, 1 equiv), 10% palladium on charcoal (50% wet, 750 mg, 7.5% w/w), NH_4COOH (11.9 g, 190 mmol, 10 equiv) H_2O (30 ml) and MeOH (60 ml). The resulting mixture was stirred at 50°C for 1.5 h, cooled to room temperature and the catalyst was filtered off through a pad of celite. Most of the MeOH was removed *in vacuo* and the residue diluted with saturated aqueous $NaHCO_3$ solution. The aqueous phase was extracted twice with AcOEt. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give an off white solid. The catalyst was then washed three times with DMF and the combined organic phases concentrated *in vacuo*. The residue was combined with the material obtained previously and was triturated with Et_2O to give amino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D4a) (3.9 g, 88%) as a white solid which was used in the next step without further purification.

Description 4a (Alternative Procedure)

3-Amino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D4a)

To a solution of 3-amino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (D6) (2.2 g, 10 mmol, 1 equiv) in MeOH/Et_2O (1:1, 20 ml) was added 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (2.3 g, 12 mmol, 1.2 equiv) , DMAP (112 mg, 1 mmol, 0.1 equiv) and the resulting mixture was stirred at room temperature for 16 h then diluted with AcOEt. The organic phase was washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with Et_2O to give 3-amino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D4a) (1.6 g, 68%) as a white solid.

Description 4b

3-Amino-5-(2-oxo-piperidin-1-yl)-benzoic acid methyl ester (D4b)

Description 4b was prepared in an analogous manner to Description 4a from 3-nitro-5-(2-oxo-piperidin-1-yl)-benzoic acid methyl ester (B82).

Description 5

3-Bromo-5-nitro-benzoic acid (D5)

To a solution of 3-amino-5-nitro-benzoic acid (17.6 g, 96.6 mmol, 1 equiv) in 48% aqueous HBr solution (180 ml) at 0°C was added portionwise $NaNO_2$ (8.67 g, 126 mmol, 1.3 equiv) over 20 min. The temperature was kept below 8°C during this addition. The resulting mixture was then added to a suspension of CuBr (9.7 g, 67.6 mmol, 0.7 equiv) in 48% aqueous HBr solution (50 ml) at 65°C over 40 min. The temperature was kept above 60°C during the addition. The resulting mixture was stirred at 70°C for 45 min, cooled to room temperature and diluted with 1L of water. The aqueous phase was extracted three times with Et_2O. The combined organic layers were washed twice with H_2O, dried over $MgSO_4$ and concentrated *in vacuo* to give 3-bromo-5-nitro-benzoic acid (D5) (21 g, 88%) as a brown solid. $[M-H]^-$ = 245.7, RT = 2.82 min

Description 6

3-Amino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (D6)

To a solution of 3-nitro-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A27) (4 g, 16 mmol, 1 equiv) in MeOH/H_2O (9:1, 40 ml) was added 10% palladium on charcoal (50% wet, 800 mg, 0.1 equiv w/w). The resulting mixture was stirred for 6 h at atmospheric pressure under an atmosphere of hydrogen. The catalyst was removed by filtration through a pad of celite and the solvent was removed *in vacuo*. The residue was dried at 60°C under vacuum for 16 h to give 3-amino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (D6) (3.34 g, 15.2 mmol, 95%) as a pale brown solid. $[M-H]^-$ = 218.8, RT = 1.86 min

Description 7

3-Bromo-5-iodo-benzoic acid (D7)

Description 7 is commercially available from Avocado Research Chemicals Ltd.

Description 8a

3-Bromo-5-iodo-benzoic acid methyl ester (D8a)

To a solution of 3-bromo-5-iodo-benzoic acid (D7) (14.6 g, 44.7 mmol, 1 equiv) in MeOH (150 ml) at 0°C was added $SOCl_2$ (3.9 ml, 53.6 mmol, 1.2 equiv). The resulting solution was refluxed for 2 h, cooled to room temperature and concentrated *in vacuo*. The residue was diluted with AcOEt and washed twice with 2N aqueous NaOH solution then brine, dried over $MgSO_4$ and concentrated *in vacuo* to give 3-bromo-5-iodo-benzoic acid methyl ester (D8a) (14.8 g, 97%) as a pale brown solid.

Description 8b

3-Bromo-5-iodo-benzoic acid *tert*-butyl ester (D8b)

To a solution of 3-bromo-5-iodo-benzoic acid (D7) (50 g, 153 mmol, 1 equiv) in CH_2Cl_2 (500 ml) was added 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (30.8 g, 160 mmol, 1.05 equiv), DMAP (14 g, 114 mmol, 0.75 equiv) and *tert*-butanol (90 ml, 917 mmol, 6 equiv). The resulting mixture was stirred at room temperature for 48 h. DMAP (4.67 g, 38 mmol, 0.25 equiv) was then added and the solution was stirred for another 24 h then concentrated *in vacuo*. The residue was dissolved in AcOEt and washed sequentially with 2N aqueous HCl solution, 1N aqueous NaOH solution and brine, dried over $MgSO_4$ and concentrated *in vacuo* to give 3-bromo-5-iodo-benzoic acid *tert*-butyl ester (D8b) (50.6 g, 86%) as a brown solid.

Description 8b (Alternative Procedure)

3-Bromo-5-iodo-benzoic acid *tert*-butyl ester (D8b)

To a solution of 3-bromo-5-iodo-benzoic acid (D7) (50 g, 153 mmol, 1 equiv) in CH_2Cl_2 (500 ml) was added 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (30.8 g, 160 mmol, 1.05 equiv), DMAP (14 g, 114 mmol, 0.75 equiv) and *tert*-butanol (90 ml, 917 mmol, 6 equiv). The resulting mixture was stirred at room temperature for 48 h then DMAP (4.67 g, 38 mmol, 0.25 equiv) was added, and the solution was stirred for another 24 h then concentrated *in vacuo*. The residue was diluted with AcOEt and washed sequentially with 2N aqueous HCl solution, 1N aqueous NaOH solution and brine, dried over $MgSO_4$ and concentrated *in vacuo* to give 3-bromo-5-iodo-benzoic acid *tert*-butyl ester (D8b) (50.6 g, 86%) as a brown solid.

Description 9a

3-Bromo-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester D9a

A flask was charged under nitrogen with 3-bromo-5-iodo-benzoic acid methyl ester (D8a) (14.8 g, 43.4 mmol, 1 equiv) , Cs_2CO_3 (21 g, 65 mmol, 1.5 equiv), tris(dibenzylideneacetone)dipalladium(0) (794 mg, 0.87 mmol, 0.02 equiv), Xantphos (1.5 g, 2.6 mmol, 0.06 equiv) and dioxan (150 ml). Pyrrolidin-2-one (5 ml, 5.54 mmol, 1.5 equiv) was then added *via syringe* and the resulting mixture was stirred at 55°C for 5 days then cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between H_2O and AcOEt and the aqueous phase was re-extracted with AcOEt. The combined organic solutions were dried over $MgSO_4$ and concentrated *in vacuo* to give a solid residue. Purification of the residue by flash chromatography on silica gel (*Iso*-hexane/AcOEt : 4/1 to 1/1) gave 3-bromo-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D9a) (6.4 g, 50%) as a white solid. $[M+H]^+$ = 299.9, RT = 2.95 min

Description 9a (Alternative Procedure)

3-Bromo-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D9a)

To a solution of 3-bromo-5-(4-chloro-butanoylamino)-benzoic acid methyl ester (D13) (530 mg, 1.6 mmol, 1 equiv) in THF (5 ml) at room temperature was added NaH (60% in mineral oil, 64 mg, 1.7 mmol, 1.1 equiv) and the resulting mixture was stirred at room temperature for 2 h. H_2O was then added and the resulting mixture was diluted with AcOEt. The two layers were separated and the organic phase dried over $MgSO_4$ and concentrated *in vacuo* to give 3-bromo-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D9a) (361 mg, 76%) as a yellow solid. $[M-H]^-$ = 296.3, RT = 2.49.

Description 9b

3-Bromo-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid *tert*-butyl ester (D9b)

A flask was charged under nitrogen with bromo-5-iodo-benzoic acid *tert*-butyl ester (D8b) (11.5 g, 30 mmol, 1 equiv), Cs_2CO_3 (13.7 g, 42 mmol, 1.5 equiv), tris(dibenzylideneacetone)dipalladium(0) (549 mg, 0.6 mmol, 0.02 equiv), Xantphos (1.04 g, 1.8 mmol, 0.06 equiv) and dioxan (100 ml). Pyrrolidin-2-one (2.5 ml, 33 mmol, 1.1 equiv) was then added *via syringe* and the resulting mixture was stirred at 60°C for 60 h then cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between H_2O and AcOEt and the aqueous phase re-extracted with AcOEt. The combined organic solutions were dried over $MgSO_4$ and concentrated *in vacuo* to give a solid residue which was triturated with Et_2O to give 3-bromo-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid *tert*-butyl ester (D9b) (6.63 g, 65%) as an off white solid. The filtrate was concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt : 4/1 to 1/1) gave a further 1.46g (14%) of 3-bromo-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid *tert*-butyl ester (D9b) as a white solid. $[M+H-tBu)]^+$ = 285.9, RT = 3.46 min

Description 10

3-Bromo-5-(2-oxo-piperidin-1-yl)-benzoic acid *tert*-butyl ester (D10)

A flask was charged under nitrogen with 3-bromo-5-iodo-benzoic acid *tert*-butyl ester (D8b) (6.42 g, 16.7 mmol, 1 equiv), Cs_2CO_3 (7.6 g, 23.4 mmol, 1.4 equiv), tris(dibenzylideneacetone)dipalladium(0) (307 mg, 0.33 mmol, 0.02 equiv), Xantphos (578 mg, 1 mmol, 0.06 equiv) and dioxan (120 ml). δ-Valerolactam (1.9 ml, 20 mmol, 1.2 equiv) was then added *via syringe* and the resulting mixture was stirred at 60°C for 40 h then cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between H_2O and AcOEt and the aqueous phase was re-extracted with AcOEt. The combined organic solutions were dried over $MgSO_4$ and concentrated *in vacuo* Purification by flash chromatography on silica gel (*iso*-hexane/AcOEt : 3/1 to 1/1) gave 3-bromo-5-(2-oxo-piperidin-1-yl)-benzoic acid *tert*-butyl ester (D10) (4 g, 68%) as a white solid. RT = 2.88 min

Description 11

3-Bromo-5-nitro-benzoic acid methyl ester (D11)

30

To a solution of 3-bromo-5-nitro-benzoic acid (D5) (22.3 g, 90.6 mmol, 1 equiv) in MeOH (300 ml) at 0°C was added $SOCl_2$ (7.9 ml, 108 mmol, 1.2 equiv) dropwise. The resulting solution was stirred at reflux for 4 hours then cooled to room temperature and concentrated *in vacuo*. The residue was diluted with AcOEt, washed twice with 2N aqueous NaOH solution and once with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give 3-bromo-5-nitro-benzoic acid methyl ester (D11) (22.1 g, 94%) as a pale brown solid. RT = 3.18 min

Description 11 (Alternative Procedure)
3-Bromo-5-nitro-benzoic acid methyl ester (D11)

To an ice cold solution of 3-bromo-5-nitro-benzoic acid (D5) (2.5 g, 10 mmol, 1 equiv) in MeOH (25 ml) was added $SOCl_2$ (1 ml, 15 mmol, 1.5 equiv) dropwise. The resulting solution was allowed to warm to room temperature and was then stirred at 60°C for 3 h, cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in AcOEt and the organic layer was washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo* to give 3-bromo-5-nitro-benzoic acid methyl ester (D11) (2.6 g, 100%) as a yellow solid. RT = 3.22 min

Description 12
3-Amino-5-bromo-benzoic acid methyl ester (D12)

To a solution of 3-bromo-5-nitro-benzoic acid methyl ester (D11) (12.1 g, 46.5 mmol, 1 equiv) in MeOH (200 ml) was added $SnCl_2$ (44 g, 233 mmol, 5 equiv). The resulting mixture was stirred at reflux for 4 h, cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between ice-cold AcOEt and H_2O. The aqueous phase was basified with 2N aqueous NaOH solution until a white precipitate appeared, then slowly with 12.5N aqueous NaOH solution until this precipitate disappeared. The temperature was kept below 10°C during this addition. The two layers were separated and the aqueous phase extracted with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give 3-amino-5-bromo-benzoic acid methyl ester (D12) (9.9 g, 93%) as a brown solid.

Description 13
3-bromo-5-(4-chloro-butanoylamino)-benzoic acid methyl ester (D13)

To a solution of 3-amino-5-bromo-benzoic acid methyl ester (D12) (460 mg, 2.0 mmol, 1 equiv) in CH_2Cl_2 (10 ml) at room temperature was added NEt_3 (306 µl, 2.2 mmol, 1.1 equiv) then 4-chlorobutyrylchloride (247 µl, 2.2 mmol, 1.1 equiv). The resulting mixture was stirred at room temperature for 16 h and then diluted with AcOEt. The organic phase was washed with 2N aqueous HCl solution, dried over $MgSO_4$ and concentrated *in vacuo* to give 3-bromo-5-(4-chloro-butanoylamino)-benzoic acid methyl ester (D13) (530 mg, 79 %) as a pale yellow oil. RT = 2.88 s

Description 14
3-(3-Chloro-propane-1-sulfonylamino)-5-nitro-benzoic acid methyl ester (D14)

3L

To a solution of 3-amino-5-nitro-benzoic acid methyl ester (D1) (45 g, 229 mmol, 1 equiv) in CH_2Cl_2 (450 ml) was added pyridine (18.5 ml, 229 mmol, 1 equiv), DMAP (100 mg, 0.8 mmol, catalytic) and 3-chloropropanesulfonyl chloride (28 ml, 230 mmol, 1 equiv). The resulting mixture was stirred for 40 h then diluted with AcOEt. The organic phase was diluted with 2N aqueous HCl solution. The resulting solid was filtered to give 3-(3-chloro-propane-1-sulfonylamino)-5-nitro-benzoic acid methyl ester (23 g, 32%). The filtrate was separated and the organic phase was washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with AcOEt and *iso*-hexane to give a further 50 g (65%) of 3-(3-chloro-propane-1-sulfonylamino)-5-nitro-benzoic acid methyl ester (D14) as a pale brown solid. $[M-H]^-$ = 334.9, RT = 3.11 min

Description 15

3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-nitro-benzoic acid methyl ester (D15)

To a solution of 3-(3-chloro-propane-1-sulfonylamino)-5-nitro-benzoic acid methyl ester (D14) (73g, 217 mmol, 1 equiv) in EtOH (600 ml) was added Et_3N (60 ml, 430 mmol, 2 equiv) and the resulting mixture was refluxed for 3 h, cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in AcOEt, washed with 2N aqueous HCl solution, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with *iso*-hexane and AcOEt to give 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-nitro-benzoic acid methyl ester (D15) (58 g, 88%) as a pale brown solid. $[M+H+NH_3]^+$ = 318.0, RT = 2.78 min

Description 15 (Alternative Procedure)

3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-nitro-benzoic acid methyl ester (D15)

A 50 ml flask was charged under nitrogen with 3-bromo-5-nitro-benzoic acid methyl ester (D11) (1 g, 3.8 mmol, 1 equiv), Cs_2CO_3 (536 mg, 4.4 mmol, 1.2 equiv) tris(dibenzylideneacetone)dipalladium(0) (5 mg, 0.0055 mmol, 0.0154 equiv), Xantphos (10 mg, 0.014 mmol, 0.04 equiv) and toluene (15 ml). Isothiazolidine 1,1-dioxide (D22a) (536 mg, 4.4 mmol, 1.1 equiv) was then added and the resulting mixture was stirred at 90°C for 16 hours then cooled to room temperature and diluted with H_2O and AcOEt. The layers were separated, the aqueous phase diluted with a saturated aqueous $NaHCO_3$ solution and extracted with AcOEt. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-nitro-benzoic acid methyl ester (D15) (187 mg, 16%) as a yellow solid. $[M+H+NH_3]^+$ = 318.0,
RT = 2.81 min

Description 16

3-Amino-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid methyl ester (D16)

A flask was charged with 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-nitro-benzoic acid methyl ester (D15) (25 g, 83 mmol, 1 equiv) and 10% palladium (0) on charcoal (50% wet, 5 g, 10% w/w) and EtOH (500 ml). The resulting suspension was stirred under an atmosphere of hydrogen (atmospheric pressure) for 4 h and the catalyst was filtered off through a pad of celite. The catalyst was washed three times with DMF and the combined organic layers were concentrated *in vacuo*. The residue was dissolved in AcOEt and filtered again through celite

In order to remove residual catalyst. The organic phase was concentrated *in vacuo*. The residue was triturated with Et_2O to give 3-amino-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid methyl ester (D16) (18 g, 80%) as a pale brown solid. $[M+H]^+$ = 271.0, RT = 2.16 min

Description 17

3-Bromo-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid *tert*-butyl ester (D17)

A flask was charged under nitrogen with 3-bromo-5-iodo-benzoic acid *tert*-butyl ester D8b (1 g, 2.6 mmol, 1 equiv), Cs_2CO_3 (1.26 g, 3.9 mmol, 1.5 equiv), tris(dibenzylideneacetone)dipalladium(0) (12 mg, 0.013 mmol, 0.005 equiv), Xantphos (22 mg, 0.038 mmol, 0.015 equiv) and toluene (20 ml). Isothiazolidine 1,1-dioxide (D22a) (350 mg, 2.9 mmol, 1.1 equiv) was then added and the resulting mixture was stirred at 100°C for 16 h then cooled to room temperature and diluted with AcOEt. The organic phase was washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with Et_2O to give 3-bromo-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid *tert*-butyl ester (D17) (350 mg 38%) as a white solid.

Description 18

3-bromo-5-(1,1-dioxo-1λ^6-[1,2]thiazinan-2-yl)-benzoic acid *tert*-butyl ester (D18)

Description 18 was prepared in an analogous manner to Description 17b from 3-bromo-5-iodo-benzoic acid *tert*-butyl ester (D8b) (5.2 g, 13.6 mmol) and [1,2] thiazinane 1,1-dioxide (D22b) which gave the title compound (D18) (1.8 g, 34%) as a pale yellow solid.
$[M+H\text{-}tert\text{-}Bu]^+$ = 335.9, RT = 3.26 min

Description 19

3-Bromo-5-(3-chloro-propane-1-sulfonylamino)-benzoic acid methyl ester (D19)

To a solution of 3-amino-5-bromo-benzoic acid methyl ester (D12) (2.3 g, 10 mmol, 1 equiv) in CH_2Cl_2 (30 ml) was added pyridine (1.6 ml, 20 mmol, 2 equiv), DMAP (320 mg, 2.5 mmol, 2.5 equiv) and 3-chlorosulphonyl chloride (1.46 ml, 12 mmol, 1.2 equiv) dropwise. The resulting mixture was stirred at room temperature for 16 h then concentrated *in vacuo*. The residue was dissolved in AcOEt and the organic phase washed sequentially with 2N aqueous HCl solution, saturated aqueous $NaHCO_3$ solution and brine, dried over $MgSO_4$ and concentrated *in vacuo* to give 3-bromo-5-(3-chloro-propane-1-sulfonylamino)-benzoic acid methyl ester (D19) (3.36 g, 91%) as a red solid.
$[M-H]^-$ = 369.9, RT = 3.25 min

Description 20

4-Chloro-1-butanesulfonyl chloride (D20)

To a mixture of [1,2]oxathiane 2,2-dioxide (D23) (50 g, 367 mmol, 1 equiv) and $SOCl_2$ (29 ml, 401 mmol, 1.1 equiv) was added DMF (4 ml, 51.6 mmol, 0.14 equiv). The resulting mixture was stirred under nitrogen at 70°C for 3 days. A second portion of $SOCl_2$ (10 ml, 137 mmol, 0.37 equiv) was added. The mixture was stirred at 70°C for another 3 days and then cooled to room temperature and concentrated *in vacuo*. The residue was diluted with toluene then

concentrated *in vacuo*. This procedure was repeated and the residue was dried under vacuum for 16 h to give crude 4-chloro-1-butanesulfonyl chloride (D20) (63 g, 90%).

Description 21a

3-Chloro-1-propanesulfonamide (D21a)

To an ice-cooled solution of 3-chloro-1-propanesulfonyl chloride (*Chem. Pharm. Bull*, 40(1),75-84,1999) (30 ml, 250 mmol, 1 equiv) in CH_2Cl_2 (150 ml) was slowly added aqueous ammonia solution (32%, 30 ml). The resulting mixture was stirred at room temperature for 16 h and H_2O (20 ml) was added. The layers were separated and the organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to give crude 3-chloro-1-propanesulfonamide (D21a) (27 g, 69%) as a white solid *Chem. Pharm. Bull*, 40(1),75-84,1999].

Description 21b

3-Chloro-1-butanesulfonamide (D21b)

To an ice-cooled solution of 4-chloro-1-butanesulfonyl chloride (D20) (43 g, 225 mmol, 1 equiv) in CH_2Cl_2 (350 ml) was slowly added aqueous ammonia solution (25%, 140 ml). The resulting mixture was stirred at room temperature for 16 h then concentrated *in vacuo*. The residue was diluted with AcOEt and washed with brine. The organic phase was dried over $MgSO_4$ and concentrated *in vacuo* to give crude 3-chloro-1-butanesulfonamide (D21b) (31g, 88%).

Description 22a

Isothiazolidine 1,1-dioxide (D22a)

To a solution of 3-chloro-1-propanesulfonamide (D21a) (27 g, 170 mmol, 1 equiv) in EtOH (250 ml) at room temperature was added NaOEt (11.7 g, 170 mmol, 1 equiv). The resulting mixture was refluxed for 5 h then cooled to room temperature and concentrated *in vacuo*. The residual solid was extracted thoroughly with CH_2Cl_2 and the extracts were concentrated *in vacuo* to give isothiazolidine 1,1-dioxide (D22a) (20 g, 100%).

Description 22b

[1,2] Thiazinane 1,1-dioxide (D22b)

To a solution of 3-chloro-1-butanesulfonamide (D21b) (31 g, 200 mmol, 1 equiv) in EtOH (500 ml) at room temperature was added NaOEt (14.9 g, 220 mmol, 1.1 equiv). The resulting mixture was refluxed for 5 h then cooled to room temperature and concentrated *in vacuo*. The residual solid was extracted thoroughly with CH_2Cl_2 and the extracts were concentrated *in vacuo*. The residual solid was triturated with Et_2O to give [1,2]thiazinane 1,1-dioxide (D22b) (18.7 g, 69%) as a pale brown solid.

Description 23

4-chloro-3,5-dinitrobenzoic acid (D23)

Description 23 is commercially available from Sigma-Aldrich Company.

Description 24

4-Methoxy-3,5-dinitro-benzoic acid (D24)

To a solution of KOH (1.12 g, 20 mmol, 1 equiv) in MeOH (20 ml) at 0°C was added portionwise 4-chloro-3,5-dinitrobenzoic acid (D23) (4.93 g, 20 mmol, 1 equiv). The resulting mixture was refluxed for 1 h then cooled to room temperature. A second portion of KOH (1.12 g, 20 mmol, 1 equiv) was added and the mixture refluxed for 90 min, cooled to room temperature and diluted with H_2O. The aqueous phase was acidified to pH 1 and extracted with AcOEt. The organic phase was dried over $MgSO_4$ and concentrated *in vacuo* to give crude 4-methoxy-3,5-dinitro-benzoic acid (D24) (4.49 g, 93%) as a light brown solid.

Description 25

4-Methoxy-3,5-dinitro-benzoic acid methyl ester (D25)

To a solution of crude 4-methoxy-3,5-dinitro-benzoic acid (D24) (4.43 g, 17.3 mmol, 1 equiv) in MeOH (60 ml) was added concentrated H_2SO_4 (4 ml). The resulting mixture was refluxed for 3 h, cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between H_2O and AcOEt. The two layers were separated and the organic phase was washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography on silica gel (*iso*-hexane/AcOEt : 85/15) gave 4-methoxy-3,5-dinitro-benzoic acid methyl ester (D25) (2.84 g, 65%) as an off white solid.

The following descriptions were prepared in an analogous manner to Description 25 from commercially available starting materials:

Description	Starting material
4-Chloro-3,5-dinitro-benzoic acid methyl ester (D25a)	D24a
3-Amino-4-chloro-benzoic acid methyl ester (D27c)	D26

Description 27a

3,5-Diamino-4-chloro-benzoic acid methyl ester (D27a)

A mixture of 4-chloro-3,5-dinitro-benzoic acid methyl ester (D25a) (2.6 g, 10 mmol, 1 equiv) and $SnCl_2$ (18.95 g, 100 mmol, 10 equiv) in MeOH (80 ml) was refluxed for 1 h, cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between AcOEt and 2N aqueous NaOH solution. The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with 1:1 Et_2O/iso-hexane to give 3,5-diamino-4-chloro-benzoic acid methyl ester (D27a) (1.56 g, 78%) as a light orange solid.

The following Description was prepared in an analogous manner to Description 27a (using 5 equivalents of $SnCl_2$ for nitroaryls and 10 equivalents for bis nitroaryls) from the starting material indicated in the below table:

Description	Starting material
3,5-Diamino-4-methoxy-benzoic acid methyl ester (D27b)	D25b

Description 28c

4-Chloro-3-(4-chloro-butanoylamino)-benzoic acid methyl ester (D28c)

4-Chlorobutyryl chloride (2.82 g, 20 mmol, 2.0 equiv) in CH_2Cl_2 (5 ml) was added over 2 min to a stirred solution of 3-amino-4-chloro-benzoic acid methyl ester (D27c) (1.66 g, 10 mmol, 1 equiv) and NEt_3 (2.22 g, 22 mmol, 2.2 equiv) in CH_2Cl_2 (40 ml). The resulting mixture was stirred for 1 h at room temperature then washed with 2N aqueous HCl solution, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with CH_2Cl_2 to give 4-chloro-3-(4-chloro-butanoylamino)-benzoic acid methyl ester (D28c) (1.81 g, 48%) as a pale pink solid.

The following Descriptions were prepared in an analogous manner to the process described in D28c from the starting material indicated in the below table:

Description	Precursor
4-Chloro-3,5-bis-(4-chloro-butanoylamino)-benzoic acid methyl ester (D28a)	D27a
3,5-Bis-(4-chloro-butanoylamino)-4-methoxy-benzoic acid methyl ester (D28b)	D27b

Description 30

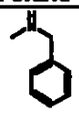
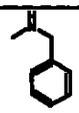
(Benzyl-ethyl-amino)-(2-oxo-pyrrolidin-1-yl)-benzoic acid *tert*-butyl ester (D30)

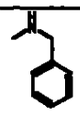
A flask was charged under nitrogen with 3-bromo-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid *tert*-butyl ester (D9b) (4.6 g ,13 mmol, 1 equiv), sodium *tert*-butoxide (1.9 g, 19.5 mmol, 1.5 equiv), tris(dibenzylideneacetone)dipalladium(0) (395 mg, 0.65 mmol, 0.05 equiv), 2-(dicyclohexylphosphino)biphenyl (341 mg, 0.97 mmol, 0.075 equiv) and toluene (100 ml). N-Ethylbenzylamine (2.9 ml, 19.5 mmol, 1.5 equiv) was then added via syringe and the resulting mixture was stirred at 90°C for 2 h then cooled to room temperature, diluted with H_2O and AcOEt. The layers were separated, the aqueous phase diluted with saturated aqueous $NaHCO_3$ solution and extracted with AcOEt. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt : 1/2) gave (benzyl-ethyl-amino)-(2-oxo-pyrrolidin-1-yl)-benzoic acid *tert*-butyl ester (D30) (3 g, 60%) as a white solid.

$[M+H]^+$ = 395.0, RT = 3.70 min.

Descriptions 31-35 (D31-D35)

Descriptions 31-35 were prepared in an analogous manner to D30 from the appropriate aryl bromide and amine starting materials listed in the below table:

Description	Aryl bromide	Amine	$[M+H]^+$	RT (min)
(Benzyl-methyl-amino)-(2-oxo-pyrrolidin-1-yl)-benzoic acid *tert*-butyl ester (D31)	D9b		381.1	3.59
(Benzyl-methyl-amino)-(2-oxo-piperidin-1-yl)-benzoic acid *tert*-butyl ester (D32)	D10		395.2	3.51
(Benzyl-ethyl-amino)-(2-oxo-piperidin-1-yl)-benzoic acid *tert*-butyl ester (D33)	D10			

(Benzyl-methyl-amino)-(1,1-dioxo-1*l*^{6}-isothiazolidin-2-yl)-benzoic acid *tert*-butyl ester (D34)	D17		417.1	3.51
(Benzyl-ethyl-amino)-(1,1-dioxo-1*l*^{6}-[1,2]thiazinan-2-yl)-benzoic acid *tert*-butyl ester (D35)	D18		445.2	3.82

Description 36

3-Hydroxy-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (D36)

To a solution of 3-amino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (D6) (280 mg, 1.25 mmol, 1 equiv) in a mixture of 2N aqueous HCl solution (2.5ml) and MeOH (5ml) at 0 °C was added NaN_3 (190 mg, 2.75 mmol, 2.2 equiv) portionwise over 20 min. H_2O (5ml) was added and the resulting mixture was heated at 90°C for 1 h then cooled to room temperature and diluted with AcOEt. The two layers were separated and the aqueous phase was extracted twice with AcOEt (20 ml). The combined organic layers were washed with brine (20 ml), dried over $MgSO_4$ and concentrated *in vacuo* to give a crude product which was triturated with Et_2O/MeOH to give 3-hydroxy-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (D36) (110 mg, 40%) as a light tan solid.

Description 37

3-Hydroxy-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D37)

3-Hydroxy-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (D36) (400 mg, 1.72 mmol, 1 equiv) was heated at reflux in a mixture of MeOH (20 ml) and concentrated H_2SO_4 (4 drops) for 7 h. The solution was then cooled to room temperature and concentrated *in vacuo* to give of 3-hydroxy-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D37) (300 mg, 74%) as a light brown solid.

Description 37 (Alternative Procedure)

3-Hydroxy-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D37)

3-Amino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D4a) (1.50 g, 6.4 mmol, 1 equiv) was dissolved in a mixture of 2N aqueous HCl solution (25 ml) and MeOH (50 ml) at 0 °C and treated portionwise with NaN_3 (950 mg, 13.8 mmol, 2.2 equiv) over 20 min. H_2O (50ml) was added and the resulting mixture was heated at 90 °C for 45 min then cooled to room temperature and diluted with Et_2O (300 ml). The two layers were separated and the organic phase was dried over $MgSO_4$ and concentrated *in vacuo* to give 3-hydroxy-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D37) (1.0 g, 67%) as a tan solid.

Description 38

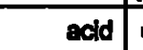
3-(3-Benzyloxy-propoxy)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D38)

A solution of 3-hydroxy-5-(2-oxopyrrolidin-1-yl)-benzoic acid methyl ester (D37) (300 mg, 1.28 mmol, 1 equiv), 3-benzyloxypropan-1-ol (0.28 ml, 1.79 mmol, 1.4 equiv) and triphenyl phosphine (470 mg, 1.79 mmol, 1.4 equiv) in THF (10 ml) at room temperature was treated dropwise with DEAD (0.282 ml, 1.79 mmol, 1.4 equiv). The mixture was stirred for 16 h at

room temperature then concentrated *in vacuo*. Purification by flash chromatography on silica gel (ethyl acetate/iso-hexane : 1/4 to 1/1) gave 3-(3-benzyloxy-propoxy)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D38).

Description 39

Description 39 was prepared in an analogous manner to Description 38 from Description 37 using the appropriate alcohol indicated in the table below:

Description	Alcohol
3-(2-Benzyloxy-ethoxy)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D39)	

Description 40

3-(2-benzyloxy-ethoxy)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (D40)

Description 40 was prepared by saponification of Description 39 in accordance with known procedures.

Description 41

3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-hydroxy-benzoic acid methyl ester (D41)

1-[3-Amino-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-phenyl]-propan-1-one (D16) (1.0 g, 3.7 mmol, 1 equiv) dissolved in a mixture of 2N aqueous HCl solution (15 ml) and MeOH (30 ml) was stirred at 0 °C and treated portionwise with sodium nitrite (550 mg, 8.0 mmol, 2.2 equiv) over 20 min. H_2O (50 ml) was added and the resulting mixture was heated at 90 °C for 45 min, cooled, and diluted with Et_2O (300 ml) The two layers were separated and the organic phase dried over $MgSO_4$ and concentrated *in vacuo* to give crude 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-hydroxy-benzoic acid methyl ester (D41) (800 mg, 80%) as a brown oil.

Description 41 (Alternative Procedure)

3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-hydroxy-benzoic acid methyl ester (D41)

A mixture of 3-benzyloxy-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid methyl ester (D54) (4.5 g, 12.5 mmol, 1 equiv), NH_4COOH (7.7 g, 125 mmol, 10 equiv) and 10% Pd on charcoal (50% wet, 1.0g, 11% w/w) in MeOH (150ml) and H_2O (10 ml) was heated at 50 °C for 2 h. The cooled reaction mixture was filtered through a pad of celite and concentrated *in vacuo*. H_2O (100 ml) was added to the filtrate which was then extracted with AcOEt (150 ml). The organic solution was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was crystallised from Et_2O to yield of 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-hydroxy-benzoic acid methyl ester (D41) (2.6 g, 77%) as a white solid.

Description 42

5-hydroxy-isophthalic acid dimethyl ester (D42)

Description 42 is commercially available from Sigma-Aldrich Company.

Description 43

5-Ethoxy-isophthalic acid dimethyl ester (D43)

K_2CO_3 (31.6 g, 223 mmol, 2.23 equiv) and iodoethane (17.8 ml, 230 mmol, 2.3 equiv) were added to a solution of 5-hydroxy-isophthalic acid dimethyl ester (D42) (21 g, 100 mmol, 1 equiv) in acetone (500 ml) at room temperature. The resulting solution was refluxed for 16 h, then cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between H_2O and AcOEt. The aqueous phase was extracted with AcOEt and the combined organic layers were washed with 2N aqueous NaOH solution and brine, dried over $MgSO_4$ and concentrated *in vacuo* to give 5-ethoxy-isophthalic acid dimethyl ester (D43) (23 g, 96%) as a white solid. RT = 3.13 min

Description 44

5-Benzyloxy-isophthalic acid dimethyl ester (D44)

K_2CO_3 (21 g, 153 mmol, 2 equiv) and benzyl bromide (11 ml, 92 mmol, 1.2 equiv) were added to a solution of 5-hydroxy-isophthalic acid dimethyl ester (D42) (16.1g, 76.7 mmol, 1 equiv) in acetone (400 ml) at room temperature. The resulting solution was refluxed for 18 h, cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between H_2O and AcOEt. The aqueous phase was extracted with AcOEt and the combined organic layers were washed with 2N aqueous NaOH solution and brine, dried over $MgSO_4$ and concentrated *in vacuo* to give 5-benzyloxy-isophthalic acid dimethyl ester (D44) (24.2 g, 105%) as a white solid. $[M+H]^+$ = 301.0, RT = 3.50 min

Description 45

5-Ethoxy-isophthalic acid monomethyl ester (D45)

To a solution of 5-ethoxy-isophthalic acid dimethyl ester (D43) (22 g, 92.4 mmol, 1 equiv) in MeOH (440 ml) was added 1N aqueous NaOH solution (87.8 ml, 87.8 mmol, 0.95 equiv) and the resulting solution was stirred at room temperature for 17 h. Most of the MeOH was removed *in vacuo* and the residue was partitioned between AcOEt and 1N aqueous NaOH solution. The aqueous layer was extracted with AcOEt, acidified to pH 1 and re-extracted with AcOEt. The second organic extract was dried over $MgSO_4$ and concentrated *in vacuo* to give 5-ethoxy-isophthalic acid monomethyl ester (D45) (17 g, 82%) as a white solid. $[M+H+NH_3]^+$ = 242.0, RT = 2.79 min

Description 46

5-Benzyloxy-isophthalic acid monomethyl ester (D46)

To a solution of 5-benzyloxy-isophthalic acid dimethyl ester (D44) (24 g, 80 mmol, 1 equiv) in MeOH (300 ml) was added 1N aqueous NaOH solution (76 ml, 76 mmol, 0.95 equiv) and the resulting solution was stirred at room temperature for 17 h. A second portion of 1N aqueous NaOH solution (15 ml, 15 mmol, 0.2 equiv) was added and the solution stirred for another 6 h. Most of the MeOH was removed *in vacuo* and the residue was partitioned between AcOEt and 1N aqueous NaOH solution. The aqueous layer was extracted with AcOEt, acidified to pH 1 and re-extracted with AcOEt. The second organic extract was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with Et_2O to give 5-benzyloxy-isophthalic acid monomethyl ester (D46) (15.5 g, 68%) as a white solid. $[M+H]^+$ = 286.0, RT = 3.32 min

Description 47

3-Benzyloxycarbonylamino-5-ethoxy-benzoic acid methyl ester (D47)

NEt_3 (14.2 ml, 102 mmol, 1.3 equiv) and diphenylphosphoryl azide (22 ml, 102 mmol, 1.3 equiv) were added to a suspension of 5-ethoxy-isophthalic acid monomethyl ester (D45) (17.6 g, 78.6 mmol, 1 equiv) in toluene (250 ml) and the mixture heated at 80°C for 3 h. Benzyl alcohol (12 ml, 118 mmol, 1.5 equiv) was added and the resulting mixture was refluxed for 4 h, cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in AcOEt (300 ml) and the resulting solution was washed with 2N aqueous HCl solution (100 ml) followed by saturated aqueous $NaHCO_3$ solution (100 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with Et_2O to give 3-benzyloxycarbonylamino-5-ethoxy-benzoic acid methyl ester (D47) (15 g, 62%) as a white solid. $[M-H]^-$ = 328.1, RT = 3.46 min

Description 48

3-Benzyloxy-5-(2-trimethylsilanyl-ethoxycarbonylamino)-benzoic acid methyl ester (D48)

NEt_3 (8.2 g, 81 mmol, 1.5 equiv) and diphenylphosphoryl azide (22.3 g, 81 mmol, 1.5 equiv) were added to a suspension of 5-benzyloxy-isophthalic acid monomethyl ester (D46) (15.5 g, 54.2 mmol, 1 equiv) in toluene (120 ml) and the resulting mixture heated at 80°C for 3 h. 2-Trimethylsilylethanol (12.7 g, 108 mmol, 2 equiv) was added and the resulting mixture was refluxed for 4 h, cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in EtOAc (300 ml) and the resulting solution was washed with 2N aqueous HCl solution (100 ml) followed by saturated aqueous $NaHCO_3$ solution (100 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with Et_2O and *iso*-hexane to give 3-benzyloxy-5-(2-trimethylsilanyl-ethoxycarbonylamino)-benzoic acid methyl ester (D48) (8.5 g, 40%) as a white solid.

Description 49

3-Amino-5-ethoxy-benzoic acid methyl ester (D49)

A mixture of 3-benzyloxycarbonylamino-5-ethoxy-benzoic acid methyl ester (D47) (15 g, 45.5 mmol, 1 equiv), 10% palladium on charcoal (50% wet, 1.5 g, 5% w/w) and NH_4COOH (15 g, 455 mmol, 10 equiv) H_2O (50 ml) and MeOH (200 ml) was stirred at 50°C for 2h. The mixture was cooled to room temperature and the catalyst was filtered off through a pad of celite. Most of the MeOH was removed *in vacuo* and the residue was partitioned between saturated aqueous $NaHCO_3$ solution and AcOEt. The aqueous phase was re-extracted with AcOEt. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give 3-amino-5-ethoxy-benzoic acid methyl ester (D49) (8.6 g, 99%) as a pale green solid which was used in the next step without further purification. $[M+H]^+$ = 196.1, RT = 2.49 min

Description 50

3-Amino-5-benzyloxy-benzoic acid methyl ester hydrochloride (D50)

3-Benzyloxy-5-(2-trimethylsilanyl-ethoxycarbonylamino)-benzoic acid methyl ester (D48) (8.5 g, 21.2 mmol, 1 equiv) in THF (40 ml) was treated with 1M tetrabutyl ammonium fluoride in

THF (40 ml, 40 mmol, 1.9 equiv) and the resulting solution stirred at room temperature for 16 h then concentrated *in vacuo*. The residue was dissolved in AcOEt (200 ml) and washed with H_2O (200 ml) then dried over $MgSO_4$ and concentrated *in vacuo*. The residue was redissolved in Et_2O/EtOAc and treated with 2N HCl in Et_2O to give, after filtration, 3-amino-5-benzyloxy-benzoic acid methyl ester hydrochloride (D50) (5.0 g, 80%) as a white solid.

Description 51

3-(4-Chloro-butanoylamino)-5-ethoxy-benzoic acid methyl ester (D51)

3-Amino-5-ethoxy-benzoic acid methyl ester (D49) (4.0 g, 20.5 mmol, 1 equiv) was suspended in CH_2Cl_2 (40 ml) and treated at room temperature with NEt_3 (2.32 g, 23mmol, 1.1 equiv). The resulting solution was cooled to 0°C and 4-chlorobutyryl chloride (3.1 g, 22 mmol, 1.1 equiv) was added dropwise. The resulting mixture was stirred at 0°C for 3 h then allowed to warm to room temperature. The solution was washed with 2N aqueous HCl solution, dried over $MgSO_4$ and concentrated *in vacuo* to give of 3-(4-chloro-butanoylamino)-5-ethoxy-benzoic acid methyl ester (D51) (7.0 g, 115%) as a brown oil.

Description 52

3-Benzyloxy-5-(3-chloro-propane-1-sulfonylamino)-benzoic acid methyl ester (D52)

A suspension of 3-amino-5-benzyloxy-benzoic acid methyl ester hydrochloride (D50) (5.0 g, 17 mmol, 1 equiv) in CH_2Cl_2 (100 ml) was treated with DMAP (400 mg, 3.2 mmol) and pyridine (3.5 g, 44 mmol, 2.6 equiv) followed by 3-chloropropanesulfonyl chloride (3.54 g, 20 mmol, 1.2 equiv) dropwise at room temperature. The resulting mixture was stirred for 16 h then concentrated *in vacuo*. The residue was dissolved in AcOEt (200 ml) and the resulting solution was washed with 2N aqueous HCl solution (100 ml) followed by saturated aqueous $NaHCO_3$ solution (100 ml), dried over $MgSO_4$ and concentrated *in vacuo* to give 3-benzyloxy-5-(3-chloro-propane-1-sulfonylamino)-benzoic acid methyl ester (D52) (6.0 g, 97%) as a pale pink solid. $[M+H]^+$ = 366.1, RT = 2.34 min

Description 53

3-(3-Chloro-propane-1-sulfonylamino)-5-ethoxy-benzoic acid methyl ester (D53)

A suspension of 3-amino-5-ethoxy-benzoic acid methyl ester (D49) (4.0 g, 20.5 mmol, 1 equiv) in CH_2Cl_2 (100 ml) was treated with DMAP (400 mg, 3.2 mmol,) and pyridine (1.74 g, 22 mmol, 1.1 equiv) followed by 3-chloropropanesulfonyl chloride (3.89 g, 22 mmol, 1.1 equiv) dropwise. The resulting mixture was stirred for 16 h then concentrated *in vacuo*. The residue was dissolved in AcOEt (200 ml) and the resulting solution was washed with 2N aqueous HCl solution (100 ml) followed by saturated aqueous $NaHCO_3$ solution (100 ml), then dried over $MgSO_4$ and concentrated *in vacuo* to give 3-(3-chloro-propane-1-sulfonylamino)-5-ethoxy-benzoic acid methyl ester (D53) (6.7 g, 98%) as a pale orange solid.

Description 54

3-Benzyloxy-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid methyl ester (D54)

A solution of 3-benzyloxy-5-(3-chloro-propane-1-sulfonylamino)-benzoic acid methyl ester (D52) (6.0 g, 17 mmol, 1 equiv) in EtOH (80 ml) was treated with NEt_3 (3.4 g, 34 mmol, 2

equiv). The resulting mixture was refluxed for 6 h, cooled to room temperature and concentrated *in vacuo* to give 3-benzyloxy-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid methyl ester (D54) (4.5 g, 74%) as a pale pink solid.

Description 55

5-Dimethylthiocarbamoyloxy-isophthalic acid dimethyl ester (D55)

o a solution of 5-hydroxy-isophthalic acid dimethyl ester (D42) (21 g, 100 mmol, 1 equiv) in DMF (300 ml) at room temperature was added DABCO (14.6 g, 130 mmol, 1.3 equiv) followed by dimethylthiocarbamoyl chloride (14.8 g, 120 mmol, 1.2 equiv). The resulting mixture was stirred at room temperature for 16 h and at 60°C for 2 h, then cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between AcOEt and H_2O and the aqueous phase re-extracted with AcOEt. The combined organic solution was washed sequentially with 5% aqueous citric acid solution, 2N aqueous NaOH solution and brine, then dried over $MgSO_4$ and concentrated *in vacuo* to give 5-dimethylthiocarbamoyloxy-isophthalic acid dimethyl ester (D55) (23.5 g, 79%) as a pale yellow oil. $[M+H]^+$ = 298.0 ,RT = 3.06 min

Description 56

5-Dimethylcarbamoylsulfanyl-isophthalic acid dimethyl ester (D56)

5-Dimethylthiocarbamoyloxy-isophthalic acid dimethyl ester (D55) (15.5 g, 52.2 mmol, 1 equiv) was stirred at 200°C for 24 h under nitrogen then cooled to room temperature. Purification by flash chromatography on silica gel (*iso*-hexane/AcOEt : 4/1 then 3/1) gave 5-dimethylcarbamoylsulfanyl-isophthalic acid dimethyl ester (D56) (7.0 g, 45%) and recovered 5-dimethylthiocarbamoyloxy-isophthalic acid dimethyl ester (D55) (2.77 g, 18%), both as white solids. $[M+H]^+$ = 298.0, RT = 2.92 min

Description 57

5-Dimethylcarbamoylsulfanyl-isophthalic acid monomethyl ester (D57)

To a solution of 5-dimethylcarbamoylsulfanyl-isophthalic acid dimethyl ester (D56) (6 g, 20.2 mmol, 1 equiv) in THF (100 ml) at room temperature was added 2N aqueous NaOH solution (9.6 ml, 19.2 mmol, 0.95 equiv). The resulting mixture was stirred for 11 h and then partitioned between AcOEt and H_2O. The two layers were separated and the aqueous phase extracted with AcOEt. After acidification to pH 1, the aqueous phase was extracted twice with AcOEt. The organic solution was dried over $MgSO_4$ then concentrated *in vacuo* to give 5-dimethylcarbamoylsulfanyl-isophthalic acid monomethyl ester (D57) (4.54 g, 79%) as a white solid.

Description 58

***tert*-Butoxycarbonylamino-dimethylcarbamoylsulfanyl-benzoic acid methyl ester (D58)**

To a solution of crude 5-dimethylcarbamoylsulfanyl-isophthalic acid monomethyl ester (D57) (4.56 g, 16.1 mmol, 1 equiv) in toluene (100 ml) was added triethylamine (6.7 ml, 48 mmol, 3 equiv) and diphenylphosphoryl azide (5.2 ml, 24 mmol, 1.5 equiv). The resulting mixture was stirred under nitrogen at 80°C for 3 h and then *tert*-butanol (4.6 ml, 48 mmol, 3 equiv) was added. The solution was stirred at 80°C for another 16 h then cooled to room temperature and

concentrated *in vacuo*. The crude product was dissolved in AcOEt and the resulting solution washed sequentially with 2N aqueous NaOH solution, 2N aqueous HCl solution and brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography on silica gel (*iso*-hexane/AcOEt : 3/1 to 6/4) gave *tert*-butoxycarbonylamino-dimethylcarbamoylsulfanyl-benzoic acid methyl ester (D58) (2.24 g, 40%) as a white solid.

Description 59

3-*tert*-Butoxycarbonylamino-5-mercapto-benzoic acid (D59)

To a solution of *tert*-butoxycarbonylamino-dimethylcarbamoylsulfanyl-benzoic acid methyl ester (D58) (2.24 g, 6.3 mmol, 1 equiv) in MeOH (30 ml) and H_2O (23 ml) was added 2N aqueous NaOH solution (7 ml, 14mmol, 2.2 equiv). The resulting mixture was refluxed for 3 h and then cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between AcOEt and 1N aqueous NaOH solution. The aqueous phase was acidified to pH 1 and extracted twice with AcOEt. The combined organic solutions were dried over $MgSO_4$ then concentrated *in vacuo* to give 3-*tert*-butoxycarbonylamino-5-mercapto-benzoic acid (D59) (1.54 g, 90%) as a white solid.

Description 60

3-*tert*-Butoxycarbonylamino-5-methylsulfanyl-benzoic acid methyl ester (D60)

To a solution of 3-*tert*-butoxycarbonylamino-5-mercapto-benzoic acid (D59) (0.68 g, 2.52 mmol, 1 equiv) in acetone (15 ml) was added K_2CO_3 (3.5 g, 25.3 mmol, 10 equiv) and iodomethane (473 µl, 7.59 mmol, 3 equiv). The resulting mixture was stirred at 50°C for 2 h, cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between AcOEt and H_2O. The organic layer was washed with H_2O and brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography on silica gel (*iso*-hexane/AcOEt : 85/15) gave 3-*tert*-butoxycarbonylamino-5-methylsulfanyl-benzoic acid methyl ester (D60) (0.47 g, 63%) as a white solid. $[M-H]^-$ = 296.1 ,RT = 3.51 min

Description 61

3-*tert*-Butoxycarbonylamino-5-ethylsulfanyl-benzoic acid ethyl ester (D61)

Description 61 was obtained from 0.68 g (2.53 mmol) of 3-*tert*-butoxycarbonylamino-5-methylsulfanyl-benzoic acid methyl ester (D59) and iodoethane using the procedure described in Description 60, which yielded the title compound (D61) (0.58 g, 71%) as a white solid. $[M-H]^-$ = 324.2, RT = 3.79 min

Description 62

3-Amino-5-methylsulfanyl-benzoic acid methyl ester hydrochloride (D62)

3-*tert*-Butoxycarbonylamino-5-methylsulfanyl-benzoic acid methyl ester (D60) (0.54 g, 1.82 mmol, 1 equiv) was dissolved in dioxan (2 ml) and 4M HCl in dioxan (16 mmol, 4 ml, 8.8 equiv) was added. The solution was stirred at room temperature for 2 h allowing the hydrochloride salt of the amine to precipitate. This precipitate was filtered off, washed with Et_2O and dried giving 3-amino-5-methylsulfanyl-benzoic acid methyl ester hydrochloride (D62) (0.224 g, 52%). $[M+H]^+$ = 198.1, RT = 2.68 min

Description 63

3-Amino-5-ethylsulfanyl-benzoic acid ethyl ester hydrochloride (D63)

Description 63 was prepared from 0.57 g (1.75 mmol) of 3-*tert*-butoxycarbonylamino-5-ethylsulfanyl-benzoic acid ethyl (D61) in an analogous manner to that described in Description 62 which yielded 0.335 g (73%) of 3-amino-5-ethylsulfanyl-benzoic acid ethyl ester hydrochloride (D63) as a white solid. $[M+H]^+$ = 226.1, RT = 3.13 min

Description 64

3-(4-Chloro-butanoylamino)-5-methylsulfanyl-benzoic acid methyl ester (D64)

To a solution of 3-amino-5-methylsulfanyl-benzoic acid methyl ester hydrochloride (D62) (0.13 g, 0.556 mmol, 1 equiv) in dry CH_2Cl_2 (2 ml) at 0°C was added NEt_3 (193 ml, 1.39 mmol, 2.5 equiv) then 4-chlorobutyryl chloride (69 ml, 0.612 mmol, 1.1 equiv), dropwise, over 2 min. The resulting solution was stirred at 0°C for 15 min then at room temperature for 30 min. The solution was then diluted with AcOEt, washed sequentially with 2N aqueous HCl solution, saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4 and concentrated *in vacuo* to give 3-(4-chloro-butanoylamino)-5-methylsulfanyl-benzoic acid methyl ester (D64) (173 mg , 103%) as pale yellow crystals. $[M+H]^+$ = 302.0, RT = 3.20 min

Description 65

3-(4-Chloro-butanoylamino)-5-ethylsulfanyl-benzoic acid ethyl ester (D65)

Description 65 was prepared from 140 mg (0.535 mmol) of 3-amino-5-ethylsulfanyl-benzoic acid ethyl ester hydrochloride (D63) in an analogous manner to that described in Description 64 which yielded 182 mg (103%) of 3-(4-chloro-butanoylamino)-5-ethylsulfanyl-benzoic acid ethyl ester (D65) as pale yellow crystals. $[M+H]^+$ = 330.0, RT = 3.51 min

Description 66

3-(3-Chloro-propane-1-sulfonylamino)-5-methylsulfanyl-benzoic acid methyl ester (D66)

To a solution of 3-amino-5-methylsulfanyl-benzoic acid methyl ester hydrochloride (D62) (130 mg, 0.556 mmol, 1 equiv) in CH_2Cl_2 (2 ml) was added pyridine (142 ml, 1.75 mmol, 3 equiv), DMAP (6.8 mg, 0.056 mmol, 0.1 equiv) and then 3-chloropropane sulfonyl chloride (71 µl, 0.584 mmol, 1.05 equiv) dropwise over 2 min. The resulting mixture was stirred at room temperature for 2 h, diluted with AcOEt, washed sequentially with 2N aqueous HCl solution, saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4 and concentrated *in vacuo* to give 3-(3-chloro-propane-1-sulfonylamino)-5-methylsulfanyl-benzoic acid methyl ester (D66) (196 mg, 104%) as light brown crystals.

$[M-H]^-$ = 336.0 RT = 3.20 min

Description 67

3-(3-Chloro-propane-1-sulfonylamino)-5-ethylsulfanyl-benzoic acid ethyl ester (D67)

Description 67 was prepared from 140 mg (0.6 mmol) of 3-amino-5-ethylsulfanyl-benzoic acid ethyl ester hydrochloride (D63) in an analogous manner to that described in Description 66

which yielded 200 mg (102%) of crude 3-(3-chloro-propane-1-sulfonylamino)-5-ethylsulfanyl-benzoic acid ethyl ester (D67) as light brown crystals.
$[M-H]^-$ = 384.0, RT = 3.49 min

Description 68

3-(2-Oxo-piperidin-1-yl)-5-(E/Z)-propenyl-benzoic acid *tert*-butyl ester (D68)

To a solution of 3-bromo-5-(2-oxo-piperidin-1-yl)-benzoic acid *tert*-butyl ester (D10) (500 mg, 1.4 mmol, 1 equiv) in DME (14 ml) and H_2O (4 ml) was added tetrakis(triphenylphosphine)-palladium(0) (81 mg, 0.07 mmol, 0.05 equiv), and the suspension was stirred for 10 min. 2,4,6 Tripropenylcyclotriboroxane-pyridine complex (394 mg, 1.4 mmol, 1 equiv) and K_2CO_3 (193 mg, 1.4 mmol, 1 equiv) were added and the resulting mixture was stirred at 90°C for 1 h, cooled to room temperature and diluted with AcOEt. The organic phase was washed with H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography on silica gel (iso-hexane/AcOEt : 4/1) gave 3-(2-oxo-piperidin-1-yl)-5-(E/Z)-propenyl-benzoic acid *tert*-butyl ester (D68) (480 mg, 100%) of adduct as a pale yellow oil. $[M+H]^+$ = 316.2, RT = 3.41 min

Descriptions 69-72

Descriptions 69-72 were prepared in an analogous manner to that described for Description 68 from the appropriate aryl bromide starting material indicated in the below table using the appropriate 2,4,6 trialkenylcyclotriboroxane-pyridine complex as described by F. Kerins and D. F. O' Shea in *J. Org. Chem*, 2002, *67*, 4968-4971:

Description	Aryl bromide	$[M+H]^+$	RT (min)
3-(1,1-Dioxo-1λ^6-[1,2]thiazinan-2-yl)-5-(E/Z)-propenyl-benzoic acid *tert*-butyl ester (D69)	D18	(-*t*Bu) 296.1	3.61
3-(2-Oxo-pyrrolidin-1-yl)-5-vinyl-benzoic acid methyl ester (D70)	D9a		
3-Isopropenyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D71)	D9a	260.0	2.96
3-(2-Oxo-pyrrolidin-1-yl)-5-(E/Z)-propenyl-benzoic acid methyl ester (D72)	D9a	260.0	2.97

Description 73

3-Cyclopent-2-enyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester;
3-Cyclopent-3-enyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester; and
3-Cyclopent-1-enyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D73)

To a solution of 3-bromo-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D9a) (686 mg, 2.3 mmol, 1 equiv) in DMF (3 ml) was added cyclopentene (409 µl, 4.6 mmol, 2 equiv), palladium(II)acetate (26 mg, 0.12 mmol, 0.05 equiv), tri(*o*-tolyl)phosphine (71 mg, 0.23 mmol, 0.1 equiv) and triethylamine (969 µl, 7 mmol, 3 equiv). The resulting mixture was stirred at 125°C for 16 h then cooled to room temperature and partitioned between H_2O and Et_2O. The two layers were separated and the organic phase was dried over Na_2SO_4 and concentrated *in vacuo* to give a mixture of 3-cyclopent-2-enyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl

ester, 3-cyclopent-3-enyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester and 3-cyclopent-1-enyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D73) (562 mg, 85%) as a brown oil.

Description 74

3-Cyclohex-2-enyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester;
3-Cyclohex-3-enyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester; and
3-Cyclohex-1-enyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D74)

Description 74 was prepared in an analogous manner to that described for Description 73 from 686 mg (mmol) of 3-bromo-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D9a) and cyclohexene which yielded 207 mg (30%) of 3-cyclohex-2-enyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester, 3-cyclohex-3-enyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester and 3-cyclohex-1-enyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D74) after purification by flash chromatography on silica gel (iso-hexane/EtOAc : 5/1)

Description 75

3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-(3-hydroxy-3-methyl-but-1-ynyl)-benzoic acid *tert*-butyl ester (D75)

To a solution of 3-bromo-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid *tert*-butyl ester (D17) (376 mg, 1 mmol, 1 equiv) in DME (5 ml) and H_2O (5 ml) were added K_2CO_3 (345 mg, 2.5 mmol, 2.5 equiv), CuI (8 mg, 0.04 mmol, 0.04 equiv), triphenyl phosphine (21 mg, 0.08 mmol, 0.08 equiv), 10% palladium on charcoal (21 mg, 0.02 mmol, 0.02 equiv) and the solution was stirred at room temperature for 15 min. 2-Methyl-3-butyne-2-ol (254 µl, 2.5 mmol, 2.5 equiv) was added and the resulting mixture was stirred at 80°C for 16 h then cooled to room temperature. The catalyst was removed by filtration through a pad of celite and the filtrate was diluted with AcOEt. The organic phase was washed with 2N aqueous HCl solution, saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography on silica gel (iso-hexane/AcOEt : 4/1 to 2/1) gave 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-(3-hydroxy-3-methyl-but-1-ynyl)-benzoic acid *tert*-butyl ester (D75) (142 mg, 37%) as a colorless oil which solidified on standing.

Description 76

3-(3-Hydroxy-3-methyl-but-1-ynyl)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid *tert*-butyl ester (D76)

Description 76 was prepared using an analogous process to that described for Description 75 from 390 mg of 3-bromo-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid *tert*-butyl ester (D9b) which yielded 300 mg (76%) of 3-(3-hydroxy-3-methyl-but-1-ynyl)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid *tert*-butyl ester (D76) as a white foam.

Description 77

5-nitro-isophthalic acid monomethyl ester (D77)

Description 77 is commercially available from Sigma-Aldrich Company.

Description 78

5-Nitro-isophthalic acid 1-*tert*-butyl ester 3-methyl ester (D78)

A mixture of 5-nitro-isophthalic acid monomethyl ester (D77) (5.0 g, 22.2 mmol, 1 equiv), *tert*-BuOH (8.2 g, 111 mmol, 5 equiv), EDAC.HCl (4.8 g, 25 mmol, 1.1 equiv) and DMAP (205 mg, 1.68 mmol, 0.07 equiv) dissolved in CH_2Cl_2 (50 ml) was stirred for 1 h at room temperature The mixture was then diluted with CH_2Cl_2 (50 ml), washed with 2N aqueous HCl solution (50 ml) and saturated aqueous $NaHCO_3$ solution (50 ml), dried over $MgSO_4$ and concentrated *in vacuo* to give of 5-nitro-isophthalic acid 1-*tert*-butyl ester 3-methyl ester (D78) (5.3 g, 85%) as a pale yellow oil.

Description 79

5-Amino-isophthalic acid 1-*tert*-butyl ester 3-methyl ester (D79)

A mixture of 5-nitro-isophthalic acid 1-*tert*-butyl ester 3-methyl ester (D78) (5.3 g, 19 mmol, 1 equiv), NH_4COOH (11.9 g, 190 mmol, 10 equiv) and 10% Palladium on charcoal (50% wet, 0.75g, 7%w/w) in EtOH (50 ml) and H_2O (25 ml) was heated at 50 °C for 30 min. MeOH (20 ml) was added and the resulting solution was heated at 50 °C for another hour then cooled to room temperature, filtered through a pad of celite and concentrated *in vacuo*. The residue was diluted with saturated aqueous $NaHCO_3$ solution (100 ml) and the aqueous phase was extracted with AcOEt (150 ml). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with *iso*-hexane to give of 5-amino-isophthalic acid 1-*tert*-butyl ester 3-methyl ester (D79) (3.4 g, 71%) as a white solid.

Description 80

5-(4-Chloro-butanoylamino)-isophthalic acid 1-*tert*-butyl ester 3-methyl ester (D80)

A suspension of 5-amino-isophthalic acid 1-*tert*-butyl ester 3-methyl ester (D79) (3.4 g, 13.5 mmol, 1 equiv) in CH_2Cl_2 (25 ml) was treated with NEt_3 (2.32 g, 23 mmol, 1.1 equiv) and cooled to 0°C. 4-chlorobutyryl chloride (1.6 g, 15.7 mmol, 1.1 equiv) was added dropwise and the resulting solution was stirred at 0 °C for 3 h then allowed to warm to room temperature and washed with 2N aqueous HCl solution, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with *iso*-hexane and Et_2O to give 5-(4-chloro-butanoylamino)-isophthalic acid 1-*tert*-butyl ester 3-methyl ester (D80) (4.5 g, 94%) as a white solid.

Description 81

5-(3-Chloro-propane-1-sulfonylamino)-isophthalic acid 1-*tert*-butyl ester 3-methyl ester (D81)

To a solution of 5-amino-isophthalic acid 1-*tert*-butyl ester 3-methyl ester (D79) (5.0 g, 20 mmol, 1 equiv), DMAP (0.3 g, 2.48 mmol, 0.12 equiv) and pyridine (1.64 g, 20 mmol, 1 equiv) in CH_2Cl_2 (80 ml) was added 3-chloropropanesulfonyl chloride (2.4 ml, 20 mmol, 1 equiv) dropwise. The resulting mixture was stirred for 16 h then diluted with AcOEt (150 ml). The organic phase was washed with 2N aqueous HCl solution and saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo* to give 5-(3-chloro-propane-1-sulfonylamino)-isophthalic acid 1-*tert*-butyl ester 3-methyl ester (D81) (7.8 g, 99%) as a pale orange solid.

47

Description 82

5-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-isophthalic acid 1-*tert*-butyl ester 3-methyl ester (D82)

A mixture of 5-(3-chloro-propane-1-sulfonylamino)-isophthalic acid 1-*tert*-butyl ester 3-methyl ester (D81) (7.8 g, 20 mmol, 1 equiv) and NEt_3 (4.0 g, 40 mmol, 2 equiv) in EtOH (100 ml) was refluxed for 3 h, cooled to room temperature and concentrated *in vacuo*. The residue was diluted with AcOEt and the organic phase was washed with 2N aqueous HCl solution and saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo* to give 5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-isophthalic acid 1-*tert*-butyl ester 3-methyl ester (D82) (4.4 g, 62%) as a white solid.

Description 83

5-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-isophthalic acid monomethyl ester (D83)

A suspension of 5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-isophthalic acid 1-*tert*-butyl ester 3-methyl ester (D82) (4.4 g, 12.4 mmol, 1 equiv) in CH_2Cl_2 (10 ml) was treated with TFA (10ml) and the resulting mixture was stirred for 2 h at room temperature. Toluene (10 ml) was added and the resulting mixture was concentrated *in vacuo*. The residue was triturated with Et_2O to give 5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-isophthalic acid monomethyl ester (D83) (3.6 g, 97%)as a white solid.

Description 84

3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-hydroxymethyl-benzoic acid methyl ester (D84)

A solution of 5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-isophthalic acid monomethyl ester (D83) (500 mg, 1.67 mmol, 1 equiv) in THF (30 ml) was treated with BH_3-Me_2S (2M solution in THF, 1.0 ml, 2 mmol, 1.2 equiv) and the mixture was refluxed for 30 min and then cooled to room temperature. MeOH (5 ml) was added dropwise and the resulting mixture was concentrated *in vacuo*. The residue was diluted with AcOEt (100 ml), and the resulting solution was washed with 2N aqueous HCl solution (100 ml) and saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated *in vacuo* to give 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-hydroxymethyl-benzoic acid methyl ester (D84) (450 mg, 95%) as a clear, colourless oil.

Description 85

3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-methanesulfonyloxymethyl-benzoic acid methyl ester (D85)

A solution of 3-(1,1-dioxo-1λ^6isothiazolidin-2-yl)-5-ethoxymethyl-benzoic acid (D84) (400 mg, 1.4 mmol, 1 equiv) in CH_2Cl_2 (20 ml) was treated with NEt_3 (303 mg, 3.0 mmol, 2.1 equiv) and methanesulfonic anhydride (261 mg, 1.5 mmol, 1.1 equiv) and stirred for 30 min at room temperature. The solution was then washed with 2N aqueous HCl solution (30 ml) and saturated aqueous $NaHCO_3$ solution (30 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated in Et_2O to give 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-methanesulfonyloxymethyl-benzoic acid methyl ester (D85) (390 mg, 77%) as a white solid.

Description 86

3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-formyl-benzoic acid methyl ester (D86)

A solution of 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-hydroxymethyl-benzoic acid methyl ester (D84) (500 mg, 1.8 mmol, 1 equiv) in CH_2Cl_2 (20 ml) was treated with MnO_2 (783 mg, 8.8 mmol, 4.9 equiv) and the resulting mixture was stirred for 3 h at room temperature. A second portion of MnO_2 (500 mg, 5.8 mmol, 3.2 equiv) was added and the mixture stirred for 3 h when a third portion of MnO_2 (300mg, 3.5 mmol, 1.9 equiv) was added. The mixture was stirred for 2 h and then filtered through a pad of celite. The filtrate was concentrated *in vacuo* to give 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-formyl-benzoic acid methyl ester (D86) (450 mg, 88%) as a yellow waxy solid.

Description 87

5-Nitro-*N,N*-dipropyl-isophthalamic acid methyl ester (D87)

A suspension of 5-nitro-isophthalic acid monomethyl ester (D77) (1.0 g, 4.44 mmol, 1 equiv) in CH_2Cl_2 (40 ml) was treated with $(COCl)_2$ (655 mg, 5.2 mmol, 1.2 equiv) followed by a few drops of DMF. The resulting mixture was stirred for 1 h at room temperature and then dipropylamine (1.65 g, 15 mmol, 3.4 equiv) was added and the resulting solution stirred for a further 30 min. The solution was then washed with 2N aqueous HCl solution (50 ml), saturated aqueous $NaHCO_3$ solution (50 ml) , dried over $MgSO_4$ and concentrated *in vacuo* to give 5-nitro-*N,N*-dipropyl-isophthalamic acid methyl ester (D87) (1.5 g, 110%) as a pale yellow oil.

Description 88

5-Amino- *N,N*-dipropyl-isophthalamic acid methyl ester (D88)

A mixture of 5-nitro-*N,N*-dipropyl-isophthalamic acid methyl ester (D87) (1.5 g, 4.9 mmol, 1 equiv), NH_4COOH (3.0 g, 49 mmol, 10 equiv), 10% Pd on charcoal (50% wet, 250 mg, 0.082 equiv w/w), EtOH (20 ml) and H_2O (10 ml) was heated at 50°C for 90 min. The mixture was cooled to room temperature, filtered through a pad of celite and concentrated *in vacuo*. The residue was dissolved in AcOEt (200 ml) and the resulting solution was washed with saturated $NaHCO_3$ solution (100ml), dried over $MgSO_4$ and concentrated *in vacuo* to give 5-amino-*N,N*-dipropyl-isophthalamic acid methyl ester (D88) (1.2 g, 88%) as a white waxy solid.

Description 89

5-(4-Chloro-butanoylamino)-*N,N*-dipropyl-isophthalamic acid methyl ester (D89)

A solution of 5-amino-*N,N*-dipropyl-isophthalamic acid methyl ester (D88) (1.2 g, 4.3 mmol, 1 equiv) in CH_2Cl_2 (10 ml) was treated with NEt_3 (525 mg, 5.2 mmol, 1.2 equiv). The solution was cooled to 0 °C and 4-chlorobutyryl chloride (733 mg, 5.0 mmol, 1.2 equiv) was added dropwise. The reaction mixture was then allowed to warm to room temperature and stirred for 1 h. The solution was washed with 2N aqueous HCl solution (20 ml), dried over $MgSO_4$ and concentrated *in vacuo* to give 5-(4-chloro-butanoylamino)-*N,N*-dipropyl-isophthalamic acid methyl ester (D89) (1.7 g, 104%) as a colourless oil.

Description 90

49

5-(5-Chloro-pentanoylamino)-*N,N*-dipropyl-isophthalamic acid methyl ester (D90)
Description 90 was prepared in an analogous manner to Description 89 from 5-amino-*N,N*-dipropyl-isophthalamic acid methyl ester (D88) and 5-chlorovaleryl chloride.

Description 91
5-(3-Chloro-propane-1-sulfonylamino)-*N,N*-dipropyl-isophthalamic acid methyl ester (D91)
A solution of 5-amino-*N,N*-dipropyl-isophthalamic acid methyl ester (D88) (1.4 g, 5.0 mmol, 1 equiv), DMAP (100 mg) and pyridine (392 mg, 5.0 mmol, 1.1 equiv) in CH_2Cl_2 (20 ml) was treated dropwise with 3-chloropropane-1-sulfonyl chloride (946 mg, 5.3 mmol, 1.1 equiv). The resulting mixture was stirred for 16 h at room temperature and then diluted with AcOEt (100 ml). The resulting solution was washed with 2N aqueous HCl solution (50 ml) followed by saturated aqueous $NaHCO_3$ solution (50 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with Et_2O to give 5-(3-chloro-propane-1-sulfonylamino)-*N,N*-dipropyl-isophthalamic acid methyl ester (D91) (1.8 g, 86%) as a pink solid.

Description 92
5-(4-Chloro-butane-1-sulfonylamino)-*N,N*-dipropyl-isophthalamic acid methyl ester (D92)
Description 92 was prepared in an analogous manner to Description 91 from 5-amino-*N,N*-dipropyl-isophthalamic acid methyl ester (D88) and 4-chloro-butane-1-sulfonyl chloride.

Description 93
(2S,3R)-3-Hydroxy-2-((S)-2-hydroxy-1-phenyl-ethylamino)-hexanoic acid methyl ester (D93)
Description 93 was obtained according to Alker, D.; Hamblett, G.; Harwood, L. M.; Robertson, S. M.; David, J.; Williams, C. E. *Tetrahedron*, **54 (22)**, 1998, 6089-6098.

Description 94
(2S,3R)-2-*tert*-Butoxycarbonylamino-3-hydroxy-hexanoic acid methyl ester (D94)
(2S,3R)-3-Hydroxy-2-((S)-2-hydroxy-1-phenyl-ethylamino)-hexanoic acid methyl ester (D93) (2.88 g, 10.25 mmol, 1 equiv), 10% palladium on charcoal (50% wet, 2 g, 35% w/w), HCOOH (5 ml, excess) in MeOH (50 ml) were stirred at 60°C for 1 h. The mixture was then cooled to room temperature, filtered through a pad of celite then concentrated *in vacuo*. The residue was dissolved in dioxan/water (1/1, 50 ml) and $NaHCO_3$ (10g, excess) then di-*tert*-butyl dicarbonate (3.37 g, 15 mmol, 1.5 equiv) were added. The resulting mixture was stirred at room temperature for 2 h then concentrated *in vacuo*. The residue was dissolved in AcOEt and the organic phase was washed successively with 2N aqueous HCl solution and saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography on silica gel (CH_2Cl_2/MeOH : 99/1) gave (2S,3R)-2-*tert*-Butoxycarbonylamino-3-hydroxy-hexanoic acid methyl ester (D94) (1.88 g, 70%) as a colourless gum.

50

Description 95
(S)-2-*tert*-butoxycarbonylamino-4-methylsulfanyl-butyric acid (D95)
Description 95 is commercially available from Sigma-Aldrich Company.

Description 96
((S)-1-Isobutylcarbamoyl-3-methylsulfanyl-propyl)-carbamic acid *tert*-butyl ester (D96)
(S)-2-*tert*-butoxycarbonylamino-4-methylsulfanyl-butyric acid (D95) (2.0 g, 8.0 mmol, 1 equiv), EDAC.HCl (1.84 g, 9.6 mmol, 1.2 equiv), HOBT (1.47 g, 9.6 mmol, 1.2 equiv), 4-ethylmorpholine (1.76 g, 16 mmol, 2 equiv) and *iso*-butylamine (952 ml, 9.6 mmol, 1.2 equiv) in CH_2Cl_2 (10 ml) were stirred at room temperature for 16 h. The solution was concentrated *in vacuo* and the residue dissolved in AcOEt. The organic phase was washed with 2N aqueous HCl solution, saturated aqueous $NaHCO_3$ solution and brine, dried over $MgSO_4$ and concentrated *in vacuo* to give ((S)-1-isobutylcarbamoyl-3-methylsulfanyl-propyl)-carbamic acid *tert*-butyl ester (D96) (2.38 g, 98%) as a colourless oil.

Description 97
(3-methoxy-phenyl)-acetic acid ethyl ester (D97)
Description 97 is commercially available from Sigma-Aldrich Company.

Description 98
2-(3-Methoxy-phenyl)-2-methyl-propionic acid ethyl ester (D98)
To a solution of (3-methoxy-phenyl)-acetic acid ethyl ester (D97) (19.72 g, 0,101 m, 1 equiv) in THF (200 ml) was added NaH (8.8g, 0.222 mol, 2.2 equiv) then Iodomethane (26 ml, 0.4 mol, 4 equiv). The resulting mixture was stirred at room temperature for 16 h then partitioned between AcOEt and a saturated $NaHCO_3$ aqueous solution. The two layers were separated and the organic phase washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give 2-(3-methoxy-phenyl)-2-methyl-propionic acid ethyl ester (D98) (20.85 g, 98%) as an orange oil.

Description 99
2-(3-Methoxy-phenyl)-2-methyl-propionic acid (D99)
To a solution of 2-(3-methoxy-phenyl)-2-methyl-propionic acid ethyl ester (D98) (20.95g, 94 mmol, 1 equiv) in EtOH (200 ml) was added 2N NaOH aqueous solution (90 ml, 180 mmol, 1.9 equiv) and the resulting mixture was stirred at 70°C for 16 h then cooled to room temperature. Most of EtOH was removed *in vacuo* and the residue extracted with AcOEt then acidified to pH 1. The aqueous phase was then extracted with AcOEt and the organic phase dried over $MgSO_4$ and concentrated *in vacuo* to give 2-(3-methoxy-phenyl)-2-methyl-propionic acid (D99) (15g, 82%) as a yellow oil.

Description 100
[1-(3-Methoxy-phenyl)-1-methyl-ethyl]-carbamic acid benzyl ester (D100)
To a solution of 2-(3-methoxy-phenyl)-2-methyl-propionic acid (D99) (1g, 5.15 mmol, 1 equiv) in toluene (20 ml) at room temperature was added NEt_3 (1.07 ml, 7.72 mmol, 1.5 equiv) and

51

then diphenylphosphoryl azide (2.2 ml, 10.3 mmol, 2 equiv). The resulting mixture was then heated at 80°C for 2 h then benzyl alcohol (1.61 ml, 15.45 mmol, 3 equiv) was added and the solution heated for a further 2 h, cooled to room temperature and partitioned between EtOAc and a saturated $NaHCO_3$ aqueous solution. The two layers were separated and the aqueous phase dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt: 9/1) gave [1-(3-methoxy-phenyl)-1-methyl-ethyl]-carbamic acid benzyl ester (D100) (1g, 65%) a yellow gum.

Description 101

((S)-(S)-1-oxiranyl-2-phenyl-ethyl)-carbamic acid *tert*-butyl ester (D101)

Description 101 is commercially available from Chirex (ref 1819W94, lot#9924382).

Description 102

((1S,2R)-3-Amino-1-benzyl-2-hydroxy-propyl)-carbamic acid *tert*-butyl ester (D102)

To a solution of ((S)-(S)-1-oxiranyl-2-phenyl-ethyl)-carbamic acid *tert*-butyl ester (D101) (25 g, 95.1 mmol, 1 equiv)) in MeOH (350 ml) was added aqueous ammonia (32% w/w, 180 ml, 3.2 mol, 3.3 equiv). The resulting mixture was stirred at room temperature for 16 h then concentrated *in vacuo* to give ((1S,2R)-3-amino-1-benzyl-2-hydroxy-propyl)-carbamic acid *tert*-butyl ester (D102) (25.2 g, 95%) as a white solid.

Description 103

((2R,3S)-3-*tert*-Butoxycarbonylamino-2-hydroxy-4-phenyl-butyl)-carbamic acid benzyl ester (D103)

A solution of ((1S,2R)-3-amino-1-benzyl-2-hydroxy-propyl)-carbamic acid *tert*-butyl ester (D102) (25.6 g, 91.4 mmol, 1 equiv) in DMF (250 ml) at 0°C was treated with NEt_3 (15 ml, 108 mmol, 1.2 equiv) and then with benzyl chloroformate (14 ml, 98 mmol, 1.1 equiv) in DMF (50 ml) dropwise. The resulting solution was stirred at 0°C for 1 h and at room temperature for 16 h and then concentrated *in vacuo*. The residue was partitioned between AcOEt and saturated aqueous $NaHCO_3$ solution. The resulting precipitate was diluted with H_2O and filtered to give ((2R,3S)-3-*tert*-butoxycarbonylamino-2-hydroxy-4-phenyl-butyl)-carbamic acid benzyl ester (D103) (31.5 g, 83%) as a white solid.

Description 104

((2R,3S)-3-Amino-2-hydroxy-4-phenyl-butyl)-carbamic acid benzyl ester (D104)

A solution of ((2R,3S)-3-*tert*-butoxycarbonylamino-2-hydroxy-4-phenyl-butyl)-carbamic acid benzyl ester (D103) (31.5 g, 76.1 mmol, 1 equiv) in THF (300 ml) was treated with 4N HCl solution in dioxan (40 ml, 160 mmol, 2.1 equiv). The resulting solution was stirred at room temperature for 2 h then concentrated *in vacuo*. The residue was triturated with Et_2O/*iso*-hexane to give ((2R,3S)-3-amino-2-hydroxy-4-phenyl-butyl)-carbamic acid benzyl ester hydrochloride (D104) (22.1 g, 83%) as a white solid.

Description 105

[(2R,3S)-2-Hydroxy-3-({1-[3-(2-oxo-pyrrolidin-1-yl)-5-pentyloxy-phenyl]-methanoyl}-amino)-4-phenyl-butyl]-carbamic acid benzyl ester (D105)

To a suspension of 3-(2-oxo-pyrrolidin-1-yl)-5-pentyloxy-benzoic acid (A13) (530 mg, 1.82 mmol, 1 equiv) in CH_2Cl_2 (20 ml) were added HOBT (300 mg, 2.2 mmol, 1.2 equiv) and EDAC.HCl (420 mg, 2.2 mmol, 1.2 equiv). After stirring for 5 min, 3-(2-oxo-pyrrolidin-1-yl)-5-pentyloxy-benzoic acid hydrochloride (D104) (570 mg, 1.82 mmol, 1 equiv) was added and the resulting mixture was stirred at room temperature for 16 h. The reaction mixture was then diluted with CH_2Cl_2 (20 ml) washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo* to give [(2R,3S)-2-hydroxy-3-({1-[3-(2-oxo-pyrrolidin-1-yl)-5-pentyloxy-phenyl]-methanoyl}-amino)-4-phenyl-butyl]-carbamic acid benzyl ester (D105) (510 mg, 48 %) as a white solid.

Description 106

[(2R,3S)-3-({1-[3-Ethylamino-5-(2-oxo-pyrrolidin-1-yl)-phenyl]-methanoyl}-amino)-2-hydroxy-4-phenyl-butyl]-carbamic acid benzyl ester (D106)

Description 106 was prepared in an analogous manner to Description 105 from 3-(2-oxo-pyrrolidin-1-yl)-5-pentyloxy-benzoic acid hydrochloride (D104) and 3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A31).

Description 107

[(2R,3S)-3-({1-[3-Isopropylamino-5-(2-oxo-pyrrolidin-1-yl)-phenyl]-methanoyl}-amino)-2-hydroxy-4-phenyl-butyl]-carbamic acid benzyl ester (D107)

Description 107 was prepared in an analogous manner to Description 105 from 3-(2-oxo-pyrrolidin-1-yl)-5-isopropylamino-benzoic acid hydrochloride (A44) and ((2R,3S)-3-amino-2-hydroxy-4-phenyl-butyl)-carbamic acid benzyl ester (D104).

Description 108-119

The following compounds (D108-D119) were prepared from Description 104 in an analogous manner to the process described for Description 105 using the appropriate acid.

Description	Acid
Phenylmethyl [(2*R*,3*S*)-3-({[3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-(ethylamino)phenyl]carbonyl}amino)-2-hydroxy-4-phenylbutyl]carbamate (D108)	A73
Phenylmethyl [(2*R*,3*S*)-3-({[3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-(ethylamino)-2-fluorophenyl]carbonyl}amino)-2-hydroxy-4-phenylbutyl]carbamate (D109)	A119
Phenylmethyl [(2*R*,3*S*)-3-({[3-cyclopentyl-5-(2-oxo-1-pyrrolidinyl)phenyl]carbonyl}amino)-2-hydroxy-4-phenylbutyl]carbamate (D110)	A107
Phenylmethyl [(2*R*,3*S*)-2-hydroxy-3-({[3-[(1-methylethyl)oxy]-5-(2-oxo-1-pyrrolidinyl)phenyl]carbonyl}amino)-4-phenylbutyl]carbamate (D111)	A12
Phenylmethyl {(2*R*,3*S*)-3-[({3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-[(1-methylethyl)oxy]phenyl}carbonyl)amino]-2-hydroxy-4-phenylbutyl}carbamate (D112)	A168
Phenylmethyl [(2*R*,3*S*)-3-({[3-cyclopentyl-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-	A126

53

2-yl)phenyl]carbonyl}amino)-2-hydroxy-4-phenylbutyl]carbamate (D113)	
Phenylmethyl [(2*R*,3*S*)-3-({[3-(ethyloxy)-5-(2-oxo-1-pyrrolidinyl)phenyl]carbonyl}amino)-2-hydroxy-4-phenylbutyl]carbamate (D114)	A11
Phenylmethyl [(2*R*,3*S*)-3-({[3-(1,1-dioxido-2-isothiazolidinyl)-5-(ethyloxy)phenyl]carbonyl}amino)-2-hydroxy-4-phenylbutyl]carbamate (D115)	A18
Phenylmethyl {(2*R*,3*S*)-3-[({3-(1,1-dioxido-2-isothiazolidinyl)-5-[(1-methylethyl)oxy]phenyl}carbonyl)amino]-2-hydroxy-4-phenylbutyl}carbamate (D116)	A19
Phenylmethyl [(2*R*,3*S*)-3-({[3-cyclopentyl-5-(1,1-dioxido-2-isothiazolidinyl)phenyl]carbonyl}amino)-2-hydroxy-4-phenylbutyl]carbamate (D117)	A169
Phenylmethyl [(2*R*,3*S*)-3-({[3-(1,1-dioxido-2-isothiazolidinyl)-5-(ethylamino)phenyl]carbonyl}amino)-2-hydroxy-4-phenylbutyl]carbamate (D118)	A70
Phenylmethyl [(2*R*,3*S*)-3-({[3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-(ethyloxy)phenyl]carbonyl}amino)-2-hydroxy-4-phenylbutyl]carbamate (D119)	A170

Description 120-131

The following compounds (D120-D131) were prepared in an analogous manner to the process described for Example 182 using the appropriate precursor:

Description	Precursor
N-[(1*S*,2*R*)-3-Amino-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-(ethylamino)benzamide (D120)	D108
N-[(1*S*,2*R*)-3-Amino-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxido tetrahydro-2*H*-1,2-thiazin-2-yl)-5-(ethylamino)-2-fluorobenzamide (D121)	D109
N-[(1*S*,2*R*)-3-Amino-2-hydroxy-1-(phenylmethyl)propyl]-3-cyclopentyl-5-(2-oxo-1-pyrrolidinyl)benzamide (D122)	D110
N-[(1*S*,2*R*)-3-Amino-2-hydroxy-1-(phenylmethyl)propyl]-3-[(1-methylethyl)oxy]-5-(2-oxo-1-pyrrolidinyl)benzamide (D123)	D111
N-[(1*S*,2*R*)-3-Amino-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-[(1-methylethyl)oxy]benzamide (D124)	D112
N-[(1*S*,2*R*)-3-Amino-2-hydroxy-1-(phenylmethyl)propyl]-3-cyclopentyl-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)benzamide (D125)	D113
N-[(1*S*,2*R*)-3-Amino-2-hydroxy-1-(phenylmethyl)propyl]-3-(ethyloxy)-5-(2-oxo-1-pyrrolidinyl)benzamide (D126)	D114
N-[(1*S*,2*R*)-3-Amino-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxido-2-isothiazolidinyl)-5-(ethyloxy)benzamide (D127)	D115
N-[(1*S*,2*R*)-3-Amino-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxido-2-isothiazolidinyl)-5-[(1-methylethyl)oxy]benzamide (D128)	D116
N-[(1*S*,2*R*)-3-Amino-2-hydroxy-1-(phenylmethyl)propyl]-3-cyclopentyl-5-(1,1-dioxido-2-isothiazolidinyl)benzamide (D129)	D117
N-[(1*S*,2*R*)-3-Amino-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxido-2-isothiazolidinyl)-5-(ethylamino)benzamide (D130)	D118
N-[(1*S*,2*R*)-3-Amino-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-(ethyloxy)benzamide (D131)	D119

54

Description 132

Methyl 3-nitro-5-[(1*E/Z*)-1-propen-1-yl]benzoate (D132)

Methyl 3-nitro-5-[(1*E/Z*)-1-propen-1-yl]benzoate (D132) was prepared from methyl 3-bromo-5-nitrobenzoate (D11) in an analogous manner to that described for Description 68 (D68). No molecular ion. RT = 3.42 min.

Description 133

Methyl 3-amino-5-propylbenzoate (D133)

Methyl 3-amino-5-propylbenzoate (D133) was prepared from methyl 3-nitro-5-[(1*E/Z*)-1-propen-1-yl]benzoate (D132) in an analogous manner to that described for Ester 116 (B116).

Description 134

Methyl 3-[(3-buten-1-ylsulfonyl)amino]-5-propylbenzoate (D134)

To a solution of methyl 3-amino-5-propylbenzoate (D133) (2.49 g, 12.9 mmol, 1 equiv) in CH_2Cl_2 (25 ml) were added pyridine (1.13 ml, 14 mmol, 1.1 equiv), 2-propene-1-sulfonyl chloride (2 g, 12.9 mmol, 1 equiv) and DMAP (350 mg, 2.9 mmol, 0.2 equiv) and the resulting mixture was stirred at room temperature for 4 days. The solution was diluted with AcOEt and the organic phase was washed with H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*Iso*-hexane/AcOEt: 4:1) gave methyl 3-[(3-buten-1-ylsulfonyl)amino]-5-propylbenzoate (D134) (1.3 g, 32%) as a colourless oil. $[M-H]^-$ = 310.0, RT = 3.39 min.

Description 135

Methyl 3-[(3-buten-1-ylsulfonyl)(2-propen-1-yl)amino]-5-propylbenzoate (D135)

To a solution of methyl 3-[(3-buten-1-ylsulfonyl)amino]-5-propylbenzoate (D134) (1.3 g, 4.2 mmol, 1 equiv), 2-propen-1-ol (280 µl, 4.2 mmol, 1 equiv) and triphenylphosphine (1.28 g, 4.9 mmol, 1.15 equiv) in toluene (20 ml) at room temperature was slowly added diisopropyl azodicarboxylate (964 ml, 4.9 mmol, 1.15 equiv). The resulting solution was stirred at this temperature for 30 min then concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*Iso*-hexane/AcOEt: 4:1) gave methyl 3-[(3-buten-1-ylsulfonyl)(2-propen-1-yl)amino]-5-propylbenzoate (D135) (1.1 g, 75%) as a yellow oil.
$[M+H]^+$ = 352.1, RT = 3.63 min.

Description 136

2-Fluoro-3,5-dinitrobenzoic acid (D136)

A 70% aqueous HNO_3 solution (80 ml) was added dropwise to H_2SO_4 (160 ml). The temperature was kept below 10°C using an ice-bath. 2-Fluoro benzoic acid (14 g, 0.1 mol, 1 equiv) was added portionwise over 5 min then the colorless suspension was slowly warmed to 90°C and stirred at this temperature for 1 h then at 100°C for 3 h. The solution was then cooled to room temperature and carefully poured into ice (1 l) diluted with H_2O (1.5 l). The aqueous phase was extracted 3 times with AcOEt and the combined organic layers dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with Et_2O to give 2-fluoro-3,5-

dinitrobenzoic acid (D136) (13.6 g, 59%) as a pale yellow solid which was used in the next step without further purification. No molecular ion, RT = 2.06 min.

Description 137

Methyl 2-fluoro-3,5-dinitrobenzoate (D137)

Methyl 2-fluoro-3,5-dinitrobenzoate (D137) was prepared in an analogous manner to Description 25 (D25) from 2-fluoro-3,5-dinitrobenzoic acid (D136).

Description 138

Methyl 3-amino-2-fluoro-5-nitrobenzoate (D138)

To a solution of methyl 2-fluoro-3,5-dinitrobenzoate (D137) (24.4 g, 0.1 mol, 1 equiv) in AcOH (1 l) was added iron (27.5 g, 0.5 mol, 5 equiv) and the resulting suspension was vigorously stirred for 1 h. The temperature was kept below 35°C by small amount of cooling using an ice bath during that period. Toluene (200 ml) was added and the suspension filtered through a pad of celite. The remaining solution was concentrated *in vacuo* and the residue partitioned between AcOEt and a saturated aqueous $NaHCO_3$ solution. The two layers were separated and the aqueous phase was extracted twice with AcOEt. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give methyl 3-amino-2-fluoro-5-nitrobenzoate (D138) (17 g, 79%) as a yellow solid which was used in the next step without further purification. $[M-H]^-$ = 212.9, RT = 2.68 min.

Description 139

Methyl 3-[(4-chlorobutanoyl)amino]-2-fluoro-5-nitrobenzoate (D139)

To a solution of methyl 3-amino-2-fluoro-5-nitrobenzoate (D138) (12 g, 56 mmol, 1 equiv) in CH_2Cl_2 (150 ml) at room temperature were added NEt_3 (11.7 ml, 84 mmol, 1.5 equiv) and 4-chlorobutanoyl chloride (6.9 ml, 61.6 mmol, 1.1 equiv) and the resulting mixture was stirred for 2 h then washed with a 2N aqueous HCl solution and a saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt: 4/1) gave methyl 3-[(4-chlorobutanoyl)amino]-2-fluoro-5-nitrobenzoate (D139) (16.2 g, 91%) as a yellow solid. $[M+H]^+$ = 319.1, RT = 3.12 min.

Description 140

Methyl 2-fluoro-5-nitro-3-(2-oxo-1-pyrrolidinyl)benzoate (D140)

To a solution of methyl 3-[(4-chlorobutanoyl)amino]-2-fluoro-5-nitrobenzoate (D139) (8.5 g, 26.7 mmol, 1 equiv) in THF (100 ml) was added NaH (60% dispersion in mineral oil, 1.17 g, 29.4 mmol, 1.1 equiv) and the resulting mixture was stirred at room temperature for 1.5 h then diluted with AcOEt. The organic phase was washed with H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt: 2/1) gave methyl 2-fluoro-5-nitro-3-(2-oxo-1-pyrrolidinyl)benzoate (D140) (3.3 g, 43%) as a yellow solid. $[M+H]^+$ = 283.1, RT = 2.53 min.

Description 141

56

Methyl 3-{bis[(3-chloropropyl)sulfonyl]amino}-2-fluoro-5-nitrobenzoate (D141)
To a solution of methyl 3-amino-2-fluoro-5-nitrobenzoate (D138) (500 mg, 2.34 mmol, 1 equiv) in CH_2Cl_2 (50 ml) was added NEt_3 (840 µl, 6.0 mmol, 2.6 equiv) then 3-chloro-1-propanesulfonyl chloride (624 µl, 5.0 mmol, 2.1 equiv) and the resulting mixture was stirred for 1 h. The organic phase was then washed with a 2N aqueous HCl solution, dried over $MgSO_4$ and concentrated *in vacuo* to give methyl 3-{bis[(3-chloropropyl)sulfonyl]amino}-2-fluoro-5-nitrobenzoate (D141) (900 mg, 78%) as a brown foam which was used in the next step without further purification. No molecular ion, RT = 3.51 min.

Description 142
Methyl 3-{bis[(4-chlorobutyl)sulfonyl]amino}-2-fluoro-5-nitrobenzoate (D142)
Methyl 3-{bis[(4-chlorobutyl)sulfonyl]amino}-2-fluoro-5-nitrobenzoate (D142) was obtained from methyl 3-amino-2-fluoro-5-nitrobenzoate (D138) in an analogous manner to that described for methyl 3-{bis[(3-chloropropyl)sulfonyl]amino}-2-fluoro-5-nitrobenzoate (D141) using 4-chloro-1-butanesulfonyl chloride (D20) instead of 3-chloro-1-propanesulfonyl chloride. $[M+H+NH_3]^+$ = 540.1, RT = 3.62 min.

Description 143
3-[[(3-Chloropropyl)sulfonyl]amino}-2-fluoro-5-nitrobenzoic acid (D143)
To a solution of crude methyl 3-{bis[(3-chloropropyl)sulfonyl]amino}-2-fluoro-5-nitrobenzoate (D141) (900 mg, 1.81 mmol, 1 equiv) in MeOH (25 ml) was added a 2N aqueous NaOH solution (15 ml, 30 mmol, excess) and the resulting mixture was stirred for 1 h. Most of MeOH was removed *in vacuo* and the residue partitioned between AcOEt and a 2N aqueous HCl solution. The two layers were separated and the aqueous phase was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with Et_2O/*iso*-hexane to give 3-[[(3-chloropropyl)sulfonyl]amino}-2-fluoro-5-nitrobenzoic acid (D143) (600 mg, 97%) as a light tan solid which was used in the next step without further purification. No molecular ion, RT = 3.05 min.

Description 144
3-[[(4-Chlorobutyl)sulfonyl]amino}-2-fluoro-5-nitrobenzoic acid (D144)
3-[[(4-Chlorobutyl)sulfonyl]amino}-2-fluoro-5-nitrobenzoic acid (D144)
was obtained from methyl 3-{bis[(4-chlorobutyl)sulfonyl]amino}-2-fluoro-5-nitrobenzoate (D142) in an analogous manner to the process described for 3-[[(3-chloropropyl)sulfonyl]amino}-2-fluoro-5-nitrobenzoic acid (D143).

Description 145
Methyl 3-[[(3-chloropropyl)sulfonyl]amino}-2-fluoro-5-nitrobenzoate (D145)
Methyl 3-[[(3-chloropropyl)sulfonyl]amino}-2-fluoro-5-nitrobenzoate (D145)
was prepared in an analogous manner to Description 25 from 3-[[(3-chloropropyl)sulfonyl]amino}-2-fluoro-5-nitrobenzoic acid (D143). $[M-H]^-$ = 353.0, RT = 3.05 min.

Description 146

Methyl 3-[[(4-chlorobutyl)sulfonyl]amino]-2-fluoro-5-nitrobenzoate (D146)

Methyl 3-[[(4-chlorobutyl)sulfonyl]amino]-2-fluoro-5-nitrobenzoate (D146) was prepared in an analogous manner to Description 25 from 3-[[(4-chlorobutyl)sulfonyl]amino]-2-fluoro-5-nitrobenzoic acid (D144). $[M+H+NH_3]^+$ = 388.1, RT = 3.13 min.

Description 147

Methyl 3-(1,1-dioxido-2-isothiazolidinyl)-2-fluoro-5-nitrobenzoate (D147)

To a solution of methyl 3-[[(3-chloropropyl)sulfonyl]amino]-2-fluoro-5-nitrobenzoate (D145) (300 mg, 0.85 mmol, 1 equiv) in EtOH (30 ml) was added NEt_3 (280 µl, 2 mmol, 2.3 equiv) and the resulting solution was refluxed for 1.5 h then cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in AcOEt and the organic phase was washed with a 2N aqueous HCl solution, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with AcOEt/Et_2O to give methyl 3-(1,1-dioxido-2-isothiazolidinyl)-2-fluoro-5-nitrobenzoate (D147) (150 mg, 55%) as a light tan solid which was used in the next step without further purification. $[M+H+ NH_3]+$ = 336.3, RT = 2.50 min.

Description 148

Methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluoro-5-nitrobenzoate (D148)

Methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluoro-5-nitrobenzoate (D148) was prepared in an analogous manner to the process for methyl 3-(1,1-dioxido-2-isothiazolidinyl)-2-fluoro-5-nitrobenzoate (D147) from methyl 3-[[(4-chlorobutyl)sulfonyl]amino]-2-fluoro-5-nitrobenzoate (D146). $[M+H+ NH_3]+$ = 350.1, RT = 2.79 min.

Description 149

Methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-(methyloxy)-5-nitrobenzoate (D149)

To a solution of methyl 3-[[(4-chlorobutyl)sulfonyl]amino]-2-fluoro-5-nitrobenzoate (D146) (1.5 g, 4.1 mmol, 1 equiv) in MeOH (30 ml) was added NEt_3 (1.2 ml 8.6 mmol, 2.1 equiv) and the resulting solution was refluxed for 15 h then cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in AcOEt and the organic phase was washed with a 2N aqueous HCl solution, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with AcOEt/Et_2O to give methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-(methyloxy)-5-nitrobenzoate (D149) (1.2 g, 55%) as a light brown solid which was used in the next step without further purification. $[M+H]+$ = 345.1, RT = 2.80 min.

Description 150

Methyl 5-amino-2-fluoro-3-(2-oxo-1-pyrrolidinyl)benzoate (D150)

To a solution of methyl 2-fluoro-5-nitro-3-(2-oxo-1-pyrrolidinyl)benzoate (D140) (3.3 g, 11.7 mmol, 1 equiv) in EtOH (100 ml) and H_2O (10 ml) were added NH_4COOH (7.4 g, 117 mmol, 10 equiv) and 10% palladium on charcoal (50% wet, 660 mg, 10% w/w) and the resulting mixture was refluxed for 2 h then cooled to room temperature. The catalyst was removed by

filtration through a pad of celite and most of the solvent removed *in vacuo*. The residue was partitioned between AcOEt and H_2O and the two layers were separated. The organic phase was dried over $MgSO_4$ and concentrated *in vacuo* to give methyl 5-amino-2-fluoro-3-(2-oxo-1-pyrrolidinyl)benzoate (D150) (1.85 g, 83%) as a pale yellow solid which was used in the next step without further purification. $[M+H]^+$ = 253.0, RT = 2.12 min.

Descriptions 151-153 (D151-153)

The following compounds have been made from the appropriate precursor in an analogous manner to the process described for methyl 5-amino-2-fluoro-3-(2-oxo-1-pyrrolidinyl)benzoate (D150).

Description	Precursor	$[M+H]^+$	RT (min)
Methyl 5-amino-3-(1,1-dioxido-2-isothiazolidinyl)-2-fluorobenzoate (D151)	D147	289.1	2.12
Methyl 5-amino-3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluorobenzoate (D152)	D148	303.1	2.33
Methyl 5-amino-3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-(methyloxy)benzoate (D153)	D149	315.1	2.18

Description 154

Methyl 2-fluoro-5-({[4-(methyloxy)phenyl]methyl}amino)-3-(2-oxo-1-pyrrolidinyl)benzoate (D154)

Methyl 2-fluoro-5-({[4-(methyloxy)phenyl]methyl}amino)-3-(2-oxo-1-pyrrolidinyl)benzoate (D154) was prepared from methyl 5-amino-2-fluoro-3-(2-oxo-1-pyrrolidinyl)benzoate (D150) in an analogous manner to the process described for Ester 35 (B35) using 4-(methyloxy)benzaldehyde instead of propionaldehyde. $[M+H]^+$ = 373.4, RT = 2.85 min.

Description 155

Methyl 5-(ethyl{[4-(methyloxy)phenyl]methyl}amino)-2-fluoro-3-(2-oxo-1-pyrrolidinyl)benzoate (D155)

Methyl 5-(ethyl{[4-(methyloxy)phenyl]methyl}amino)-2-fluoro-3-(2-oxo-1-pyrrolidinyl)benzoate (D155) was prepared from methyl 2-fluoro-5-({[4-(methyloxy)phenyl]methyl}amino)-3-(2-oxo-1-pyrrolidinyl)benzoate (D154) in an analogous manner to the process described for Ester 35 (B35) using acetaldehyde instead of propionaldehyde. $[M+H]^+$ = 401.4, RT = 3.11 min.

Description 156

Methyl 5-bromo-2-fluoro-3-(2-oxo-1-pyrrolidinyl)benzoate (D156)

To a solution of methyl 5-amino-2-fluoro-3-(2-oxo-1-pyrrolidinyl)benzoate (D150) (650 mg, 2.6 mmol, 1 equiv) in a 48% aqueous HBr solution at 0°C was added $NaNO_2$ portionwise and the resulting mixture was stirred at 0°C for 30 min. CuBr (260 mg, 1.82 mmol, 0.7 equiv) in a 48% aqueous HBr solution (1 ml) was added and the resulting mixture stirred at 90°C for 1 h then cooled to room temperature and partitioned between H_2O and AcOEt. The two layers were separated and the organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt: 2/1)

gave methyl 5-bromo-2-fluoro-3-(2-oxo-1-pyrrolidinyl)benzoate (D156) (145 mg, 18%) as a white solid. $[M+H]^+$ = 318.1, RT = 2.51 min.

Descriptions 157-158 (D157-158)

The following compounds were prepared in an analogous manner to the process described for Description 156 (D156) from the appropriate aniline:

Description	Precursor	RT (min)
Methyl 5-bromo-3-(1,1-dioxido-2-isothiazolidinyl)-2-fluorobenzoate (D157)	D151	2.55
Methyl 5-bromo-3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluorobenzoate (D158)	D152	

Descriptions 159-161 (D159-161)

The following compounds were prepared in an analogous manner to the process described for Description 68 (D68) from the appropriate aryl bromide indicated in the below table:

Description	Precursor	$[M+H]^+$	RT (min)
Methyl 2-fluoro-3-(2-oxo-1-pyrrolidinyl)-5-[(1*E/Z*)-1-propen-1-yl]benzoate (D159)	D156	278.4	2.60
Methyl 3-(1,1-dioxido-2-isothiazolidinyl)-2-fluoro-5-[(1*E/Z*)-1-propen-1-yl]benzoate (D160)	D157	314.2	2.67
Methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluoro-5-[(1*E/Z*)-1-propen-1-yl]benzoate (D161)	D158		

Description 162

Methyl 4-methyl-3,5-dinitrobenzoate (D162)

Methyl 4-methyl-3,5-dinitrobenzoate (D162) was prepared in an analogous manner to Description 25 from commercially available 4-methyl-3,5-dinitrobenzoic acid. $[M+H]^+$ = 240.2, RT = 3.07 min.

Description 163

Methyl 3-amino-4-(methyloxy)-5-nitrobenzoate (D163)

To a solution of methyl 4-(methyloxy)-3,5-dinitrobenzoate (D25) (5.0 g, 19.5 mmol, 1 equiv) in AcOH (150 ml) at room temperature was added iron powder (9.0 g, 161 mmol, 8.2 equiv) portionwise and the resulting mixture was stirred for 3 h. Toluene (500 ml) was added and the organic phase was filtered through a pad of celite then concentrated *in vacuo*. The residue was dissolved in AcOEt and the organic phase was washed with a saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo*. Trituration of the residue with Et_2O/*iso*-hexane gave methyl 3-amino-4-(methyloxy)-5-nitrobenzoate (D163) (3.65 g, 83%) as a yellow solid which was used in the next step without further purification. $[M+H]^+$ = 226.9, RT = 2.76 min.

Description 164

Methyl 3-amino-4-methyl-5-nitrobenzoate (D164)

Methyl 3-amino-4-methyl-5-nitrobenzoate (D164) was obtained from methyl 4-methyl-3,5-dinitrobenzoate (D162) in an analogous manner to the process described for methyl 3-amino-4-(methyloxy)-5-nitrobenzoate (D163). $[M+H]^+$ = 211.0, RT = 2.81 min.

Description 165

Methyl 3-iodo-4-(methyloxy)-5-nitrobenzoate (D165)

To a solution of methyl 3-amino-4-(methyloxy)-5-nitrobenzoate (D163) (370 mg, 1.64 mmol, 1 equiv) in toluene (20 ml) at 0°C was added iodine (218 mg, 0.86 mmol, 0.5 equiv) then 1,1-dimethylethyl nitrite (200 mg, 1.75 mmol, 1.1 equiv) and the resulting mixture was stirred at room temperature for 15 h then partitioned between AcOEt and brine. The two layers were separated and the organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel gave methyl 3-iodo-4-(methyloxy)-5-nitrobenzoate (D165) (280 mg, 51%) as a light brown solid. No molecular ion. RT = 3.33 min.

Description 166

Methyl 4-(methyloxy)-3-nitro-5-[(1*E/Z*)-1-propen-1-yl]benzoate (D166)

Methyl 4-(methyloxy)-3-nitro-5-[(1*E/Z*)-1-propen-1-yl]benzoate (D166) was prepared from methyl 3-iodo-4-(methyloxy)-5-nitrobenzoate (D165) in an analogous manner to the process described for Description 68 (D68). No molecular ion. RT = 3.46 min.

Description 167

Methyl 3-amino-4-(methyloxy)-5-[(1*E/Z*)-1-propen-1-yl]benzoate (D167)

To a solution of methyl 4-(methyloxy)-3-nitro-5-[(1*E/Z*)-1-propen-1-yl]benzoate (D166) (1.0 g, 4.0 mmol, 1 equiv) in AcOH (150 ml) at room temperature was added iron powder (1.4 g, 25 mmol, 6.25 equiv) portionwise and the resulting mixture was stirred for 3 h at room temperature. Iron powder (1 g, 17.9 mmol, 4.2 equiv) was added and the mixture stirred for another hour. Iron powder (1 g, 17.9 mmol, 4.2 equiv) was then added again and the mixture stirred at 45°C for 3 h then cooled to room temperature and stirred at this temperature for 14 h. Toluene (200 ml) was added and the organic phase was filtered through a pad of celite then concentrated *in vacuo*. The residue was dissolved in AcOEt and the organic phase was washed with a saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo* to give methyl 3-amino-4-(methyloxy)-5-[(1*E/Z*)-1-propen-1-yl]benzoate (D167) (800 mg, 90%) as a brown oil which was used in the next step without further purification. $[M+H]^+$ = 222.1, RT = 2.99 min.

Description 168

Methyl 3-[bis[(4-chlorobutyl)sulfonyl]amino]-4-(methyloxy)-5-[(1*E/Z*)-1-propen-1-yl]benzoate (D168)

To a solution of 3-amino-4-(methyloxy)-5-[(1*E/Z*)-1-propen-1-yl]benzoate (D167) (800 mg, 3.6 mmol, 1 equiv) in CH_2Cl_2 (50 ml) was added NEt_3 (1.5 ml, 10.8 mmol, 3.0 equiv) then 4-chloro-1-butanesulfonyl chloride (D20) (2 g, 10.8 mmol, 3.0 equiv) and the resulting mixture was stirred for 1 h. The organic phase was then washed with a 2N aqueous HCl solution and

a saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*Iso*-hexane/AcOEt: 9/1 to 3/1) gave methyl 3-[bis[(4-chlorobutyl)sulfonyl]amino]-4-(methyloxy)-5-[(1*E/Z*)-1-propen-1-yl]benzoate (D168) (1.0 g, 52%) as a pale yellow oil.

Description 169

3-[[(4-Chlorobutyl)sulfonyl]amino]-4-(methyloxy)-5-[(1*E/Z*)-1-propen-1-yl]benzoic acid (D169)

To a solution of methyl 3-[bis[(4-chlorobutyl)sulfonyl]amino]-4-(methyloxy)-5-[(1*E/Z*)-1-propen-1-yl]benzoate (D168) (1.0 g, 1.88 mmol, 1 equiv) in MeOH (20 ml) was added a 2N aqueous NaOH solution (10 ml, 20 mmol, excess) and the resulting mixture was stirred for 1 h. Most of MeOH was removed *in vacuo* and the residue partitioned between AcOEt and a 2N aqueous HCl solution. The two layers were separated and the aqueous phase was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with Et_2O/*Iso*-hexane to give 3-[[(4-chlorobutyl)sulfonyl]amino]-4-(methyloxy)-5-[(1*E/Z*)-1-propen-1-yl]benzoic acid (D169) (470 mg, 69%) as a light cream solid which was used in the next step without further purification. $[M-H]^-$ = 360.0, RT = 3.19 min.

Description 170

Methyl 3-[[(4-chlorobutyl)sulfonyl]amino]-4-(methyloxy)-5-[(1*E*)-1-propen-1-yl]benzoate (D170)

Methyl 3-[[(4-chlorobutyl)sulfonyl]amino]-4-(methyloxy)-5-[(1*E/Z*)-1-propen-1-yl]benzoate (D170) was prepared from 3-[[(4-chlorobutyl)sulfonyl]amino]-4-(methyloxy)-5-[(1*E/Z*)-1-propen-1-yl]benzoic acid (D169) in an analogous manner to Description 25 (D25).

Descriptions 171-172 (D171-172)

The following compounds have been obtained from their corresponding precursors in an analogous manner to the process described for Description 2 (D2):

Description	Precursor	$[M+H]^+$	RT (min)
Methyl 3-[(4-chlorobutanoyl)amino]-4-(methyloxy)-5-nitrobenzoate (D171)	D163	331.0	3.13
Methyl 3-[(4-chlorobutanoyl)amino]-4-methyl-5-nitrobenzoate (D172)	D164	315.1	3.02

Descriptions 173-174 (D173-174)

The following compounds have been obtained from their corresponding precursors in an analogous manner to the process described for Description 14 (D14):

Description	Precursor	$[M-H]^-$	RT (min)
Methyl 3-[[(3-chloropropyl)sulfonyl]amino]-4-(methyloxy)-5-nitrobenzoate (D173)	D163	364.9	3.10
Methyl 3-[[(3-chloropropyl)sulfonyl]amino]-4-methyl-5-nitrobenzoate (D174)	D164	349.0	3.12

Descriptions 175-176 (D175-176)

The following compounds have been obtained from their corresponding precursors in an analogous manner to the process described for Description 14 (D14) using 4-chloro-1-butanesulfonyl chloride (D20) instead of 3-chloro-1-propanesulfonyl chloride:

Description	Precursor	$[M-H]^-$	RT (min)
Methyl 3-[[(4-chlorobutyl)sulfonyl]amino}-4-(methyloxy)-5-nitrobenzoate (D175)	D163		
Methyl 3-[[(4-chlorobutyl)sulfonyl]amino}-4-methyl-5-nitrobenzoate (D176)	D164	362.8	3.21

Descriptions 177-178 (D177-178)

The following compounds have been obtained from their corresponding precursors in an analogous manner to the process described for Ester 27 (B27):

Description	Precursor	$[M+H]^+$	RT (min)
Methyl 4-(methyloxy)-3-nitro-5-(2-oxo-1-pyrrolidinyl) benzoate (D177)	D171	295.1	2.61
Methyl 4-methyl-3-nitro-5-(2-oxo-1-pyrrolidinyl) benzoate (D178)	D172	279.0	2.60

Descriptions 179-182 (D179-182)

The following compounds have been obtained from their corresponding precursors in an analogous manner to the process described for Description 15 (D15):

Description	Precursor	$[M+H]^+$	RT (min)
Methyl 3-(1,1-dioxido-2-isothiazolidinyl)-4-(methyloxy)-5-nitrobenzoate (D179)	D173	331.0	2.78
Methyl 3-(1,1-dioxido-2-isothiazolidinyl)-4-methyl-5-nitrobenzoate (D180)	D174		
Methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-4-(methyloxy)-5-nitrobenzoate (D181)	D175	345.0	2.90
Methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-4-methyl-5-nitrobenzoate (D182)	D176	329.0	2.93

Descriptions 183-185 (D183-185)

The following compounds have been obtained from their corresponding precursors in an analogous manner to the process described for the synthesis of Description 16 (D16) using the appropriate precursor indicated in the below table:

Description	Precursor	$[M+H]^+$	RT (min)
methyl 3-amino-4-(methyloxy)-5-(2-oxo-1-pyrrolidinyl) benzoate (D183)	D177	265.1	2.18
methyl 3-amino-4-methyl-5-(2-oxo-1-pyrrolidinyl) benzoate (D184)	D178	249.1	2.16
methyl 3-amino-5-(1,1-dioxido-2-isothiazolidinyl)-4-(methyloxy) benzoate (D185)	D179	301.0	2.25

G3

methyl 3-amino-5-(1,1-dioxido-2-isothiazolidinyl)-4-methylbenzoate (D186)	D180	285.0	2.22
methyl 3-amino-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-4-(methyloxy) benzoate (D187)	D181	315.1	2.40
methyl 3-amino-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-4-methylbenzoate (D188)	D182	299.0	2.42

Description 189

4-((Z/E)-But-2-enylamino)-3,5-diiodo-benzoic acid ethyl ester (D189)

To a solution of 4-amino-3,5-diiodo-benzoic acid ethyl ester (commercially available from Maybridge) (72.6 g, 0.17 mmol, 1 equiv) in DMF (450 ml) at 0°C under nitrogen was added NaH (60% in mineral oil, 7.3 g, 0.18 mmol, 1.05 equiv) portionwise over 2 min. After 10 min crotyl bromide (21.5 ml, 0.21 mmol, 1.2 equiv) in DMF (50 ml) was added *via cannula* over 5 min and the resulting mixture was allowed to warm to room temperature over 30 min. 5 Ml of EtOH were added and the mixture was concentrated *in vacuo*. The residue was dissolved in AcOEt and the organic phase was washed with H_2O. The aqueous phase was extracted with AcOEt and the combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give 4-((Z/E)-but-2-enylamino)-3,5-diiodo-benzoic acid ethyl ester (D189) (82 g, 100%) as a pink solid which was used in the next step without further purification. $[M+H]^+$ = 472.0, RT = 4.93 min.

Description 190

3-Ethyl-7-iodo-1 *H*-indole-5-carboxylic acid ethyl ester (D190)

To a solution of 4-((Z/E)-but-2-enylamino)-3,5-diiodo-benzoic acid ethyl ester (D189) (15 g, 31.8 mmol, 1 equiv) in DMF (150 ml) at room temperature under nitrogen were added $Pd(OAc)_2$ (357 mg, 1.6 mmol, 0.05 equiv), NaCOOH (6.5 g, 95.6 mmol, 3 equiv), Na_2CO_3 (8.4 g, 79.6 mmol, 2.5 equiv) and NBu_4Cl (8.0 g, 35.0 mmol, 1.1 equiv). The resulting suspension was stirred under nitrogen at 80°C for 30 min then cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between AcOEt and H_2O and the two phases were separated. The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*Iso*-hexane/AcOEt : 9/1) gave 3-ethyl-7-iodo-1 *H*-indole-5-carboxylic acid ethyl ester (D190) (6.3 g, 58%) as a white solid. $[M+H]^+$ = 344.0, RT = 3.86 min.

Description 191

1,1-Dimethylethyl 3-bromo-5-(2-oxo-5-phenyl-1-piperidinyl)benzoate (D191)

A flask was charged under nitrogen with 3-bromo-5-iodo-benzoic acid methyl ester (D8b) (840 mg, 2.2 mmol, 1.1 equiv) , Cs_2CO_3 (900 mg, 2.8 mmol, 1.4 equiv), tris(dibenzylideneacetone)dipalladium(0) (92 mg, 0.1 mmol, 0.05 equiv), Xantphos (120 mg, 0.2 mmol, 0.1 equiv) and toluene (40 ml). 5-Phenyl-2-piperidinone (Koelsch, *J. Am. Chem. Soc.* 1943, (65), 2093, 350 mg, 2 mmol, 1equiv) was then added and the resulting mixture was stirred at 100°C for 2.5 h then cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between AcOEt and a saturated aqueous $NaHCO_3$ solution. The

layers were separated and the organic phase was dried over $MgSO_4$ and concentrated *in vacuo* to give a solid residue. Purification of the residue by flash chromatography on silica gel (*Iso*-hexane/AcOEt : 4/1 to 1/1) gave 1,1-dimethylethyl 3-bromo-5-(2-oxo-5-phenyl-1-piperidinyl)benzoate (D191) (480 mg, 51%) as a white solid. $[M+H]^+$ = 432.2, RT = 3.82 min.

Description 192

1,1-Dimethylethyl 3-(2-oxo-5-phenyl-1-piperidinyl)-5-[(1*E/Z*)-1-propen-1-yl]benzoate (D192)

1,1-Dimethylethyl 3-(2-oxo-5-phenyl-1-piperidinyl)-5-[(1*E/Z*)-1-propen-1-yl]benzoate (D192) was prepared in an analogous manner to the process described for Description 68 (D68) from 1,1-dimethylethyl 3-bromo-5-(2-oxo-5-phenyl-1-piperidinyl)benzoate (D191). $[M+H]^+$ = 392.3, RT = 3.83 min.

Description 193

Methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-nitrobenzoate (D193)

Methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-nitrobenzoate (D193) was obtained from methyl 3-bromo-5-nitrobenzoate (D11) in an analogous manner to the process described for Description 15 (D15) (*alternative procedure*) using tetrahydro-2*H*-1,2-thiazine 1,1-dioxide (D22b) instead of isothiazolidine 1,1-dioxide (D22a). $[M+H+NH_3]^+$ = 332.2, RT = 2.75 min.

Description 194

Methyl 3-amino-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)benzoate (D194)

Methyl 3-amino-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)benzoate (D194) was obtained from methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-nitrobenzoate (D193) in an analogous manner to the process described for Description 2 (D2).
$[M+H]^+$ = 285.1, RT = 2.12 min.

Description 195

Methyl 3-[(4-chlorobutanoyl)amino]-5-(1,1-dioxido-2-isothiazolidinyl)benzoate (D195)

Methyl 3-[(4-chlorobutanoyl)amino]-5-(1,1-dioxido-2-isothiazolidinyl)benzoate (D195) was obtained from methyl 3-amino-5-(1,1-dioxido-2-isothiazolidinyl)benzoate (D16) in an analogous manner to the process described for Description 13 (D13).

Description 196

Methyl 3-amino-4-methyl-5-nitrobenzoate (D196)

To a solution of methyl 4-methyl-3,5-dinitrobenzoate (D162) (30 g, 0.125 mmol, 1 equiv) in MeOH (150 ml) and cyclohexene (300 ml) was added 10% palladium on charcoal (50% wet, 3 g, 5% w/w) and the resulting suspension was refluxed for 7 h then cooled to room temperature. The catalyst was filtered off through a pad of celite and most of the solvent was removed *in vacuo*. The precipitate formed was filtered off to give methyl 3-amino-4-methyl-5-nitrobenzoate (D196) (22 g, 84%) as a yellow solid which was used in the next step without further purification. $[M+H]^+$ = 211.0, RT = 2.81 min.

Description 197

Methyl 4-nitro-1*H*-indazole-6-carboxylate (D197)

To a suspension of 3-amino-4-methyl-5-nitrobenzoate (D196) (3.5 g, 16.7 mmol, 1 equiv) in H_2O (100 ml) at 0°C was added 36% aqueous HCl solution (15 ml) and the resulting suspension was treated with $NaNO_2$ (1.35 g, 19.6 mmol, 1.2 equiv) then warmed to room temperature and stirred for 1.5 h. The insoluble material was removed by filtration and small amounts of urea were added to the mother liquors. The resulting solution was diluted with H_2O (500 ml) and treated with H_2SO_4 (17.5 ml) then heated at 50°C for 15 min, cooled to room temperature and extracted with AcOEt. The organic phase was dried over $MgSO_4$ then concentrated *in vacuo*. The residue was triturated with MeOH to give methyl 4-nitro-1*H*-indazole-6-carboxylate (D197) (0.8 g, 22%) as a cream solid which was used in the next step without further purification. $[M+H]^+$ = 222.1, RT = 2.84 min.

Description 198

Methyl 1-ethyl-4-nitro-1*H*-indazole-6-carboxylate (D198)

To a solution of methyl 4-nitro-1*H*-indazole-6-carboxylate (D197) (500 mg, 2.3 mmol, 1 equiv) in DMF (10 ml) at room temperature was added K_2CO_3 (346 mg, 2.5 mmol, 1.1 equiv) then ethyl iodide (200 µl, 2.5 mmol, 1.1 equiv). The resulting suspension was stirred at room temperature for 15 min then at 40°C for 30 min, cooled to room temperature and partitioned between AcOEt and a 2N aqueous HCl solution. The two layers were separated and the organic phase dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt: 2/1) gave methyl 1-ethyl-4-nitro-1*H*-indazole-6-carboxylate (D198) (200 mg, 35%) as a pale yellow solid. $[M+H]^+$ = 250.1, RT = 3.11 min.

Description 199

Methyl 4-amino-1-ethyl-1*H*-indazole-6-carboxylate (D199)

To a solution of methyl 1-ethyl-4-nitro-1*H*-indazole-6-carboxylate (D198) (2.2 g, 8.8 mmol, 1 equiv) in MeOH (100 ml) and H_2O (10 ml) was added 10% palladium on charcoal (50% wet, 700 mg, 16% w/w) and the resulting mixture was stirred at 60°C for 30 min then cooled to room temperature. The catalyst was removed by filtration through a pad of celite and most of the solvent removed *in vacuo*. The residue was partitioned between AcOEt and a saturated aqueous $NaHCO_3$ solution and the two layers were separated. The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with *iso*-hexane to give methyl 4-amino-1-ethyl-1*H*-indazole-6-carboxylate (D199) (1.55 g, 80%) which was used in the next step without further purification. $[M+H]^+$ = 220.1, RT = 3.31 min.

Description 200

Methyl 4-[(*E*)-2-(dimethylamino)ethenyl]-3,5-dinitrobenzoate (D200)

To a solution of methyl 4-methyl-3,5-dinitrobenzoate (D162) (20 g, 83.3 mmol, 1 equiv) in DMF (30 ml) was added *N,N*-dimethylformamide dimethylacetal (35 ml, excess) and the resulting solution was stirred at 45°C for 30 min then cooled to room temperature and concentrated *in vacuo*. Trituration of the residue with Et_2O/*iso*-hexane gave methyl 4-[(*E*)-2-

66

(dimethylamino)ethenyl]-3,5-dinitrobenzoate (D200) (20 g, 81%) as a dark red solid which was used in the next step without further purification.

Description 201

Methyl 4-amino-1*H*-indole-6-carboxylate (D201)

To a solution of methyl 4-[(*E*)-2-(dimethylamino)ethenyl]-3,5-dinitrobenzoate (D200) (10 g, 34 mmol, 1 equiv) in MeOH (250 ml) was added 10% palladium on charcoal (50% wet, 1.0 g, 5% w/w) and the resulting mixture was stirred under an atmosphere of hydrogen for 7 h. The catalyst was removed by filtration through a pad of celite and the solution concentrated *in vacuo*. The residue was triturated with AcOEt/*iso*-hexane to give methyl 4-amino-1*H*-indole-6-carboxylate (D201) (5 g, 77%) as a dark pink solid. $[M+H]^+$ = 191.0, RT = 1.20 min.

Description 202

Methyl 4-amino-1-ethyl-1*H*-indole-6-carboxylate (D202)

To a solution of methyl 4-amino-1*H*-indole-6-carboxylate (D201) (900 mg, 4,74 mmol, 1 equiv) in DMF (25 ml) at room temperature was added NaH (60% dispersion in mineral oil, 200 mg, 5 mmol, 1.05 equiv) and after 15 min ethyl iodide (400 µl, 5 mmol, 1.05 equiv). The resulting mixture was stirred for 30 min then most of the solvent was removed *in vacuo*. The residue was diluted with AcOEt and the organic phase was washed with a 2N aqueous HCl solution, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt: 1/1) gave an oil which was diluted with Et_2O and treated with a 4N HCl solution in Et_2O. The precipitate obtained was filtrated off to give methyl 4-amino-1-ethyl-1*H*-indole-6-carboxylate hydrochloride salt (D202) (800 mg, 66%) as a white solid. $[M+H]^+$ = 219.0, RT = 2.50 min.

Description 203

Methyl 4-amino-3,5-dinitrobenzoate (D203)

Methyl 4-amino-3,5-dinitrobenzoate (D203) was prepared in an analogous manner to Description 25 from commercially available 4-amino-3,5-dinitrobenzoic acid.
$[M-H]^-$ = 240.1, RT = 2.42 min.

Description 204

Methyl 3,4-diamino-5-nitrobenzoate (D204)

To a solution of methyl 4-amino-3,5-dinitrobenzoate (D203) (3.0 g, 12.4 mmol, 1 equiv) in MeOH (40 ml) and cyclohexane (80 ml) was added 10% palladium on charcoal (50% wet, 2.0 g, 33% w/w) and the resulting mixture was refluxed for 30 min then cooled to room temperature. The catalyst was filtered off through a pad of celite and washed with DMF. The combined organic phases were concentrated *in vacuo* and the residue triturated with Et_2O/*iso*-hexane to give methyl 3,4-diamino-5-nitrobenzoate (D204) (2.1 g, 80%) as a red solid which was used in the next step without further purification.
$[M+H]^+$ = 212.2, RT = 2.46 min.

67

Description 205

Methyl 4-amino-3-(ethylamino)-5-nitrobenzoate (D205)

To a solution of methyl 3,4-diamino-5-nitrobenzoate (D204) (1.5 g, 7.1 mmol, 1 equiv) in DMF (30 ml) at room temperature was added K_2CO_3 (2.2 g, 16.0 mmol, 2.25 equiv) then ethyl iodide (1.28 ml, 16.0 mmol, 2.25 equiv). The resulting suspension was stirred at 60°C for 2 h then ethyl iodide (1 ml, 12.5 mmol, 1.8 equiv) was added and the resulting mixture stirred for another 6 h then cooled to room temperature and partitioned between AcOEt and a saturated aqueous $NaHCO_3$ solution. The two layers were separated and the organic phase washed with H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with Et_2O to give methyl 4-amino-3-(ethylamino)-5-nitrobenzoate (D205) (0.85 g, 50%) as a red solid which was used in the next step without further purification. $[M+H]^+$ = 240.2, RT = 2.95 min.

Description 206

Methyl 1-ethyl-4-nitro-1*H*-benzimidazole-6-carboxylate (D206)

Methyl 4-amino-3-(ethylamino)-5-nitrobenzoate (D205) (850 mg, 3.55 mmol, 1 equiv) was dissolved in formic acid (20 ml) and the resulting solution was stirred at 100°C for 45 min then cooled to room temperature and diluted with AcOEt (200 ml). The organic phase was washed with a 2N aqueous NaOH solution, dried over $MgSO_4$ and concentrated *in vacuo* to give methyl 1-ethyl-4-nitro-1*H*-benzimidazole-6-carboxylate (D206) (700 mg, 79%) as a tan solid which was used in the next step without further purification. $[M+H]^+$ = 250.1, RT = 2.41 min.

Description 207

Methyl 4-amino-1-ethyl-1*H*-benzimidazole-6-carboxylate (D207)

To a solution of methyl 1-ethyl-4-nitro-1*H*-benzimidazole-6-carboxylate (D206) (700 mg, 2.81 mmol, 1 equiv) in MeOH (50 ml) and H_2O (5 ml) was added 10% palladium on charcoal (50% wet, 400 mg, 28% w/w) and NH_4COOH (1.77 g, 28.1 mmol, 10 equiv) and the resulting mixture was stirred at 70°C for 30 min then cooled to room temperature. The catalyst was filtered off through a pad of celite and most of the MeOH was removed *in vacuo*. The residue was diluted with AcOEt and the organic layer was washed with a saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo* to give methyl 4-amino-1-ethyl-1*H*-benzimidazole-6-carboxylate (D207) (500 mg, 81%) as a white solid which was used in the next step without further purification. $[M+H]^+$ = 220.2, RT = 2.17 min.

Description 208

Methyl 4-[(2-chloroethyl)amino]-3,5-dinitrobenzoate (D208)

To a solution of methyl 4-chloro-3,5-dinitrobenzoate (D25a) (5.0 g, 19.2 mmol, 1 equiv) in MeOH (300 ml) was added 2-chloroethylamine hydrochloride (4.64 mg, 40 mmol, 2.1 equiv) and NEt_3 (5.5 ml, 40 mmol, 2.1 equiv) and the resulting mixture was refluxed for 5 min then cooled to room temperature. Most of the solvent was evaporated *in vacuo* and the residue filtered off to give methyl 4-[(2-chloroethyl)amino]-3,5-dinitrobenzoate (D208) (9 g, 156%) as a yellow solid which was used in the next step without further purification.
$[M+H]^+$ = 304.1, RT = 3.06 min.

Description 209

Methyl 8-nitro-1,2,3,4-tetrahydro-6-quinoxalinecarboxylate (D209)

To a solution of crude methyl 4-[(2-chloroethyl)amino]-3,5-dinitrobenzoate (D208) (9 g, 19.2 mmol, 1 equiv) in MeOH (75 ml) and cyclohexene (150 ml) was added 10% palladium on charcoal (50% wet, 4.5 g, 25% w/w) and the resulting mixture was refluxed for 3 h then cooled to room temperature. The catalyst was filtered off through a pad of celite and most of the solvent was removed *in vacuo*. The residue was partitioned between AcOEt and a 2N aqueous HCl solution and the two layers were separated. The aqueous phase was extracted twice with AcOEt and the combined organic layers were washed with a saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt: 1/1) gave methyl 8-nitro-1,2,3,4-tetrahydro-6-quinoxalinecarboxylate (D209) (1.5 g, 34%) as a red solid. $[M-H]^-$ = 236.2 ,RT = 2.65 min.

Description 210

Methyl 4-ethyl-8-nitro-1,2,3,4-tetrahydro-6-quinoxalinecarboxylate (D210)

Methyl 4-ethyl-8-nitro-1,2,3,4-tetrahydro-6-quinoxalinecarboxylate (D210) was prepared from methyl 8-nitro-1,2,3,4-tetrahydro-6-quinoxalinecarboxylate (D209) in an analogous manner to the process described for Ester 35 (B35) using acetaldehyde instead of propionaldehyde. $[M+H]^+$ = 266.3, RT = 3.07 min.

Description 211

Methyl 8-amino-4-ethyl-1,2,3,4-tetrahydro-6-quinoxalinecarboxylate (D211)

Methyl 8-amino-4-ethyl-1,2,3,4-tetrahydro-6-quinoxalinecarboxylate (D211) was prepared from methyl 4-ethyl-8-nitro-1,2,3,4-tetrahydro-6-quinoxalinecarboxylate (D210) in an analogous manner to the process described for Description 207 (D207). $[M+H]^+$ = 236.2, RT = 2.23 min.

Description 212

Ethyl 4-amino-3-nitrobenzoate (D212)

Ethyl 4-amino-3-nitrobenzoate (D212) was prepared in an analogous manner to Description 25 from commercially available 4-amino-3-nitrobenzoic acid using EtOH as solvent instead of MeOH.

Description 213

Ethyl 4-amino-3-bromo-5-nitrobenzoate (D213)

To a solution of ethyl 4-amino-3-nitrobenzoate (D212) (21.0 g, 100 mmol, 1 equiv) in CH_2Cl_2 (500 ml) at room temperature was added bromine (6.7 ml, 130 mmol, 1.3 equiv) and the resulting mixture was refluxed for 4 h then bromine (2 ml, 40 mmol, 0.4 equiv) was added and the resulting mixture refluxed for another 3 h then cooled to room temperature. The organic phase was washed twice with a 10% aqueous $Na_2S_2O_3$ solution and twice with H_2O, dried over $MgSO_4$ and concentrated *in vacuo* to give ethyl 4-amino-3-bromo-5-nitrobenzoate (D213) (27.1 g, 94%) as a yellow solid which was used in the next step without further purification.

Description 214

Ethyl 3-bromo-5-nitro-4-[(trifluoroacetyl)amino]benzoate (D214)

To a solution of ethyl 4-amino-3-bromo-5-nitrobenzoate (D213) (27.1 g, 93.1 mmol, 1 equiv) in CH_2Cl_2 (500 ml) at room temperature was added *N,N*-diisopropylethylamine (22 ml, 130 mmol, 1.4 equiv) and trifluoroacetic acid anhydride (15.8 ml, 111.7 mmol, 1.2 equiv) and the resulting mixture was stirred for 2 h. *N,N*-diisopropylethylamine (22 ml, 130 mmol, 1.4 equiv) and trifluoroacetic acid anhydride (15.8 ml, 111.7 mmol, 1.2 equiv) were added and the resulting mixture was stirred for another 2 h. H_2O was added and the two layers were separated. The organic phase was washed twice with a 2N aqueous HCl solution, H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt: 9/1 to 3/1) gave ethyl 3-bromo-5-nitro-4-[(trifluoroacetyl)amino]benzoate (D214) (29.4 g, 82%) as a yellow solid.

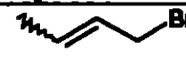
Description 215

Ethyl 3-bromo-4-[(3-methyl-2-buten-1-yl)(trifluoroacetyl)amino]-5-nitrobenzoate (D215)

To a solution of ethyl 3-bromo-5-nitro-4-[(trifluoroacetyl)amino]benzoate (D214) (12.0 g, 31.3 mmol, 1 equiv) in CH_3CN (100 ml) was added K_2CO_3 (5.6 g, 40 mmol, 1.3 equiv) and 1-bromo-3-methyl-2-butene (5.1 ml, 43.8 mmol, 1.4 equiv) and the resulting mixture was refluxed for 1 h then cooled to room temperature. The precipitate formed was filtered off through a pad of celite and washed with CH_3CN. The combined organic layers were concentrated *in vacuo* and the residue diluted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt: 9/1 to 4/1) gave ethyl 3-bromo-4-[(3-methyl-2-buten-1-yl)(trifluoroacetyl)amino]-5-nitrobenzoate (D215) (12.9 g, 91%) as an orange oil.

Descriptions 216-217 (D216-217)

The following compounds were obtained from ethyl 3-bromo-5-nitro-4-[(trifluoroacetyl)amino]benzoate (D214) in an analogous manner using the appropriate allyl bromide:

Description	Allyl bromide
Ethyl 3-bromo-4-[(2*E/Z*)-2-buten-1-yl(trifluoroacetyl)amino]-5-nitrobenzoate (D216)	
Ethyl 3-bromo-5-nitro-4-[2-propen-1-yl(trifluoroacetyl)amino]benzoate (D217)	

Description 218

Ethyl 3-(1-methylethyl)-7-nitro-1*H*-indole-5-carboxylate (D218)

To a solution of ethyl 3-bromo-4-[(3-methyl-2-buten-1-yl)(trifluoroacetyl)amino]-5-nitrobenzoate (D215) (12.9 g, 28.5 mmol, 1 equiv) in DMF (130 ml) were added HCOONa (1.94 g, 28.5 mmol, 1 equiv), Na_2CO_3 (7.54 g, 71.2 mmol, 2.5 equiv), Bu_4NCl (8.7 g, 31.3 mmol, 1.1 equiv) and palladium (II) acetate (320 mg, 1.42 mmol, 0.05 equiv) and the resulting mixture was stirred under nitrogen for 1 h then cooled to room temperature and *concentrated*

in vacuo. The residue was partitioned between AcOEt and H_2O and the two layers were separated. The insoluble material in the aqueous phase was filtered off through a pad of celite and the aqueous layer extracted twice with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give methyl 3-(1-methylethyl)-7-nitro-1*H*-indole-5-carboxylate (D218) (10.1 g, 128%) as a black solid which was used in the next step without further purification.

Descriptions 219-220 (D219-220)

The following compounds were obtained in an analogous manner using the appropriate precursor:

Description	Precursor
Ethyl 3-ethyl-7-nitro-1*H*-indole-5-carboxylate (D219)	D216
Ethyl 3-methyl-7-nitro-1*H*-indole-5-carboxylate (D220)	D217

Description 221

Ethyl 7-amino-3-(1-methylethyl)-1*H*-indole-5-carboxylate (D221)

To a solution of crude ethyl 3-(1-methylethyl)-7-nitro-1*H*-indole-5-carboxylate (D218) (10.1 g, 28.5 mmol, 1 equiv) in MeOH (250 ml) and H_2O (25 ml) was added 10% palladium on charcoal (50% wet, 1.5 g, 8% w/w) and NH_4COOH (17 g, 280 mmol, 10 equiv) and the resulting mixture was stirred at 70°C for 3 h then cooled to room temperature. The catalyst was filtered off through a pad of celite and most of the MeOH was removed *in vacuo*. The residue was diluted with AcOEt and the organic layer was washed with a saturated $NaHCO_3$ aqueous solution, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt: 3/1 to 1/1) gave methyl 7-amino-3-(1-methylethyl)-1*H*-indole-5-carboxylate (D221) (1.47 g, 21%) as a white solid.

Descriptions 222-223 (D222-223)

The following compounds were obtained in an analogous manner to the process described for Description 221 using the appropriate precursor:

Description	Precursor
Ethyl 7-amino-3-ethyl-1*H*-indole-5-carboxylate (D222)	D219
Ethyl 7-amino-3-methyl-1*H*-indole-5-carboxylate (D223)	D220

Descriptions 224-230 (D224-230)

The following compounds have been obtained from their corresponding precursors in an analogous manner to the process described for Description 2 (D2):

Description	Precursor	$[M+H]^+$	RT (min)
Ethyl 7-[(4-chlorobutanoyl)amino]-3-methyl-1*H*-indole-5-carboxylate (D224)	D223		
Ethyl 7-[(4-chlorobutanoyl)amino]-3-ethyl-1*H*-indole-5-carboxylate (D225)	D222		
Ethyl 7-[(4-chlorobutanoyl)amino]-3-(1-	D221		

methylethyl)-1*H*-indole-5-carboxylate (D226)			
Methyl 4-[(4-chlorobutanoyl)amino]-1-ethyl-1*H*-benzimidazole-6-carboxylate (D227)	D207		
Methyl 4-[(4-chlorobutanoyl)amino]-1*H*-indole-6-carboxylate (D228)	D201	295.0	2.63
Methyl 4-[(4-chlorobutanoyl)amino]-1-ethyl-1*H*-indazole-6-carboxylate (D229)	D199	324.3	2.70
Methyl 8-[(4-chlorobutanoyl)amino]-4-ethyl-1,2,3,4-tetrahydro-6-quinoxalinecarboxylate (D230)	D211	340.2	2.73

Description 231

Methyl 4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-1*H*-indole-6-carboxylate (D231)

Methyl 4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-1*H*-indole-6-carboxylate (D231) was obtained from 4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-1*H*-indole-6-carboxylic acid (A155) in an analogous manner to Description 25 (D25).

Description 232

1-(1,1-Dimethylethyl) 6-methyl 4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-1*H*-indole-1,6-dicarboxylate (D232)

To a solution of methyl 4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-1*H*-indole-6-carboxylate (D231) (308 mg, 1.0 mmol, 1 equiv) in CH_2Cl_2 (10 ml) were added NEt_3 (166 µl, 1.2 mmol, 1.2 equiv), bis(1,1-dimethylethyl) dicarbonate (251 mg, 1.15 mmol, 1.15 equiv) and DMAP (12 mg, 0.1 mmol, 0.1 equiv) and the resulting mixture was stirred at room temperature for 30 min. The organic phase was washed with a 2N aqueous HCl solution and a saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo*. Trituration in Et_2O/*iso*-hexane gave 1-(1,1-dimethylethyl) 6-methyl 4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-1*H*-indole-1,6-dicarboxylate (D232) (150 mg, 37%) as a white solid which was used in the next step without further purification. $[M+H+NH_3]^+$ = 426.2, RT = 3.38 min.

Description 233

1-(1,1-Dimethylethyl) 6-methyl 4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2,3-dihydro-1*H*-indole-1,6-dicarboxylate (D233)

1-(1,1-Dimethylethyl) 6-methyl 4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2,3-dihydro-1*H*-indole-1,6-dicarboxylate (D233) was obtained from 1-(1,1-dimethylethyl) 6-methyl 4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-1*H*-indole-1,6-dicarboxylate (D232) in an analogous manner to the process described for Ester 116 (B116). No molecular ion, RT = 3.23 min.

Description 234

Methyl 4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2,3-dihydro-1*H*-indole-6-carboxylate hydrochloride salt (D234)

1-(1,1-Dimethylethyl) 6-methyl 4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2,3-dihydro-1*H*-indole-1,6-dicarboxylate (D233) (500 mg, 1.2 mmol, 1 equiv) was dissolved in a 4N HCl

solution in Et_2O (10 ml, 40 mmol, excess) and the resulting solution was stirred at room temperature for 1 h then concentrated *in vacuo*. Trituration of the residue with Et_2O gave methyl 4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2,3-dihydro-1*H*-indole-6-carboxylate hydrochloride salt (D234) (430 mg, 100%) as a white solid which was used in the next step without further purification. $[M+H]^+$ = 311.0, RT = 2.16 min.

Description 235

Methyl 1-acetyl-4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2,3-dihydro-1*H*-indole-6-carboxylate (D235)

To a solution of methyl 4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2,3-dihydro-1*H*-indole-6-carboxylate hydrochloride salt (D234) (350 mg, 1.0 mmol, 1 equiv) in AcOEt (5 ml) were added NEt_3 (140 ml, 1.0 mmol, 1 equiv) and acetic anhydride (0.5 ml, 5.6 mmol, 5.6 equiv) and the resulting mixture was stirred at 50°C for 30 min then cooled to room temperature and washed with a 2N aqueous HCl solution followed by a saturated aqueous $NaHCO_3$ solution, then dried over $MgSO_4$ and concentrated *in vacuo* to give methyl 1-acetyl-4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2,3-dihydro-1*H*-indole-6-carboxylate (D235) as a white solid which was used in the next step without further purification. $[M+H]^+$ = 353.2, RT = 2.24 min.

Description 236

Methyl 4-{bis[(3-chloropropyl)sulfonyl]amino}-1-ethyl-1*H*-indole-6-carboxylate (D236)

To a solution of methyl 4-amino-1-ethyl-1*H*-indole-6-carboxylate hydrochloride salt (D202) (1.7 g, 6.68 mmol, 1 equiv) in CH_2Cl_2 (50 ml) was added NEt_3 (4.2 ml, 30 mmol, 4.5 equiv) then 3-chloro-1-propanesulfonyl chloride (1.8 ml, 15.0 mmol, 2.2 equiv) and the resulting mixture was stirred for 2 h. The organic phase was washed with a 2N aqueous HCl solution and a saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (AcOEt/*iso*-hexane: 1/1) gave methyl 4-{bis[(3-chloropropyl)sulfonyl]amino}-1-ethyl-1*H*-indole-6-carboxylate (D236) (1.85 g, 55%) as a light tan solid. $[M-H]^-$ = 498.1, RT = 3.51 min.

Description 237

Methyl 4-{bis[(3-chloropropyl)sulfonyl]amino}-1-ethyl-1*H*-indazole-6-carboxylate (D237)

Methyl 4-{bis[(3-chloropropyl)sulfonyl]amino}-1-ethyl-1*H*-indazole-6-carboxylate (D237) was obtained from methyl 4-amino-1-ethyl-1*H*-indazole-6-carboxylate in an analogous manner to the process described for methyl 4-{bis[(3-chloropropyl)sulfonyl]amino}-1-ethyl-1*H*-indole-6-carboxylate (D236). $[M+H]^+$ = 500.1, RT = 3.50 min.

Description 238

Methyl 8-{bis[(3-chloropropyl)sulfonyl]amino}-4-ethyl-1,2,3,4-tetrahydro-6-quinoxalinecarboxylate (D238)

Methyl 8-{bis[(3-chloropropyl)sulfonyl]amino}-4-ethyl-1,2,3,4-tetrahydro-6-quinoxalinecarboxylate (D238) was obtained from methyl 8-amino-4-ethyl-1,2,3,4-tetrahydro-6-quinoxalinecarboxylate (D211) in an analogous manner to the process described for methyl

4-{bis[(3-chloropropyl)sulfonyl]amino}-1-ethyl-1*H*-indole-6-carboxylate (D236). $[M+H]^+$ = 517.2, RT = 3.32 min.

Description 239

Methyl 4-{bis[(3-chloropropyl)sulfonyl]amino}-1-ethyl-1*H*-benzimidazole-6-carboxylate (D239)

Methyl 4-{bis[(3-chloropropyl)sulfonyl]amino}-1-ethyl-1*H*-benzimidazole-6-carboxylate (D239) was obtained from methyl 4-amino-1-ethyl-1*H*-benzimidazole-6-carboxylate (D207) in an analogous manner to the process described for methyl 4-{bis[(3-chloropropyl)sulfonyl]amino}-1-ethyl-1*H*-indole-6-carboxylate (D236). $[M+H]^+$ = 500.3, RT = 3.20 min.

Description 240

4-[[(3-Chloropropyl)sulfonyl]amino}-1-ethyl-1*H*-indole-6-carboxylic acid (D240)

To a solution of methyl 4-{bis[(3-chloropropyl)sulfonyl]amino}-1-ethyl-1*H*-indole-6-carboxylate (D236) (1.8 g, 3.6 mmol, 1 equiv) in MeOH (100 ml) was added a 2N aqueous NaOH solution (20 ml, 40 mmol, excess) and the resulting mixture was stirred for 1 h. Most of MeOH was removed *in vacuo* and the residue partitioned between AcOEt and a 2N aqueous HCl solution. The two layers were separated and the aqueous phase was dried over $MgSO_4$ and concentrated *in vacuo* to give 4-[[(3-chloropropyl)sulfonyl]amino}-1-ethyl-1*H*-indole-6-carboxylic acid (D240) (930 mg, 75%) as a brown oil which was used in the next step without further purification.

Description 241

Methyl 4-[[(3-chloropropyl)sulfonyl]amino}-1-ethyl-1*H*-indole-6-carboxylate (D241)

Methyl 4-[[(3-chloropropyl)sulfonyl]amino}-1-ethyl-1*H*-indole-6-carboxylate (D241) was obtained from 4-[[(3-chloropropyl)sulfonyl]amino}-1-ethyl-1*H*-indole-6-carboxylic acid (D240) in an analogous manner to Description 25 (D25). $[M+H]^+$ = 359.2, RT = 3.12 min.

Description 242

Ethyl 7-[[(4-chlorobutyl)sulfonyl]amino}-3-ethyl-1*H*-indole-5-carboxylate (D242)

To a solution of ethyl 7-amino-3-ethyl-1*H*-indole-5-carboxylate (D222) (150 mg, 0.65 mmol, 1 equiv) in CH_2Cl_2 (10 ml) at room temperature were added pyridine (115 µl, 1.42 mmol, 2.2 equiv), 4-chloro-1-butanesulfonyl chloride (D20) (259 mg, 1.36 mmol, 2.1 equiv) and DMAP (8 mg, 0.065 mmol, 0.1 equiv) and the resulting mixture was stirred for 1 h then diluted with AcOEt and washed with a 2N aqueous HCl solution and brine, then dried over $MgSO_4$ and concentrated *in vacuo* to give ethyl 7-[[(4-chlorobutyl)sulfonyl]amino}-3-ethyl-1*H*-indole-5-carboxylate (D242) (230 mg, 92%) as a purple oil which was used in the next step without further purification. $[M+H]^+$ = 387.3, RT = 3.35 min.

Description 243

Ethyl 7-[[(3-chloropropyl)sulfonyl]amino}-3-ethyl-1*H*-indole-5-carboxylate (D243)

Ethyl 7-[[(3-chloropropyl)sulfonyl]amino}-3-ethyl-1*H*-indole-5-carboxylate (D243) was obtained from ethyl 7-amino-3-ethyl-1*H*-indole-5-carboxylate (D222) in an analogous manner to the

process described for Description 242 (D242) using 3-chloro-1-propanesulfonyl chloride instead of 4-chloro-1-butanesulfonyl chloride (D20). $[M+H]^+$ = 373.0, RT = 3.49 min.

Description 244

3,4-Diamino-5-nitrobenzoic acid (D244)

To a solution of 4-amino-3,5-dinitrobenzoic acid (10 g, 44 mmol, 1 equiv) in DME (100 ml) and $CHCl_3$ (10 ml) under nitrogen was added 10% palladium on charcoal (50% wet, 1 g, 5% w/w) and the resulting suspension was stirred under an atmosphere of nitrogen (35 psi) for 15 h. 10% Palladium on charcoal (50% wet, 1 g, 5% w/w) was added and the resulting suspension was stirred under an atmosphere of hydrogen (35 psi) for another 15 h. The catalyst was filtered off through a pad of celite and the solution was concentrated *in vacuo* to give 3,4-diamino-5-nitrobenzoic acid (D244) (9.85 g, 113%) as a red solid which was used in the next step without further purification. $[M-H]^-$ = 196.1, RT = 2.15 min

Description 245

Methyl 3,4-diamino-5-nitrobenzoate (D245)

Methyl 3,4-diamino-5-nitrobenzoate (D245) was prepared in an analogous manner to Description 25 from 3,4-diamino-5-nitrobenzoic acid (D244).$[M+H]^+$ = 212.2, RT = 2.40 min.

Description 246

Methyl 4-nitro-1*H*-1,2,3-benzotriazole-6-carboxylate (D246)

To a solution of methyl 3,4-diamino-5-nitrobenzoate (D245) (2.5 g, 12 mmol, 1 equiv)in AcOH (10 ml) at room temperature was added $NaNO_2$ (900 mg, 13 mmol, 1.1 equiv) and the resulting mixture was stirred at 60°C for 1 h, cooled to room temperature and concentrated *in vacuo*. the residue was partitioned between AcOEt and a 5% aqueous citric acid solution and the layers were separated. The organic phase was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Trituration of the residue in Et_2O/*iso*-hexane gave methyl 4-nitro-1*H*-1,2,3-benzotriazole-6-carboxylate (D246) (2.08 g, 78%) as an orange solid which was used in the next step without further purification.

$[M+H]^+$ = 223.3, RT = 2.31 min.

Description 247

Methyl 4-amino-1*H*-1,2,3-benzotriazole-6-carboxylate (D247)

Methyl 4-amino-1*H*-1,2,3-benzotriazole-6-carboxylate (D247) was obtained from methyl 4-nitro-1*H*-1,2,3-benzotriazole-6-carboxylate (D246) in an analogous manner to the process described for methyl 5-amino-2-fluoro-3-(2-oxo-1-pyrrolidinyl)benzoate (D150).

$[M+H]^+$ = 193.3, RT = 2.01 min.

Description 248

Methyl 4-[(4-chlorobutanoyl)amino]-1*H*-1,2,3-benzotriazole-6-carboxylate (D248)

Methyl 4-[(4-chlorobutanoyl)amino]-1*H*-1,2,3-benzotriazole-6-carboxylate (D248) was obtained from methyl 4-amino-1*H*-1,2,3-benzotriazole-6-carboxylate (D247) in an analogous manner to the process described for Description 2 (D2). No molecular ion, RT = 3.19 min.

Description 249

Methyl 4-(2-oxo-1-pyrrolidinyl)-1*H*-1,2,3-benzotriazole-6-carboxylate (D249)

Methyl 4-(2-oxo-1-pyrrolidinyl)-1*H*-1,2,3-benzotriazole-6-carboxylate (D249) was obtained from methyl 4-[(4-chlorobutanoyl)amino]-1*H*-1,2,3-benzotriazole-6-carboxylate (D248) in an analogous manner to the process described for Ester 27 (B27). $[M+H]^+$ = 261.2, RT = 2.25 min.

Description 250

Methyl 4-nitro-1*H*-benzimidazole-6-carboxylate (D250)

A solution of methyl 3,4-diamino-5-nitrobenzoate (D245) (1.3 g, 6.16 mmol, 1 equiv) in HCOOH (20 ml) was stirred at 100°C for 1 h then cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between AcOEt and a 2N aqueous NaOH solution and the layers were separated. The organic phase was dried over $MgSO_4$ and concentrated *in vacuo* to give methyl 4-nitro-1*H*-benzimidazole-6-carboxylate (D250) (1.5 g, 110%) as a light brown solid which was used in the next step without further purification. $[M+H]^+$ = 222.3, RT = 2.29 min.

Description 251

Methyl 4-amino-1*H*-benzimidazole-6-carboxylate (D251)

Methyl 4-amino-1*H*-benzimidazole-6-carboxylate (D251) was obtained from methyl 4-nitro-1*H*-benzimidazole-6-carboxylate (D250) in an analogous manner to the process described for methyl 5-amino-2-fluoro-3-(2-oxo-1-pyrrolidinyl)benzoate (D150). $[M+H]^+$ = 192.3, RT = 1.55 min.

Description 252

Methyl 4-{[(4-chlorobutyl)sulfonyl]amino}-1*H*-benzimidazole-6-carboxylate (D252)

To a solution of methyl 4-amino-1*H*-benzimidazole-6-carboxylate (D251) (1.1 g, 5.76 mmol, 1 equiv) in CH_2Cl_2 (80 ml) at room temperature were added pyridine (1.02 ml, 12.67 mmol, 2.2 equiv), 4-chloro-1-butanesulfonyl chloride (D20) (2.31 g, 12.1 mmol, 2.1 equiv) and DMAP (704 mg, 5.76 mmol, 1 equiv) and the resulting mixture was stirred for 1 h then concentrated *in vacuo*. The residue was diluted with AcOEt and the organic phase was washed with a 2N aqueous HCl solution and brine, then dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (AcOEt/*iso*-hexane: 2/3) gave methyl 4-{[(4-chlorobutyl)sulfonyl]amino}-1*H*-benzimidazole-6-carboxylate (D252) (1 g, 50%) as a colorless oil. $[M+H]^+$ = 346.1, RT = 2.97 min.

Description 253

Methyl 4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-1*H*-benzimidazole-6-carboxylate (D253)

To a solution of methyl 4-{[(4-chlorobutyl)sulfonyl]amino}-1*H*-benzimidazole-6-carboxylate (D252) (1 g, 3.23 mmol, 1 equiv) in EtOH (50 ml) was added NEt_3 (2 ml, excess) and the resulting solution was stirred at 70°C for 2 days. then cooled to room temperature and

concentrated *in vacuo*. The residue was dissolved in AcOEt and the organic phase was washed with a 5% aqueous citric acid solution. The aqueous phase was saturated with NaCl and extracted twice with AcOEt. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (CH_2Cl_2/MeOH: 98/4 to 90/10) gave methyl 4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-1*H*-benzimidazole-6-carboxylate (D253) (250 mg, 25%) as a pale yellow solid. $[M+H]^+$ = 310.3, *RT* = 2.11 min.

Description 254

Methyl 4-hydroxy-3,5-diiodobenzoate (D254)

Methyl 4-hydroxy-3,5-diiodobenzoate (D254) was prepared in an analogous manner to Description 25 (D25) from commercially available 4-hydroxy-3,5-diiodobenzoic acid.

Description 255

Methyl 4-[(2*E*/*Z*)-2-buten-1-yloxy]-3,5-diiodobenzoate (D255)

To a solution of methyl 4-hydroxy-3,5-diiodobenzoate (D254) (26.9 g, 66.7 mmol, 1 equiv) in acetone (250 ml) at room temperature were added K_2CO_3 (13.8 g, 100 mmol, 1.5 equiv) and 1-bromo-2-butene (8.25 ml, 80 mmol, 1.2 equiv) and the resulting suspension was stirred at 55°C for 15 h then cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between AcOEt and H_2O and the two layers were separated. The organic phase was washed with a 2N aqueous NaOH solution and brine, dried over $MgSO_4$ and concentrated *in vacuo* to give methyl 4-[(2*E*/*Z*)-2-buten-1-yloxy]-3,5-diiodobenzoate (D255) (28.6 g, 94%) as a white solid which was used in the next step without further purification.

Description 256

Methyl 3,5-diiodo-4-(2-propen-1-yloxy)benzoate (D256)

Methyl 3,5-diiodo-4-(2-propen-1-yloxy)benzoate (D256) was obtained from methyl 4-hydroxy-3,5-diiodobenzoate (D254) in an analogous manner to the process described for Description 255 (D255) using 3-bromo-1-propene instead of 1-bromo-2-butene.

Description 257

Methyl 4-(3-buten-1-yloxy)-3,5-diiodobenzoate (D257)

Methyl 4-(3-buten-1-yloxy)-3,5-diiodobenzoate (D257) was obtained from methyl 4-hydroxy-3,5-diiodobenzoate (D254) in an analogous manner to the process described for Description 255 (D255) using 4-bromo-1-butene instead of 1-bromo-2-butene. $[M+H]^+$ = 458.8, RT = 4.05 min.

Description 258

Methyl 4-[(2*E*/*Z*)-2-buten-1-yloxy]-3-iodo-5-(2-oxo-1-pyrrolidinyl)benzoate (D258)

To a solution of methyl 4-[(2*E*/*Z*)-2-buten-1-yloxy]-3,5-diiodobenzoate (D255) (5 g, 11 mmol, 1 equiv) in toluene (50 ml) were added 2-pyrrolidinone (1.08 g, 13 mmol, 1.2 equiv), K_3PO_4 (4.46 g, 21 mmol, 2 equiv), CuI (105 mg, 0.55 mmol, 0.05 equiv) and dimethyl ethylene diamine (117 µl, 1.1 mmol, 0.1 equiv) and the resulting mixture was stirred at 100°C for 15 h

then cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between AcOEt and H_2O and the layers were separated. The organic phase was dried under $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (AcOEt/*iso*-hexane: 1/1) gave methyl 4-[(2*E*/*Z*)-2-buten-1-yloxy]-3-iodo-5-(2-oxo-1-pyrrolidinyl)benzoate (D258) (1.4 g, 31%) as a colorless oil. $[M+H]^+$ = 415.9 ,RT = 3.27 min.

Description 259

Methyl 3-iodo-5-(2-oxo-1-pyrrolidinyl)-4-(2-propen-1-yloxy)benzoate (D259)

Methyl 3-iodo-5-(2-oxo-1-pyrrolidinyl)-4-(2-propen-1-yloxy)benzoate (D259) was obtained from methyl 3,5-diiodo-4-(2-propen-1-yloxy)benzoate (D256) in an analogous manner to the process described for Description 258 (D258).

Description 260

Methyl 4-(3-buten-1-yloxy)-3-iodo-5-(2-oxo-1-pyrrolidinyl)benzoate (D260)

Methyl 4-(3-buten-1-yloxy)-3-iodo-5-(2-oxo-1-pyrrolidinyl)benzoate (D260) was obtained from methyl 4-(3-buten-1-yloxy)-3,5-diiodobenzoate (D257) in an analogous manner to the process described for Description 258 (D258). $[M+H]^+$ = 416.0, RT = 3.02 min.

Description 261

Methyl 4-methyl-8-(2-oxo-1-pyrrolidinyl)-2*H*-chromene-6-carboxylate and methyl 4-(ethyloxy)-3-[ethyl(propanoyl)amino]-5-(1-methylethenyl)benzoate (D261)

Methyl 4-methyl-8-(2-oxo-1-pyrrolidinyl)-2*H*-chromene-6-carboxylate and methyl 4-(ethyloxy)-3-[ethyl(propanoyl)amino]-5-(1-methylethenyl)benzoate (D261) were obtained from methyl 4-(3-buten-1-yloxy)-3-iodo-5-(2-oxo-1-pyrrolidinyl)benzoate (D260) in an analogous manner to the process described for methyl 3-ethyl-7-(2-oxo-1-pyrrolidinyl)-1-benzofuran-5-carboxylate (B163). $[M+H]^+$ = 288.1, RT = min.

Description 262

Methyl 3-bromo-5-(1,1-dioxido-2-isothiazolidinyl)benzoate (D262)

Methyl 3-bromo-5-(1,1-dioxido-2-isothiazolidinyl)benzoate (D262) was obtained from methyl 3-bromo-5-iodobenzoate (D8a) in an analogous manner to the process described for Description 17 (D17) using D8a instead of D8b as starting material.

Description 263

Methyl 3-bromo-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)benzoate (D263)

Methyl 3-bromo-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)benzoate (D263) was obtained from methyl 3-bromo-5-iodobenzoate (D8a) in an analogous manner to the process described for Description 18 (D18) using D8a instead of D8b as starting material.

Description 264

Methyl 3-(3-cyclopenten-1-yl)-5-(1,1-dioxido-2-isothiazolidinyl)benzoate;
Methyl 3-(2-cyclopenten-1-yl)-5-(1,1-dioxido-2-isothiazolidinyl)benzoate;
Methyl 3-(1-cyclopenten-1-yl)-5-(1,1-dioxido-2-isothiazolidinyl)benzoate (D264)

Methyl 3-(3-cyclopenten-1-yl)-5-(1,1-dioxido-2-isothiazolidinyl)benzoate, methyl 3-(2-cyclopenten-1-yl)-5-(1,1-dioxido-2-isothiazolidinyl)benzoate and methyl 3-(1-cyclopenten-1-yl)-5-(1,1-dioxido-2-isothiazolidinyl)benzoate (D264) have been obtained from methyl 3-bromo-5-(1,1-dioxido-2-isothiazolidinyl)benzoate (D262) in an analogous manner to the process described for Description 73 (D73)

Description 265

Methyl 3-(1-cyclopenten-1-yl)-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)benzoate; Methyl 3-(2-cyclopenten-1-yl)-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)benzoate; Methyl 3-(3-cyclopenten-1-yl)-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)benzoate (D265)

Methyl 3-(1-cyclopenten-1-yl)-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)benzoate, methyl 3-(2-cyclopenten-1-yl)-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)benzoate and methyl 3-(3-cyclopenten-1-yl)-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)benzoate (D265) have been obtained from methyl 3-bromo-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)benzoate (D263) in an analogous manner to the process described for Description 73 (D73).

Description 266

Methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-nitrobenzoate (D266)

Methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-nitrobenzoate (D266) was obtained from methyl 3-bromo-5-nitrobenzoate (D11) in an analogous manner to the process described for Description 15 (D15) using Description 22b (D22b) instead of Description D22a (D22a).

Description 267

Methyl 3-amino-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)benzoate (D267)

Methyl 3-amino-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)benzoate (D267) was obtained from methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-nitrobenzoate (D266) in an analogous manner to the process described for Description 16 (D16).

Description 268

Methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-hydroxybenzoate (D268)

To a solution of methyl 3-amino-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)benzoate (D267) (7.5 g, 26.4 mol, 1 equiv) in a 2N aqueous HCl solution (75 ml) and MeOH (75 ml) at 0°C was added $NaNO_2$ (4.0 g, 58.1 mmol, 2.2 equiv) portionwise over 20 min. MeOH (50 ml) and H_2O (200 ml) were added and the resulting mixture was stirred at 95°C for 1 h then cooled to room temperature. Most of the MeOH was removed *in vacuo* and the resulting aqueous phase was extracted with AcOEt. The insoluble material was filtered off to give methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-hydroxybenzoate (D) (0.63 g, 8%). The organic phase was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give a brown residue which was redissolved in AcOEt. The organic phase was extracted with a saturated aqueous Na_2CO_3 solution and the aqueous phase was extracted three times with Et_2O then acidified to pH 1 and re-extracted three times with AcOEt. The combined organic phases were washed

with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-hydroxybenzoate (D268) (2.2 g, 30%).

Description 269

Methyl 5-(1-cyclopenten-1-yl)-3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluorobenzoate; methyl 5-(2-cyclopenten-1-yl)-3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluorobenzoate; methyl 5-(3-cyclopenten-1-yl)-3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluorobenzoate (D269)

Methyl 5-(1-cyclopenten-1-yl)-3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluorobenzoate; methyl 5-(2-cyclopenten-1-yl)-3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluorobenzoate; methyl 5-(3-cyclopenten-1-yl)-3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluorobenzoate (D269) were obtained from Description 158 (D158) in an analogous manner to the process described for Description 73 (D73)

Description 270

Ethyl 2-methyl-2-[3-(trifluoromethyl)phenyl]propanoate (D270)

Ethyl 2-methyl-2-[3-(trifluoromethyl)phenyl]propanoate (D270) was obtained from ethyl [3-(trifluoromethyl)phenyl]acetate in an analogous manner to the process described for Description 98 (D98).

Description 271

2-Methyl-2-[3-(trifluoromethyl)phenyl]propanoic acid (D271)

2-Methyl-2-[3-(trifluoromethyl)phenyl]propanoic acid (D271) was obtained from ethyl 2-methyl-2-[3-(trifluoromethyl)phenyl]propanoate (D270) in an analogous manner to the process described for Description 99 (D99).

Description 272

Phenylmethyl {1-methyl-1-[3-(trifluoromethyl)phenyl]ethyl}carbamate (D272)

Phenylmethyl {1-methyl-1-[3-(trifluoromethyl)phenyl]ethyl}carbamate (D272) was obtained from 2-methyl-2-[3-(trifluoromethyl)phenyl]propanoic acid (D271) in an analogous manner to the process described for Description 100 (D100).

Description 273

2-({[(1,1-Dimethylethyl)oxy]carbonyl}amino)-2-methylpropyl methanesulfonate (D273)

To a solution of 1,1-dimethylethyl (2-hydroxy-1,1-dimethylethyl)carbamate (5.1 g, 27 mmol, 1 equiv) in CH_2Cl_2 (100 ml) at room temperature were added NEt3 (11.3 ml, 81 mmol, 3 equiv) and methanesulfonyl chloride (28.3 mmol, 2.2 ml, 1.05 equiv)and the resulting solution was stirred for 2 h then partitioned between AcOEt and a saturated aqueous $NaHCO_3$ solution. The two layers were separated and the organic phase dried over $MgSO_4$ and concentrated *in vacuo* to give 2-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-2-methylpropyl methanesulfonate (D273) (7.8 g, 108%) as a yellow oil which was used in the next step without further purification.

89

Description 274

1,1-Dimethylethyl [1,1-dimethyl-2-(phenyloxy)ethyl]carbamate (D274)

To a solution of phenol (2.1 g, 22.4 mmol, 3 equiv) in DMF (10 ml) at room temperature were added NaH (60% dispersion in mineral oil, 360 mg, 9.0 mmol, 1.2 equiv) and after 10 min 2-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-2-methylpropyl methanesulfonate (D273) (2 g, 7.5 mmol, 1 equiv) and the resulting solution was stirred at 50°C for 2 h then cooled to room temperature and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt: 9/1 to 6/1) gave 1,1-dimethylethyl [1,1-dimethyl-2-(phenyloxy)ethyl]carbamate (D274) (180 mg, 9%) as a yellow oil.

Description 275

1,1-Dimethylethyl {1,1-dimethyl-2-[(phenylmethyl)oxy]ethyl}carbamate (D275)

1,1-Dimethylethyl {1,1-dimethyl-2-[(phenylmethyl)oxy]ethyl}carbamate (D275) was prepared from 2-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-2-methylpropyl methanesulfonate (D273) in an analogous manner to 1,1-dimethylethyl [1,1-dimethyl-2-(phenyloxy)ethyl]carbamate (D274) using phenylmethanol instead of phenol.

Description 276

1,1-Dimethylethyl {1,1-dimethyl-2-[(2-methylpropyl)thio]ethyl}carbamate (D276)

1,1-Dimethylethyl {1,1-dimethyl-2-[(2-methylpropyl)thio]ethyl}carbamate (D276) was prepared from 2-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-2-methylpropyl methanesulfonate (D273) in an analogous manner to 1,1-dimethylethyl [1,1-dimethyl-2-(phenyloxy)ethyl]carbamate (D274)using 2-methyl-1-propanethiol instead of phenol.

Description 277

1,1-Dimethylethyl (4,4-difluorocyclohexyl)carbamate (D277)

To a solution of 1,1-dimethylethyl (4-oxocyclohexyl)carbamate (1 g, 4.69 mmol, 1 equiv) in CH_2Cl_2 (15 ml) was added DAST (1.05 ml, 7.98 mmol, 1.7 equiv) and the resulting mixture was stirred for 15 h. A saturated aqueous $NaHCO_3$ solution was added and the resulting biphasic mixture was stirred vigorously for 1 h. The two layers were separated and the aqueous phase extracted with CH_2Cl_2. The combined organic phase were dried over $MgSO_4$ and concentrated *in vacuo* to give 1,1-dimethylethyl (4,4-difluorocyclohexyl)carbamate (D277) (1.03 g, 93%) as a beige solid which was used in the next step without further purification.

Descriptions 278-281 (D278-281)

The following acids have been obtained by alkylation of cyclobutanecarboxylic acid as described in: K. Tani, A. Naganawa, A. Ishida, K. Sagawa, H. Harada, M. Ogawa, T. Maruyama, S. Ohuchida, H. Nakai, K. Kondo, M. Toda *Bio. Med. Chem.* 2002, 10, 1093-1106:

Description
1-Ethylcyclobutanecarboxylic acid (D278)
1-Propylcyclobutanecarboxylic acid (D279)
1-(1-Methylethyl)cyclobutanecarboxylic acid (D280)

1-[(3-Chlorophenyl)methyl] cyclobutanecarboxylic acid (D281)

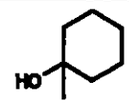
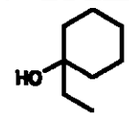
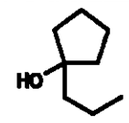
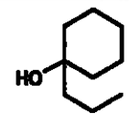
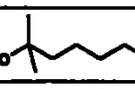
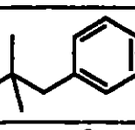
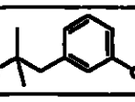
Descriptions 282-285 (D282-285)

The following compounds have been obtained from their precursors in an analogous manner to the process described for Description 100 (D100):

Description	Precursor
Phenylmethyl (1-ethylcyclobutyl) carbamate (D282)	D278
Phenylmethyl (1-propylcyclobutyl) carbamate (D283)	D279
Phenylmethyl [1-(1-methylethyl)cyclobutyl] carbamate (D284)	D280
Phenylmethyl {1-[(3-chlorophenyl)methyl] cyclobutyl}carbamate (D285)	D281

Descriptions 286-293 (D286-293)

The following amides were obtained via a Ritter reaction as described in: M. Mousseron Bull. Soc. Chim. Fr. 1957, 596.:

Description	Precursor
N-(1-Methylcyclohexyl) acetamide (D286)	
N-(1-Ethylcyclohexyl) acetamide (D287)	
N-(1-Methylcyclopentyl) acetamide (D288)	
N-(1-Propylcyclopentyl) acetamide (D289)	
N-(1-Propylcyclohexyl) acetamide (D290)	
N-(1,1-Dimethylhexyl)acetamide (D291)	
N-[2-(3-Chlorophenyl)-1,1-dimethylethyl] acetamide (D292)	
N-(1,1-Dimethyl-2-[3-(methyloxy)phenyl]ethyl)acetamide (D293)	

Description 294

4,4-Dimethylcyclohexanone (D294)

4,4-Dimethylcyclohexanone (D294) was obtained from 4,4-dimethyl-2-cyclohexen-1-one in an analogous manner to the process described for ester 116 (B116).

Description 295

3,3-Dimethylcyclopentanone (D295)

3,3-Dimethylcyclopentanone (D295) was obtained from 4,4-dimethyl-2-cyclopenten-1-one in an analogous manner to the process described for 4,4-dimethylcyclohexanone (D294).

Description 296

4,4-Dimethylcyclohexanone oxime (D296)

To a solution of 4,4-dimethylcyclohexanone (D294) (9.2 g, 73 mmol, 1 equiv) in EtOH (50 ml) and H_2O (50 ml) were added $NH_2OH.HCl$ (6.6 g, 94.5 mmol, 1.3 equiv) and Na_2CO_3 (10.06 g, 94.5 mmol, 1.3 equiv) and the resulting cloudy solution was refluxed for 2 h then cooled to room temperature. Most of EtOH was removed in vacuo and the aqueous phase was extracted twice with AcOEt. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give 4,4-dimethylcyclohexanone oxime (D296) (10 g, 97%) as a colourless solid which was used in the next step without purification.

Descriptions 297-298 (D297-298)

The following oxime were obtained for their precursor in an analogous manner to the process described for Description (D296).

Description	Precursor
(1*E/Z*)-2,2-Dimethylcyclohexanone oxime (D297)	D294
(*1E/Z*)-3,3-Dimethylcyclopentanone oxime (D298)	D295

Descriptions 299-311 (D299-311)

The following compounds have been obtained from (2*S*)-2-(1-methylethyl)-3,6-bis(methyloxy)-2,5-dihydropyrazine according to the general procedure described in: P. dalla Croce, C. la Rosa, E. Pizzatti *Tetrahedron: Asymmetry* 2000, *11*, 2635-2642:

Description
3,5-Difluoro-L-phenylalaninate (D299)
3-Fluoro-L-phenylalaninate (D300)
3,4-Difluoro-L-phenylalaninate (D301)
2-Chloro-L-phenylalaninate (D302)
Methyl-3-chloro-L-phenylalaninate (D303)
Methyl 4-chloro-L-phenylalaninate (D304)
Methyl 3-(2-thienyl)-L-alaninate (D305)
Methyl 3-(3-thienyl)-L-alaninate (D306)
Methyl 3-(2-furanyl)-L-alaninate (D307)
Methyl 3-(2-pyridinyl)-L-alaninate (D308)
Methyl 3-(1,3-thiazol-2-yl)-L-alaninate (D309)
Methyl 3-(1*H*-pyrazol-1-yl)-L-alaninate (D310)
Methyl 3-(3-pyridinyl)-L-alaninate (D311)

Descriptions 312-313 (D312-313)

Descriptions 312-313 were prepared in an analogous manner to Example 1 from the appropriate acid and amines indicated in the below table:

Description	Acid	Amine	$[M+H]^+$	RT (min)
3-(1,1-dioxido-6,7-dihydro-1,2-thiazepin-2(3H)-yl)-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-5-propylbenzamide (D312)	A117	C16	630.4	2.89
3-(1,1-dioxido-6,7-dihydro-1,2-thiazepin-2(3H)-yl)-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-5-propylbenzamide (D313)	A117	C14	592.4	2.75

Description 314

1-[3-(Methyloxy)phenyl]cyclohexanol (D314)

To a solution of 3-methoxyphenylmagnesium bromide (1M in THF, 61 ml, 61 mmol, 1 equiv) at 0°C was slowly added cyclohexanone (6g, 61 mmol, 1 equiv) in Et_2O (30 ml). The resulting mixture was stirred at room temperature for 4 h then poured in H_2O at 0°C. The two layers were separated and the aqueous phase was extracted three times with Et_2O. The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give 1-[3-(methyloxy)phenyl]cyclohexanol (D314) (12.4 g, 100%) as a pale yellow oil which was used in the next step without further purification.

Description 315

1-(1-Azidocyclohexyl)-3-(methyloxy)benzene (D315)

To a solution of 1-[3-(methyloxy)phenyl]cyclohexanol (2.93 g, 14.22 mmol, 1 equiv) in CH_2Cl_2 (25 ml) under nitrogen at 0°C was added sodium azide (1.85 g, 28.44 mmol, 2 equiv) then TFA (4.4 ml, 56.89 mmol, 4 equiv) slowly. 40 Ml of CH_2Cl_2 were then added and the resulting suspension was stirred at room temperature for 16 h then partitioned between Et_2O and H_2O. The two layers were separated and the organic phase was washed with H_2O and a 1N aqueous NaOH solution then dried over $MgSO_4$ and concentrated *in vacuo* to give 1-(1-azidocyclohexyl)-3-(methyloxy)benzene (D315) (2.78 g, 85%) as a clear oil which was used in the next step without further purification.

Description 316

(1*E/Z*)-Propanal oxime (D316)

(1*E/Z*)-Propanal oxime was obtained from propanal in a similar manner to the process described for Description 298 (D298).

Description 317

1,1-Dimethylethyl 2-propyn-1-ylcarbamate (D317)

To a solution of 2-propyn-1-amine (2 g, 36.4 mmol, 1 equiv) in CH_2Cl_2 (20 ml) were added NEt_3 (5.3 ml, 38.18 mmol, 1.05 equiv) and bis(1,1-dimethylethyl) dicarbonate (8.32 g, 38.18 mmol, 1.05 equiv). The resulting mixture was stirred at room temperature for 3 h then poured in a 2N aqueous HCl solution. The two layers were separated and the organic phase was washed with a saturated aqueous $NaHCO_3$ solution then dried over $MgSO_4$ and concentrated *in vacuo* to give 1,1-dimethylethyl 2-propyn-1-ylcarbamate (D317) (4.05 g, 72%) as a colourless crystal.

Description G33

((1S,2R)-2-hydroxy-1-isobutylcarbamoyl-pentyl)-carbamic acid *tert*-butyl ester (G33)

(2S,3R)-2-*tert*-Butoxycarbonylamino-3-hydroxy-hexanoic acid methyl ester (D94) (1.57g, 6.02 mmol, 1 equiv) was refluxed in *iso*-butylamine (10 ml) for 2 h. The solution was concentrated *in vacuo* and the residue purified by flash chromatography on silica gel to give ((1S,2R)-2-hydroxy-1-isobutylcarbamoyl-pentyl)-carbamic acid *tert*-butyl ester (G33) (1.52g, 84%) as a white solid.

The following compounds were obtained in an analogous manner to Description 96a using the appropriate (commercially available) acid and amine:

Name
((S)-1-Cyclohexylcarbamoyl-3-methylsulfanyl-propyl)-carbamic acid *tert*-butyl ester (G6)
[(S)-1-(3,3-Dimethyl-butylcarbamoyl)-ethyl]-carbamic acid *tert*-butyl ester (G36)

Description G38

((S)-1-Isobutylcarbamoyl-3-methanesulfonyl-propyl)-carbamic acid *tert*-butyl ester (G38)

To ((S)-1-Isobutylcarbamoyl-3-methylsulfanyl-propyl)-carbamic acid *tert*-butyl ester (D96) (1.19 g, 3.9 mmol, 1 equiv) in CH_2Cl_2 (25 ml) at 0°C was added *m*-chloroperbenzoic acid (50-55%, 4.0 g, 11.6 mmol, 3 equiv) portionwise. The resulting mixture was stirred 2 h at 0°C then diluted with AcOEt and washed with saturated $NaHCO_3$ aqueous solution, dried over $MgSO_4$ and concentrated *in vacuo* to give ((S)-1-Isobutylcarbamoyl-3-methanesulfonyl-propyl)-carbamic acid *tert*-butyl ester (G38) (1.06 g, 81%) as a colourless solid.

Description G157

1,1-Dimethylethyl [(3-ethyl-5-isoxazolyl)methyl]carbamate (G157)

To a solution of (1*E/Z*)-propanal oxime (D316) (4g, 54.8 mmol, 1 equiv) in CH_2Cl_2 (200 ml) at room temperature was added N-chloro succinamide (7.44 g, 55.8 mmol, 1.02 equiv) and the resulting solution was stirred at this temperature for 2.5 h then NEt_3 (20 ml, excess) was added and the resulting mixture stirred for 2 h. DIPEA (9.52 mmol, 55.8 mmol, 1.02 equiv) and 1,1-dimethylethyl 2-propyn-1-ylcarbamate (D317) (1.34 g, 8.76 mmol, 0.16 equiv) were added and the solution stirred for 48 h then poured into a 1M aqueous HCl solution. The two layers were separated and the organic phase was washed with a saturated aqueous $NaHCO_3$ solution then dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash

chromatography on silicagel (iso-hexane/AcOEt: 4/1 to 3/1) gave 1,1-dimethylethyl [(3-ethyl-5-isoxazolyl)methyl]carbamate (G157) (1.28 g, 83%).

Description F5

1,1,5-Trimethyl-hexylamine (F5)

Description F5 was obtained according to S. S. Berg and D. T. Cowling, *J. Chem. Soc.* (C) 1971, 1653-1658.

Description F33

(2S,3R)-2-Amino-3-hydroxy-hexanoic acid isobutyl-amide hydrochloride salt (F33)

(2S,3R)-2-*tert*-Butoxycarbonylamino-3-hydroxy-hexanoic acid methyl ester (G33) (235 mg, 0.86 mmol, 1 equiv) was dissolved in 4M HCl in dioxan (4 ml) and the solution was stirred for 1 h at room temperature then concentrated *in vacuo*. The residue was triturated with Et_2O to give (2S,3R)-2-amino-3-hydroxy-hexanoic acid isobutyl-amide hydrochloride salt (F33) (176 mg, 95%) as a white solid.

The following compounds (as their hydrochloride salts) have been obtained from the appropriate precursors as indicated in the below table according to an analogous manner to that described for Description F33:

Name	Precursor
(S)-2-Amino-*N*-cyclohexyl-propionamide (F6)	G6
(S)-2-Amino-hexanoic acid *isobutyl*-amide (F36)	G36

Description F15

1-(3-Methoxy-phenyl)-1-methyl-ethylamine (F15)

A flask was charged with [1-(3-methoxy-phenyl)-1-methyl-ethyl]-carbamic acid benzyl ester (D100) (1 g, 3.34 mmol, 1 equiv), 10% palladium on charcoal (50% wet, 100 mg, 10% w/w), NH_4COOH (2.1 g, 33 mmol, 10 equiv), EtOH (40 ml) and H_2O (8 ml). The resulting mixture was stirred at 80°C for 2 h, cooled to room temperature and the catalyst was filtered off using a pad of celite. Most of the EtOH was removed *in vacuo* and the residue was diluted with 1N HCl aqueous solution. The aqueous phase was extracted with AcOEt then basified to pH 13 and extracted twice with AcOEt. These combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to yield 1-(3-methoxy-phenyl)-1-methyl-ethylamine (F15) (290 mg, 53%) as a yellow gum.

Description F40

2-[3-(Trifluoromethyl)phenyl]-2-propanamine (F40)

2-[3-(Trifluoromethyl)phenyl]-2-propanamine (F40) was obtained from phenylmethyl {1-methyl-1-[3-(trifluoromethyl)phenyl]ethyl}carbamate (D272) in an analogous manner to the process described for Description F15 (F15).

Description F41

{1-[3-(Methyloxy)phenyl]cyclohexyl}amine (F41)

To a solution of 1-(1-azidocyclohexyl)-3-(methyloxy)benzene (D315) (2.78 g, 12.0 mmol, 1 equiv) in THF (20 ml) at room temperature was added $LiAlH_4$ (1M in THF, 36 ml, 36 mmol, 3 equiv) and the resulting mixture was stirred at this temperature for 4 h. The mixture was then carefully quenched with a 1N aqueous NaOH solution (6 ml, 60 mmol, 1 equiv) then H_2O. The mixture was filtered through a pad of celite then acidified with a 2N aqueous HCl solution (50 ml). The two layers were separated and the pH of the aqueous phase adjusted to 9 using a 2N aqueous NaOH solution. The aqueous phase was extracted three times with Et_2O and the combined organic phase were dried over $MgSO_4$ then concentrated *in vacuo* to give {1-[3-(methyloxy)phenyl]cyclohexyl}amine (F41) (1.55 g, 63%) as a clear oil which was used in the next step without further purification. $[M+H]^+$ = 189.0, RT = 1.90 min.

Descriptions F48, F61, F81 and F110-114

The following amines were obtained from their corresponding amides in an analogous manner to the process described for Description F5 (F5):

Description	Precursor
2-Methyl-2-heptanamine (F48)	D291
2-Methyl-1-[3-(methyloxy)phenyl]-2-propanamine (F61)	D293
1-Methylcyclohexanamine (F81)	D286
1-Methylcyclohexanamine (F110)	D287
1-Methylcyclopentanamine (F111)	D288
1-Propylcyclopentanamine (F112)	D289
1-Propylcyclohexanamine (F113)	D290
1-(3-Chlorophenyl)-2-methyl-2-propanamine (F114)	D292

Description F52

7-(Methyloxy)-1,2,3,4-tetrahydro-1-naphthalenamine (F52)

7-(Methyloxy)-1,2,3,4-tetrahydro-1-naphthalenamine (F52) was obtained from 7-(methyloxy)-3,4-dihydro-1(2*H*)-naphthalenone in an analogous manner to the process described in US Patent 4,132,737.

Descriptions F54-56 and F155

The following amines were prepared from their precursor in an analogous manner to the process described for Amine 1 (C1):

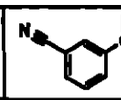
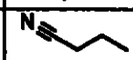
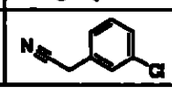
Description	Precursor
2-Methyl-1-[(2-methylpropyl)thio]-2-propanamine hydrogen chloride (F54)	D276
2-Methyl-1-(phenyloxy)-2-propanamine hydrogen chloride (F55)	D274
2-Methyl-1-[(phenylmethyl)oxy]-2-propanamine hydrogen chloride (F56)	D275
4,4-Difluorocyclohexanamine hydrochloride (F155)	D277

Descriptions F63, F73-75 and F77-80

The following amines were prepared from their corresponding nitriles according to the general method described in: P. Bertus, J. Szymoniak *Chem. Comm.*, 2001, 1792:

Description	Precursor

87

1-[3-(methyloxy)phenyl] cyclopropanamine (F63)	
1-(4-methylpentyl) cyclopropanamine (F73)	
1-ethylcyclopropanamine (F74)	
1-(1-methylethyl) cyclopropanamine (F75)	
1-propylcyclopropanamine (F77)	
1-(3-methylbutyl) cyclopropanamine (F78)	
1-(2-methylpropyl) cyclopropanamine (F79)	
1-[(3-chlorophenyl)methyl] cyclopropanamine (F80)	

Descriptions F69 and F148-150

The following compounds have been obtained from their precursors in an analogous manner to the process described for Description F15 (F15):

Description	Precursor
1-Ethylcyclobutanamine (F69)	D282
1-Propylcyclobutanamine (F148)	D283
1-(1-Methylethyl) cyclobutanamine (F149)	D284
1-[(3-Chlorophenyl)methyl] cyclobutanamine (F150)	D285

Description F70

2-Methyl-1-[(2-methylpropyl)oxy]-2-propanamine (F70)

2-Methyl-1-[(2-methylpropyl)oxy]-2-propanamine (F70) was obtained from 2-Methyl-1-[(2-methyl-2-propen-1-yl)oxy]-2-propanamine (F71) in an analogous manner to the process described for Ester 166 (B116).

Description F71

2-Methyl-1-[(2-methyl-2-propen-1-yl)oxy]-2-propanamine (F71)

To a solution of NaH (60% dispersion in mineral oil, 2.0 g, 50 mmol, 1 equiv) in DMF at 0°C was added 2-amino-2-methyl-1-propanol (4.8 ml, 50 mmol, 1 equiv) and after 1 h 3-bromo-2-methyl-1-propene (5.5 ml, 55 mmol, 1.1 equiv). The resulting solution was stirred at room temperature for 15 h then partitioned between AcOEt and H_2O. The two layers were separated and the organic phase was washed with H_2O and brine, dried over $MgSO_4$ and distillated (45°C, P = 150 mbar) to give 2-methyl-1-[(2-methyl-2-propen-1-yl)oxy]-2-propanamine (F71) as a light pink solid.

Description F83

4,4-Dimethylcyclohexanamine (F83)

4,4-Dimethylcyclohexanone oxime (D296) (10 g, 71 mmol, 1 equiv) in EtOH (100 ml) was stirred with Raney Ni (1 g, 10% w/w) under an atmosphere of H_2 (50 psi) for 4 days. The

catalyst was filtered off through a pad of celite and HCl (1M in Et_2O, 100 ml, 100 mmol, 1.4 equiv) were added. The precipitate formed was filtered off and dissolved in water. The aqueous phase was washed with Et_2O and made strongly basic with KOH pellets then extracted twice with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo to give 4,4-dimethylcyclohexanamine (F83) (8 g, 89%) as a clear oil which was used in the next step without further purification.

Descriptions F86 and F92

The following amines were obtained from their precursor in an analogous manner to the process described for 4,4-dimethylcyclohexanamine (F83):

Amine	Precursor
2,2-Dimethyl cyclohexanamine (F86)	D297
3,3-Dimethyl cyclopentanamine (F92)	D298

Description F157

[(3-Ethyl-5-isoxazolyl)methyl]amine (F157)

[(3-Ethyl-5-isoxazolyl)methyl]amine (F157) was obtained from 1,1-dimethylethyl [(3-ethyl-5-isoxazolyl)methyl]carbamate (G157) in an analogous manner to the process described in Description F33 (F33).

Preparation of Esters

Ester 1

3-Methylsulfanyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B1)

To a solution of crude 3-(4-chloro-butanoylamino)-5-methylsulfanyl-benzoic acid methyl ester (D64) (0.17 g, 0.56 mmol, 1 equiv) in THF (2 ml) at 0°C was added portionwise NaH (60% in mineral oil, 24.6 mg, 0.616 mmol, 1.1 equiv) over 2 min. The resulting mixture was stirred at room temperature for 40 min and one drop of MeOH was added to destroy the remaining NaH. The resulting mixture was then diluted with AcOEt, washed sequentially with 2N aqueous HCl solution, saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography on silica gel (*Iso*-hexane/AcOEt: 1/1) gave 3-(4-chloro-butanoylamino)-5-methylsulfanyl-benzoic acid methyl ester (B1) (122 mg, 82%) as a white solid. $[M+H]^+$ = 266.0, RT = 2.86 min

Ester 2

3-Ethylsulfanyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid ethyl ester (B2)

Ester 2 was prepared from 177 mg (0.54 mmol) of 3-(4-chloro-butanoylamino)-5-ethylsulfanyl-benzoic acid ethyl ester (D65) in an analogous manner to that described for Ester 1 which yielded 129 mg (82%) of 3-ethylsulfanyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid ethyl ester (B2) as a clear colorless gum after purification by flash chromatography on silica gel (*Iso*-hexane/AcOEt : 60/40). $[M+H]^+$ = 294.1, RT = 3.23 min

Ester 3

3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-methylsulfanyl-benzoic acid methyl ester (B3)

To a solution of 3-(3-chloro-propane-1-sulfonylamino)-5-methylsulfanyl-benzoic acid methyl ester (D66) (183 mg, 0.54 mmol, 1 equiv) in MeOH (3 ml) was added NEt_3 (150 µl, 1.08 mmol, 2 equiv). The resulting mixture was stirred at 70°C for 2 h then left to cool to room temperature overnight. A further portion of NEt_3 (75 µl, 0.54 mmol, 1 equiv) was added and the mixture was stirred at 80°C for 3 h when another portion of NEt_3 (75 µl, 0.54 mmol, 1 equiv) was added. After another 2 h at 80°C, the solution was cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between AcOEt and 2N aqueous HCl solution. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography on silica gel (*iso*-hexane/AcOEt : 60/40) gave 3-(1,1-dioxo-1*l*^{6}-isothiazolidin-2-yl)-5-methylsulfanyl-benzoic acid methyl ester (B3) (150 mg, 92%). $[M+H]^+ = 302.0$
RT = 2.89 min

Ester 4

3-(1,1-Dioxo-1*l*^{6}-isothiazolidin-2-yl)-5-ethylsulfanyl-benzoic acid ethyl ester (B4)
Ester 4 was prepared from 190 mg (0.52 mmol) 3-(3-chloro-propane-1-sulfonylamino)-5-ethylsulfanyl-benzoic acid ethyl ester (D67) in an analogous manner to that described for Ester 3 which yielded 154 mg (90%) of 3-(1,1-dioxo-1*l*^{6}-isothiazolidin-2-yl)-5-ethylsulfanyl-benzoic acid ethyl ester (B4) after purification by flash chromatography on silica gel (*iso*-hexane/AcOEt : 60/40). $[M+H]^+ = 330.0$, RT = 3.24 min

Ester 11

3-Ethoxy-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B11)
To 3-hydroxy-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D37) (0.80 g, 3.4 mmol, 1 equiv) dissolved in DMF (10 ml) was added K_2CO_3 (0.94 g, 6.8 mmol, 2 equiv) and ethyl iodide (1.1 g, 6.8 mmol, 2 equiv). The resulting mixture was heated at 50 °C for 4 h, cooled to room temperature, diluted with 2N aqueous HCl solution (50 ml) and extracted with Et_2O (50 ml). The organic phase was then washed with water (50 ml), dried over $MgSO_4$ and concentrated in *vacuo* to give of 3-ethoxy-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B11) (0.85 g, 95%) as a brown oil which slowly solidified to a tan solid.

Ester 11 (Alternative Procedure)
3-Ethoxy-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B11):
3-(4-Chloro-butanoylamino)-5-ethoxy-benzoic acid methyl ester (D51) (7 g, 20 mmol, 1 equiv) in THF (50 ml) was treated portionwise with NaH (60% in mineral oil, 0.88 g, 22 mmol, 1.1 equiv) over 15 min at room temperature. The resulting mixture was stirred for 30 min and then diluted with AcOEt (300 ml). The resulting solution was washed with 2N aqueous HCl solution (200 ml), dried over $MgSO_4$ and concentrated *in vacuo*. Recrystallisation of the residue from Et_2O/hexane gave 3-ethoxy-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B11) (3.5 g, 66%) as white solid.

The following esters were prepared in an analogous manner to Ester 11 from D37 using an appropriate commercially available reagent:

9c

Ester
3-Methoxy-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B9)
3-(2-Oxo-pyrrolidin-1-yl)-5-propoxy-benzoic acid methyl ester (B10)
3-Isopropoxy-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B12)
3-(2-Oxo-pyrrolidin-1-yl)-5-pentyloxy-benzoic acid methyl ester (B13)

Ester 14

The following ester was prepared in an analogous manner to Description 38 from Description 37 using the appropriate alcohol indicated in the table below:

Ester	Alcohol
3-(2-Methoxy-ethoxy)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B14)	

Ester 15

3-(3-Hydroxy-propoxy)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B15)

3-(3-Benzyloxy-propoxy)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D38) in MeOH (15 ml) was hydrogenolysed initially with 10% Pd on charcoal (50% wet, 0.25 g, 0.25 equiv w/w) at atmospheric pressure for 24 hrs and then a further 0.25 g of 10% Pd on charcoal (50% wet, 0.25 g, 0.25 equiv w/w) was added and the mixture hydrogenolysed at 50psi for a further 48 hrs. The mixture was filtered through Celite and concentrated *in vacuo*. Purification by flash chromatography on silica gel (AcOEt/*iso*-hexane : 1/1) gave 3-(3-hydroxy-propoxy)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B15) (260 mg, 69% over 2 steps). $[M+H]^+ = 294.0$

Ester 17

3-(3-Methoxy-propoxy)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B17)

3-(3-Hydroxy-propoxy)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B15) (127 mg, 0.43 mmol, 1 equiv) in CH_2Cl_2 (2 ml) was treated with proton sponge (279 mg, 1.30 mmol, 3 equiv) and trimethyloxonium tetrafluoroborate (192 mg, 1.30 mmol, 3 equiv). After 3 hrs, further quantities of proton sponge (93 mg, 0.43 mmol, 1 equiv) and trimethyloxonium tetrafluoroborate (65 mg, 0.43 mmol, 1 equiv) were added and stirring was continued for a further 2 h. The mixture was then partitioned between AcOEt and 2N aqueous HCl solution. The two layers were separated and the aqueous phase extracted with AcOEt. The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution, 2N aqueous HCl solution and brine and then dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography on silica gel (ethyl acetate/iso-hexane: 1/4 to 1/3) gave 3-(3-methoxy-propoxy)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B17) (76 mg, 58%). $[M+H]^+ =$ 308.1

Ester 18

3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-ethoxy-benzoic acid methyl ester (B18)

To 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-hydroxy-benzoic acid methyl ester (D41) (0.80 g, 3.0 mmol, 1 equiv) dissolved in DMF (10 ml) was added K_2CO_3 (0.94 g, 6.8 mmol, 2 equiv) and

ethyl iodide (1.1g, 6.8 mmol, 2 equiv) and the resulting mixture was heated at 50 °C for 4 h then cooled to room temperature and diluted with 2N aqueous HCl solution (50 ml). The aqueous phase was extracted with Et_2O (50 ml). The organic phase was washed with H_2O (50 ml), dried over $MgSO_4$ and concentrated in *vacuo*. Purification by flash chromatography on silica gel (AcOEt/*iso*-hexane: 1/1) gave 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-ethoxy-benzoic acid methyl ester (B18) (220 mg, 25%) as a pale yellow oil.

Ester 18 (Alternative Procedure)

3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-ethoxy-benzoic acid methyl ester (B18)

A solution of 3-(3-chloro-propane-1-sulfonylamino)-5-ethoxy-benzoic acid methyl ester (D53) (6.7 g, 20 mmol, 1 equiv) in EtOH (100 ml) was treated with NEt_3 (4.0 g, 40 mmol, 2 equiv). The resulting mixture was refluxed for 4 h, cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in AcOEt (200 ml) and the resulting solution was washed with 2N aqueous HCl solution (100 ml) followed by saturated aqueous $NaHCO_3$ solution (100 ml) then dried over $MgSO_4$ and concentrated *in vacuo* to give a brown oil. Crystallisation from Et_2O/hexane gave 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-ethoxy-benzoic acid methyl ester (B18) (4.7 g, 78%) as a light tan solid.

Ester 19

3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-isopropoxy-benzoic acid methyl ester (B19)

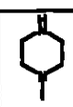
To 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-hydroxy-benzoic acid methyl ester (D41) (0.30 g, 1.1 mmol, 1 equiv) dissolved in DMF (5 ml) was added K_2CO_3 (0.306 g, 2.2 mmol, 2 equiv) and 2-iodopropane (374 mg, 2.2 mmol, 2 equiv) and the mixture heated at 50 °C for 4 h then cooled to room temperature and diluted with 2N aqueous HCl solution (50 ml). The aqueous phase was extracted with Et_2O (50 ml) and the organic phase was washed with H_2O (50 ml), dried over $MgSO_4$ and concentrated *in vacuo* to give 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-isopropoxy-benzoic acid methyl ester (B19) (290 mg, 88%) as a pale yellow oil.

The following esters were prepared from Description 41 in an analogous manner to the process described for Ester 19 using the appropriate commercially available reagents:

Ester
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-methoxy-benzoic acid methyl ester (B20)
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-propoxy-benzoic acid methyl ester (B21)
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-pentyloxy-benzoic acid methyl ester (B22)

The following esters were prepared in an analogous manner to the process described in Description 30 from the appropriate aryl bromide and amine starting materials listed in the below table:

Ester	Aryl bromide	Amine	$[M+H]^+$	RT (min)
3-(2-Oxo-pyrrolidin-1-yl)-5-pyrrolidin-1-yl-benzoic acid methyl ester (B113)	D9a		289.1	3.03
3-Morpholin-4-yl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B29)	D9a		305.0	2.59

3-(4-Methyl-piperazin-1-yl)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B115)	D9a		318.1	1.91
3-(2-Oxo-pyrrolidin-1-yl)-5-piperidin-1-yl-benzoic acid methyl ester (B28)	D9a		303.1	2.93
3-(2-Oxo-piperidin-1-yl)-5-pyrrolidin-1-yl-benzoic acid *tert*-butyl ester (B54)	D10		345.2	3.35
3-Morpholin-4-yl-5-(2-oxo-piperidin-1-yl)-benzoic acid *tert*-butyl ester (B56)	D10		361.2	2.95
3-(2-Oxo-piperidin-1-yl)-5-piperidin-1-yl-benzoic acid *tert*-butyl ester (B55)	D10		359.2	3.35
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-pyrrolidin-1-yl-benzoic acid *tert*-butyl ester (B114)	D17		87.1	3.43
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-morpholin-4-yl-benzoic acid *tert*-butyl ester (B61)	D17		383.1	3.04

Ester 24

3,5-Bis-(2-oxo-pyrrolidin-1-yl)benzoic acid methyl ester (B24)

To a solution of 3-bromo-5-iodobenzoic acid methyl ester (D8a) (588 mg, 1.72 mmol, 1.5 equiv) in dioxan (10 ml) was added pyrrolidin-2-one (120 µl, 1.14 mmol, 1 equiv), Cs_2CO_3 (720 mg, 2.21 mmol, 2 equiv), Xantphos (51 mg, 0.09 mmol, 0.08 equiv) and tris(dibenzylideneacetone)dipalladium (0) (28 mg, 0.03 mmol, 0.026 equiv). The reaction mixture was stirred at 100 °C for 16 h, then cooled to room temperature and filtered through a pad of celite and concentrated *in vacuo*. Purification by column chromatography on silica gel (EtOAc) yielded 3,5-bis-(2-oxo-pyrrolidin-1-yl)benzoic acid methyl ester (B24) (411 mg, 79%) as light yellow solid.

$[M+H]^+ = 303.2$

The following esters were prepared in an analogous manner to Ester 23 from the appropriate starting materials indicated in the below table:

Ester	Precursor
4-Chloro-3,5-bis-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B25)	D28a
4-Methoxy-3,5-bis-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B26)	D28b

Ester 27

3-Nitro-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B27)

To a solution of 3-(4-chloro-butanoylamino)-5-nitro-benzoic acid methyl ester (D2) (56 g, 186 mmol, 1 equiv) in THF (500 ml) under nitrogen was added portionwise NaH (60% w/w in mineral oil, 8 g, 200 mmol, 1.07 equiv) over 10 min. The resulting mixture was stirred at room temperature for 1 h then cooled to 0°C and MeOH was added dropwise until bubbling ceased.

The solution was concentrated *in vacuo* and the residue diluted with AcOEt. The organic phase was washed with H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with *iso*-hexane to give 3-nitro-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B27) (38.5 g, 78%) as a light tan solid.

Ester 30

3-(2-Oxo-pyrrolidin-1-yl)-5-phenylamino-benzoic acid methyl ester (B30)

A flask was charged under nitrogen with 3-bromo-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D9a) (298 mg, 1 mmol, 1 equiv), Cs_2CO_3 (488 mg, 1.5 mmol, 1.5 equiv), tris(dibenzylideneacetone)dipalladium(0) (18.3 mg, 0.02 mmol, 0.02 equiv), 2-(di-*tert*-butylphosphino)biphenyl (18 mg, 0.06 mmol, 0.06 equiv) and DME (8 ml). Aniline (136 µl, 1.5 mmol, 1.5 equiv) was then added *via syringe* and the resulting mixture was stirred at 100°C for 16 h then cooled to room temperature, diluted with H_2O and AcOEt. The layers were separated and the aqueous phase was extracted with AcOEt. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt : 3/1 to 1/1) gave 3-(2-oxo-pyrrolidin-1-yl)-5-phenylamino-benzoic acid methyl ester (B30) (100 mg, 32%) as a white solid. $[M+H]^+$ = 311.0, RT = 3.14 min

Ester 31

3-Ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid *tert*-butyl ester (B31)

A flask was charged with (benzyl-ethyl-amino)-(2-oxo-pyrrolidin-1-yl)-benzoic acid *tert*-butyl ester (D30) (3 g, 7.6 mmol, 1 equiv), 10% Pd on charcoal (50% wet, 600 mg, 10% w/w), NH_4COOH (4.8 g, 76 mmol, 10 equiv), MeOH (30 ml) and H_2O (50 ml). The resulting mixture was stirred at 50°C for 16 h, cooled to room temperature and the catalyst was filtered off using a pad of celite. Most of the MeOH was removed *in vacuo* and the residue was diluted with saturated aqueous $NaHCO_3$ solution. The aqueous phase was extracted twice with AcOEt. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give 3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid *tert*-butyl ester (B31) (2.2 g, 95%) as a yellow oil. $[M+H]^+$ = 305.2, RT = 3.11 min

The following esters were prepared in an analogous manner to the process described in Ester 31 (B31) from the appropriate benzyl aniline precursor listed in the below table:

Ester	Precursor	$[M+H]^+$	RT (min)
3-Methylamino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid *tert*-butyl ester (B32)	D31	291.1	2.96
3-Methylamino-5-(2-oxo-piperidin-1-yl)-benzoic acid *tert*-butyl ester (B57)	D32	249.1 (- tBu)	2.91
3-Ethylamino-5-(2-oxo-piperidin-1-yl)-benzoic acid *tert*-butyl ester (B59)	D33	319.2	3.10
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-methylamino-benzoic acid *tert*-butyl ester (B62)	D34		
3-(1,1-Dioxo-1λ^6-[1,2]thiazinan-2-yl)-5-ethylamino-	D35	355.2	3.32

94

benzoic acid *tert*-butyl ester (B73)			

Ester 33

Diethylamino-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B33)

To a solution of 3-amino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D4a) (100 mg, 0.43 mmol, 1 equiv) in $(CH_2Cl)_2$ (1.5 ml) was added acetaldehyde (0.072 ml, 1.29 mmol, 3 equiv) and sodium triacetoxyborohydride (273 mg, 1.29 mmol, 3 equiv). The resulting solution was stirred at room temperature for 1 h, diluted with AcOEt (20 ml), washed with 2N aqueous NaOH solution (20 ml), dried over $MgSO_4$ and concentrated *in vacuo* to give diethylamino-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B33) (110 mg, 98%) as a pale yellow oil.

The following esters were prepared in an analogous manner to the process described in Ester 33 (B33) using the appropriate aldehyde and the appropriate aniline indicated in the below table:

Ester	Aniline	$[M+H]^+$	RT (min)
Dimethylamino-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B34)	D4a	263.0	2.63
Diethylamino-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid methyl ester (B63)	D16	327.0	2.96
Diethylamino-(2-oxo-piperidin-1-yl)-benzoic acid methyl ester (B60)	D4b		

Ester 35

3-(2-Oxo-pyrrolidin-1-yl)-5-propylamino-benzoic acid methyl ester (B35)

To a solution of 3-amino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D4a) (500 mg, 2,14 mmol, 1 equiv) in $(CH_2Cl)_2$ (10 ml) was added sodium triacetoxyborohydride (640 mg, 3.02 mmol, 1.4 equiv), propionaldehyde (0.156 ml, 2.14 mmol, 1 equiv) and CH_3COOH (0.125 ml, 2.18 mmol, 1.02 equiv) .The resulting mixture was stirred at room temperature for 2 h, diluted with CH_2Cl_2 (20 ml), washed with saturated aqueous $NaHCO_3$ solution (20 ml), dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt : 3/2) gave 3-(2-oxo-pyrrolidin-1-yl)-5-propylamino-benzoic acid methyl ester (B35) (250 mg, 42%) as a colourless oil.

The following esters were obtained in an analogous manner to the process described in Ester 35 (B35) using the appropriate aldehyde and the appropriate aniline indicated in the table below:

Ester	Aniline	$[M+H]^+$	RT (min)
3-Benzylamino-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid methyl ester (B64)	D16		
3-Butylamino-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid methyl ester (B65)	D16	327.0	3.10
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-(3-methyl-butylamino)-benzoic acid methyl ester (B66)	D16	341.1	3.26

3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-phenethylamino-benzoic acid methyl ester (B67)	D16	375.0	3.23
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-pentylamino-benzoic acid methyl ester (B68)	D16	341.1	3.29
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-propylamino-benzoic acid methyl ester (B69)	D16	313.0	2.90
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-ethylamino-benzoic acid methyl ester (B70)	D16	299.0	2.91
3-(Cyclopropylmethyl-amino)-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid methyl ester (B71)	D16	325.0	2.91
3-Isobutylamino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B36)	D4a	291.1	3.03
3-Benzylamino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B37)	D4a		
3-(3-Methyl-butylamino)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B38)	D4a		
3-(2-Oxo-pyrrolidin-1-yl)-5-pentylamino-benzoic acid methyl ester (B39)	D4a		
3-Butylamino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B40)	D4a		
3-(2,2-Dimethyl-propylamino)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B41)	D4a	305.0	3.22
3-(Cyclopropylmethyl-amino)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B42)	D4a		
3-(2-Oxo-piperidin-1-yl)-5-propylamino-benzoic acid methyl ester (B58)	D4b		

Ester 43

3-(1-Ethyl-propylamino)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B43)

To a solution of 3-amino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D4a) (200mg, 0.87mmol, 1equiv) in $(CH_2Cl)_2$ (5ml) were added sodium triacetoxyborohydride (1.536 g, 5.22 mmol, 6 equiv), 3-pentanone (0.546 ml, 5.22 mmol, 6 equiv) and AcOH (0.050 ml, 0.87 mmol, 1 equiv). The resulting mixture was stirred at room temperature for 48 h, diluted with CH_2Cl_2 (20ml), washed with saturated aqueous $NaHCO_3$ solution (20ml), dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOH: 3/2) gave 3-(1-ethyl-propylamino)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B43) (106 mg, 40%) as a colourless oil.

$[M+H]^+$ = 305.0

RT = 3.19

The following esters were obtained in an analogous manner to Ester 43 (B43) using the appropriate ketone and the appropriate aniline indicated in the table below:

Ester	Aniline	[M+H]	RT (min)

3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-isopropylamino-benzoic acid methyl ester (B72)	D16	313.0	2.82
3-Isopropylamino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B44)	D4a	227.0	2.75
3-Cyclopentylamino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B45)	D4a		
3-Cyclohexylamino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B46)	D4a		

Ester 47

(Acetyl-methyl-amino)-(ethyl-propionyl-amino)-benzoic acid *tert*-butyl ester (B47)

To a solution of 3-methylamino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid *tert*-butyl ester (B32) (200 mg, 0.69 mmol, 1 equiv) in CH_2Cl_2 (5 ml) was added NEt_3 (278 µl, 2 mmol, 2.9 equiv) and acetic anhydride (195 µl, 2 mmol, 2.9 equiv). The resulting mixture was stirred at room temperature for 16h, diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo* to give (acetyl-methyl-amino)-(ethyl-propionyl-amino)-benzoic acid *tert*-butyl ester (B47) (203 mg, 89%) as a pale yellow oil which was used in the next step without further purification.

$[M+H]^+ = 333.1$

RT = 2.76 min

The following esters were prepared in an analogous manner to the process described in Ester 47 from the appropriate amine starting materials:

Ester	Amine
(Acetyl-propyl-amino)-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B48)	B35
(Acetyl-isopropyl-amino)-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B49)	B44

Ester 50

3-Acetylamino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B50)

To a solution of 3-amino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D4a) (80 mg, 0.34 mmol, 1 equiv) in CH_2Cl_2 (10 ml) was added NEt_3 (0.142 ml, 1.02 mmol, 2 equiv) and acetic anhydride (0.078 ml, 0.82 mmol, 2.4 equiv). The resulting mixture was stirred at room temperature for 16h. The reaction was then diluted with AcOEt (20ml), washed with 2N aqueous HCl solution (20ml), dried over $MgSO_4$, and concentrated *in vacuo* to give 3-acetylamino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B50) (67 mg, 71%) as a pale yellow foam.

Ester 51

(Methanesulfonyl-methyl-amino)-(2-oxo-pyrrolidin-1-yl)-benzoic acid *tert*-butyl ester (B51)

To a solution of 3-methylamino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid *tert*-butyl ester (B32) (200 mg, 0.69 mmol, 1 equiv) in CH_2Cl_2 (5 ml) was added NEt_3 (278 µl, 2 mmol, 2.9 equiv) and methanesulphonyl chloride (162 µl, 2 mmol, 2.9 equiv). The resulting mixture was stirred

at room temperature for 16 h, diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo* to give (methanesulfonyl-methyl-amino)-(2-oxo-pyrrolidin-1-yl)-benzoic acid *tert*-butyl ester (B51) (203 mg, 89%) as a pale yellow oil. $[M+H]^+$ = 313.0, RT = 2.95 min

Ester 52

(Methanesulfonyl-propyl-amino)-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B52)

Ester 52 was prepared from 3-(2-oxo-pyrrolidin-1-yl)-5-propylamino-benzoic acid methyl ester (B35) in an analogous manner to that described for Ester 51 (B51).

Ester 53

3-Methanesulfonylamino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B53)

To a solution of 3-amino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D4a) (200 mg, 0.85 mmol, 1 equiv) in CH_2Cl_2 (5 ml) and DMF (5 ml) was added NEt_3 (0.181 ml, 1.3 mmol, 1.5 equiv) and methanesulphonyl chloride (0.071 ml, 1 mmol, 1.2 equiv). The resultant mixture was stirred at room temperature for 1 h, diluted with AcOEt (30 ml), washed with 2N aqueous HCl solution (30 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with Et_2O and then filtered to give 3-methanesulfonylamino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B53) as a pale yellow solid (100 mg, 38%).

Ester 74

5-(2-Oxo-pyrrolidin-1-yl)-isophthalic acid 1-*tert*-butyl ester 3-methyl ester (B74)

A solution of 1-*tert*-butyl ester 3-methyl ester (D80) (4.5 g, 12.7 mmol, 1 equiv) in THF (60 ml) was treated portionwise with NaH (60% suspension in mineral oil, 560 mg, 14 mmol, 1.1 equiv) over 5 min at room temperature. The resulting mixture was stirred for 1 h, then MeOH (5 ml) was added and the mixture was concentrated *in vacuo*. The residue was diluted with AcOEt (200 ml) and the organic phase was washed with H_2O (100 ml), dried over $MgSO_4$ and concentrated *in vacuo* to give 5-(2-oxo-pyrrolidin-1-yl)-isophthalic acid 1-*tert*-butyl ester 3-methyl ester (B74) (3.9 g, 97%) as a white solid.

Ester 76

3-Hydroxymethyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B76)

A suspension of 5-(2-oxo-pyrrolidin-1-yl)-isophthalic acid monomethyl ester (A75) (200 mg, 0.76 mmol, 1 equiv) in THF (20 ml) was cooled to 0 °C and treated with BH_3-Me_2S (2M solution in THF, 0.64 ml, 1.28 mmol, 1.3 equiv). The resulting mixture was refluxed for 1 h and then cooled to room temperature. MeOH (5 ml) was added and the resulting mixture was concentrated *in vacuo*. The residue was diluted with AcOEt (50 ml) and the resulting solution was washed with saturated aqueous $NaHCO_3$ solution (30 ml) and 2N aqueous HCl solution (30 ml), dried over $MgSO_4$ and concentrated *in vacuo* to give 3-hydroxymethyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B76) (70 mg, 37%) as a pale yellow oil.

Ester 77

5-(2-Oxo-pyrrolidin-1-yl)-*N*-propyl-isophthalamic acid methyl ester (B77)

A suspension of 5-(2-oxo-pyrrolidin-1-yl)-isophthalic acid monomethyl ester (A75) (200 mg, 76 mmol, 1 equiv) in CH_2Cl_2 (20 ml) at room temperature was treated with a few drops of DMF followed by $(COCl)_2$ (100 mg, 0.8 mmol, 1.1 equiv). The resulting mixture was stirred for 1 h and then propylamine (140 mg, 2.4 mmol, 3.3 equiv) was added and the resulting solution was stirred for 30 min. The solution was then washed with 2N aqueous HCl solution (30ml), saturated aqueous $NaHCO_3$ solution (30 ml), dried over $MgSO_4$ and concentrated *in vacuo* to give 5-(2-oxo-pyrrolidin-1-yl)-*N*-propyl-isophthalamic acid methyl ester (B77) (127 mg, 55%) as a cream waxy solid.

The following compounds were prepared in an analogous manner to that described for Ester 77 from 5-(2-oxo-pyrrolidin-1-yl)-isophthalic acid monomethyl ester (A75) and the appropriate amine:

Ester
N,N-Dimethyl-5-(2-oxo-pyrrolidin-1-yl)-isophthalamic acid methyl ester (B78)
N-Methyl-5-(2-oxo-pyrrolidin-1-yl)-isophthalamic acid methyl ester (B79)

Ester 80

5-(2-Oxo-pyrrolidin-1-yl)-*N,N*-dipropyl-isophthalamic acid methyl ester (B80)

A solution of 5-(4-chloro-butanoylamino)-*N,N*-dipropyl-isophthalamic acid methyl ester (D89) (1.7 g, 4.4 mmol, 1 equiv) THF (20 ml) was treated portionwise with NaH (60% dispersion in mineral oil, 180 mg, 4.5 mmol, 1.1 equiv) and the resulting mixture was stirred for 1 h and then was diluted with AcOEt (100 ml). The resulting solution was washed with 2N aqueous HCl solution (50 ml), dried over $MgSO_4$ and concentrated *in vacuo* to give 5-(2-oxo-pyrrolidin-1-yl)-*N,N*-dipropyl-isophthalamic acid methyl ester (B80) (1.38 g, 91%) as a colourless oil.

Ester 81

5-(2-Oxo-piperidin-1-yl)-*N,N*-dipropyl-isophthalamic acid methyl ester (B81)

Ester 81 was prepared in an analogous manner to Ester 80 from 5-(5-chloro-pentanoylamino)-*N,N*-dipropyl-isophthalamic acid methyl ester (D90).

Ester 82

3-Nitro-5-(2-oxo-piperidin-1-yl)-benzoic acid methyl ester (B82)

NaH (60% w/w in mineral oil, 680 mg, 17 mmol, 0.9 equiv) was added portionwise to a solution of 3-(5-chloro-pentanoylamino)-5-nitro-benzoic acid methyl ester (D3) (6 g, 19 mmol, 1 equiv) in THF (40 ml) under nitrogen. The resulting mixture was stirred at room temperature for 1 h and then MeOH was added dropwise. The solution was concentrated *in vacuo* and the residue diluted with AcOEt. The organic phase was washed with H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography on silica gel (AcOEt/*iso*-hexane : 1/2) gave 3-nitro-5-(2-oxo-piperidin-1-yl)-benzoic acid methyl ester (B82) (2.8 g, 53%) as a pale orange oil.

Ester 83

3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-fluoromethyl-benzoic acid methyl ester (B83)

A solution of 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-hydroxymethyl-benzoic acid methyl ester (D84) (400 mg, 1.4 mmol, 1 equiv) in CH_2Cl_2 (40 ml) at 0 °C was treated with (diethylamino)sulfur trifluoride (240 mg, 1.5 mmol, 1.1 equiv). The mixture was stirred at 0 °C for 1 h and then allowed to warm to room temperature. The solution was washed with 2N aqueous HCl solution (40 ml), dried over $MgSO_4$ and concentrated *in vacuo* to give 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-fluoromethyl-benzoic acid methyl ester (B83) (250 mg, 62%) as a white solid.

Ester 84

3-Dimethylaminomethyl-5-(dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid methyl ester (B84)

A solution of 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-methanesulfonyloxymethyl-benzoic acid methyl ester (D85) (200 mg, 0.55 mmol, 1 equiv) in EtOH (3 ml) was treated with dimethylamine (33% in EtOH, 3 ml, excess). The resulting mixture was stirred for 15 min and then concentrated *in vacuo* and reevaporated with toluene (5 ml). The residue was dissolved in AcOEt (50 ml) and the resulting solution was washed with saturated aqueous $NaHCO_3$ solution (50 ml), dried over $MgSO_4$ and concentrated *in vacuo* to give 3-dimethylaminomethyl-5-(dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid methyl ester (B84) (170 mg, 99%) as a yellow waxy solid.

Ester 85

3-Azidomethyl-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid methyl ester (B85)

A solution of 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-methanesulfonyloxymethyl-benzoic acid methyl ester (D85) (200 mg, 0.55 mmol, 1 equiv) in DMF (2 ml) was treated with NaN_3 (39 mg, 0.6 mmol, 1.1 equiv) and the resulting mixture was stirred for 1 h at room temperature and then diluted with AcOEt (50 ml). The resulting solution was washed sequentially with 2N aqueous HCl solution (30 ml), saturated aqueous $NaHCO_3$ solution (30 ml) and H_2O (50 ml), dried over $MgSO_4$ and concentrated *in vacuo* to give 3-azidomethyl-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid methyl ester (B85) as a white solid (129 mg, 76%).

Ester 89

3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-(Z)-propenyl-benzoic acid methyl ester (B89)

A suspension of (ethyl)triphenylphosphonium bromide (371 mg, 1.0 mmol, 1.4 equiv) in THF (20 ml) was treated with KO^{t}Bu (112 mg, 1.0 mmol, 1.4 equiv) and the resulting mixture was stirred for 15 min at room temperature. A solution of 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-formyl-benzoic acid methyl ester (D86) (200 mg, 0.7 mmol, 1 equiv) in THF (10 ml) was added and the resulting mixture was stirred for 1 h at room temperature and then diluted with AcOEt (100 ml). The resulting solution was washed with 2N aqueous HCl solution (100 ml), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography on silica gel (EtOAc/*iso*-hexane : 1/1) gave 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-(E/Z)-propenyl-benzoic acid methyl ester (B89) (135 mg, 65%) as a colourless oil.

The following compounds were prepared in an analogous manner to the process described for Ester 89 from 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-formyl-benzoic acid methyl ester (D86) and the appropriate commercially available starting material:

Ester
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-vinyl-benzoic acid methyl ester (B88)
(Z/E)-But-1-enyl-(ethanesulfonyl-ethyl-amino)-benzoic acid methyl ester (B90)
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-(2-methyl-propenyl)-benzoic acid methyl ester (B91)

Ester 92

5-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-isophthalamic acid methyl ester (B92)

A suspension of 5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-isophthalic acid monomethyl ester (D83) (750 mg, 2.5 mmol, 1 equiv) in CH_2Cl_2 (30 ml) was treated with 2M $(COCl)_2$ in CH_2Cl_2 (1.5 ml, 3.0 mmol, 1.2 equiv) followed by a few drops of DMF. The resulting mixture was stirred for 30 min and then 32% aqueous ammonia (5 ml, excess) was added. The resulting mixture was stirred for 15 min and then diluted with CH_2Cl_2 (50 ml) and washed with 2N aqueous HCl solution (50 ml). The resulting white precipitate was filtered to give 5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-isophthalamic acid methyl ester **B92** (650 mg, 87%) as a white solid.

Ester 93

3-Cyano-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid methyl ester (B93)

A suspension of 5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-isophthalamic acid methyl ester (B92) (500 mg, 1.68 mmol, 1 equiv) in CH_2Cl_2 (100 ml) was treated with NEt_3 (404 mg, 4.0 mmol, 2.4 equiv) and trifluoroacetic anhydride (378 mg, 1.8 mmol, 1.1 equiv). The resulting mixture was stirred for 1 h at room temperature and then treated with further portions of NEt_3 (404 mg, 4.0 mmol, 2.4 equiv) and trifluoroacetic anhydride (378 mg, 1.8 mmol, 1.1 equiv) and stirred for another 45 min. The resulting solution was washed with 2N aqueous HCl solution (50 ml), saturated aqueous $NaHCO_3$ solution (50 ml), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was triturated with Et_2O to give 3-cyano-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid methyl ester (B93) (350 mg, 75%) as a white solid.

Ester 94

5-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-*N,N*-dipropyl-isophthalamic acid methyl ester (B94)

A solution of 5-(3-chloro-propane-1-sulfonylamino)-*N,N*-dipropyl-isophthalamic acid methyl ester (D91) (1.7 g, 4.0 mmol, 1 equiv) in EtOH (20 ml) was treated with NEt_3 (799 mg, 7.9 mmol, 2 equiv) and the mixture was refluxed for 3 h and then cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in AcOEt (100 ml) and the organic phase was washed with 2N aqueous HCl solution (50 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with Et_2O to give 5-(1,1-dioxo-1 λ^6-isothiazolidin-2-yl)-*N,N*-dipropyl-isophthalamic acid methyl ester (B94) (1.2 g, 78%) as a white solid.

Ester 95

5-(1,1-Dioxo-1λ^6-[1,2]thiazinan-2-yl)-*N,N*-dipropyl-isophthalamic acid methyl ester (B95)

101

Ester 95 was prepared in an analogous manner to Ester 94 from 5-(4-chloro-butane-1-sulfonylamino)-*N*,*N*-dipropyl-isophthalamic acid methyl ester (D92).

Ester 100

Fluoro-(2-oxo-pyrrolidin-1-yl)-trifluoromethyl-benzoic acid methyl ester (B100)

3-Bromo-2-fluoro-5-trifluoromethylbenzoic acid methyl ester (D29a) (500 mg, 1.95 mmol, 1 equiv), Cs_2CO_3 (950 mg, 2.92 mmol, 1.5 equiv), pyrrolidin-2-one (248 mg, 2.92 mmol, 1.5 equiv), Xantphos (68 mg, 0.117 mmol, 0.06 equiv) and tris(dibenzylideneacetone)dipalladium (0) (36 mg, 0.039 mmol, 0.02 equiv) were refluxed under argon in dioxan (7 ml) for 18h. After cooling, the mixture was filtered and evaporated *in vacuo*. Purification by flash chromatography on silica gel (AcOEt/iso-hexane : 1/4 to 1/2) gave fluoro-(2-oxo-pyrrolidin-1-yl)-trifluoromethyl-benzoic acid methyl ester (B100) (195 mg, 32%). $[M+H]^+$ 306.2.

The following compounds (Esters 101-102) were prepared in an analogous manner to that described for Description 68 from the appropriate aryl bromide starting material indicated in the below table using the appropriate 2,4,6 trialkenylcyclotriboroxane-pyridine complex as described by F. Kerins and D. F. O' Shea in *J. Org. Chem*, 2002, *67*, 4968-4971:

Description	Aryl bromide	$[M+H]^+$	RT (min)
3-(2-Methyl-propenyl)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B101)	D9a	274.1	3.14
3-(2-Oxo-pyrrolidin-1-yl)-5-((E)-styryl)-benzoic acid methyl ester (B102)	D9a		

The following compounds were prepared in an analogous manner to the process described for 3-(2-oxo-piperidin-1-yl)-5-propyl-benzoic acid *tert*-butyl ester (B116):

Ester	Alkene	$[M+H]^+$	RT (min)
3-Isopropyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B104)	D71	248.1	2.77
3-(2-Oxo-pyrrolidin-1-yl)-5-propyl-benzoic acid methyl ester (B106)	D72	262.1	3.04
3-Cyclopentyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B107)	D74	288.1	3.26
3-Cyclohexyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B108)	D74		
3-(1,1-Dioxo-1λ^6-[1,2]thiazinan-2-yl)-5-propyl-benzoic acid *tert*-butyl ester (B112)	D69		

Ester 109

3-Ethynyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid *tert*-butyl ester (B109)

Ester 109 was prepared in an analogous manner to the process described for Ester 111 from 300 mg (mmol) of 3-(3-hydroxy-3-methyl-but-1-ynyl)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid *tert*-butyl ester (D76) which yielded 220 mg (88%) of 3-ethynyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid *tert*-butyl ester (B109) as an off white solid.

Ester 111

3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-ethynyl-benzoic acid *tert*-butyl ester (B111)

To a solution of 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-(3-hydroxy-3-methyl-but-1-ynyl)-benzoic acid *tert*-butyl ester (D75) (142 mg, 0.37 mmol, 1 equiv) in toluene (20 ml) was added NaH (60% dispersion in mineral oil, 4 mg, 0.1 mmol, 0.3 equiv). The resulting mixture was stirred at 110°C for 30 min, cooled to room temperature and diluted with AcOEt. The organic phase was washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo* to give 3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-ethynyl-benzoic acid *tert*-butyl ester (B111) (142 mg, 118%) as a pale yellow oil.

Ester 116

3-(2-Oxo-piperidin-1-yl)-5-propyl-benzoic acid *tert*-butyl ester (B116)

To a solution of 3-(2-oxo-piperidin-1-yl)-5-(E/Z)-propenyl-benzoic acid *tert*-butyl ester (D68) (485 mg, 1.5 mmol, 1 equiv) in EtOH (10 ml) and H_2O (2 ml) was added 10% palladium on charcoal (50% wet, 485 mg, 5% w/w) and NH_4COOH (945 mg, 15 mmol, 10 equiv). The resulting mixture was stirred at 65°C for 1h then cooled to room temperature. Most of the EtOH was removed *in vacuo* and the residue dissolved in AcOEt. The organic phase was washed with H_2O, dried over $MgSO_4$ and concentrated *in vacuo* to give 3-(2-oxo-piperidin-1-yl)-5-propyl-benzoic acid *tert*-butyl ester (B116) (300 mg, 70%) as a colorless oil.

Ester 117

Methyl 3-(1,1-dioxido-6,7-dihydro-1,2-thiazepin-2(3*H*)-yl)-5-propylbenzoate (B117)

To a solution of methyl 3-[(3-buten-1-ylsulfonyl)(2-propen-1-yl)amino]-5-propylbenzoate (D135) (1 g, 2.8 mmol, 1 equiv) in CH_2Cl_2 (200 ml) was added bis(tricyclohexylphosphino)benzylidene ruthenium (IV) dichloride(117 mg, 0.14 mmol, 0.05 equiv) and the resulting solution was stirred at room temperature for 48 h then concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt: 9:1) gave methyl 3-(1,1-dioxido-6,7-dihydro-1,2-thiazepin-2(3*H*)-yl)-5-propylbenzoate (B117) (700 mg, 76%) as a pale purple oil. $[M+H]^+$ = 324.4, RT = 3.10 min.

Ester 118

Methyl 5-(ethylamino)-2-fluoro-3-(2-oxo-1-pyrrolidinyl)benzoate (B118)

To a solution of methyl 5-(ethyl{[4-(methyloxy)phenyl]methyl}amino)-2-fluoro-3-(2-oxo-1-pyrrolidinyl)benzoate (D155) (7 g, 17.5 mmol, 1 equiv) in EtOH (150 ml) was added 10% palladium on charcoal (50% wet, 1.4 g, 10% w/w) and the resulting mixture was stirred under an atmosphere of hydrogen (1 atm) for 3 h. The catalyst was filtered off through a pad of celite and the solution concentrated *in vacuo*. The residue was triturated with AcOEt/*iso*-hexane to give methyl 5-(ethylamino)-2-fluoro-3-(2-oxo-1-pyrrolidinyl)benzoate (B118) (4.8 g, 98%) as a

pale greenish solid which was used in the next step without further purification. $[M+H]^+$ = 281.2, RT = 2.35 min.

The following esters have been obtained from the appropriate precursor in an analogous manner to the process described for Ester 35 (B35) using acetaldehyde instead of propionaldehyde.

Ester	Precursor	$[M+H]^+$	RT (min)
Methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-(ethylamino)-2-fluorobenzoate (B119)	D152	331.2	2.80
Methyl 3-(1,1-dioxido-2-isothiazolidinyl)-5-(ethylamino)-2-fluorobenzoate (B122)	D151	317.1	2.64
Methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-(ethylamino)-2-(methyloxy)benzoate (B139)	D153	343.2	2.64

The following compounds were prepared in an analogous manner to the process described for 3-(2-oxo-piperidin-1-yl)-5-propyl-benzoic acid *tert*-butyl ester (B116) from their appropriate precursor:

Ester	Precursor	$[M+H]^+$	RT (min)
Methyl 2-fluoro-3-(2-oxo-1-pyrrolidinyl)-5-propylbenzoate (B120)	D159	280.2	2.73
Methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluoro-5-propylbenzoate (B173)	D161	330.2	2.91
Methyl 3-(1,1-dioxido-2-isothiazolidinyl)-2-fluoro-5-propylbenzoate (B174)	D160	-	2.74

Ester 121

1,1-Dimethylethyl 3-(2-oxo-5-phenyl-1-piperidinyl)-5-propylbenzoate (B121)

1,1-Dimethylethyl 3-(2-oxo-5-phenyl-1-piperidinyl)-5-propylbenzoate (B121) was prepared from 1,1-dimethylethyl 3-(2-oxo-5-phenyl-1-piperidinyl)-5-[(1*E/Z*)-1-propen-1-yl]benzoate (D192) in an analogous manner to the process described for 3-(2-oxo-piperidin-1-yl)-5-propyl-benzoic acid *tert*-butyl ester (B116). $[M+H]^+$ = 394.3, RT = 3.88 min.

Ester 123

Methyl 3-(1,1-dioxido-4-phenyltetrahydro-2*H*-1,2-thiazin-2-yl)-5-nitrobenzoate (B123)

A flask was charged under nitrogen with methyl 3-bromo-5-nitrobenzoate (D11) (136 mg, 0.52 mmol, 1,1 equiv) , Cs_2CO_3 (216 mg, 0.66 mmol, 1.4 equiv), tris(dibenzylideneacetone)dipalladium(0) (22 mg, 0.023 mmol, 0.05 equiv), Xantphos (27 mg, 0.047 mmol, 0.1 equiv) and toluene (10 ml). 4-phenyltetrahydro-2*H*-1,2-thiazine 1,1-dioxide (J. Morris, D. G. Wishka *J. Org. Chem.* 1991, *56*, 3549-3556, 100 mg, 0.47 mmol, 1 equiv) was then added and the resulting mixture was stirred at 120°C for 5 h then cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between H_2O and AcOEt and the aqueous phase was re-extracted with AcOEt. The combined organic solutions were dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash

chromatography on silica gel (*iso*-hexane/AcOEt : 7/3) gave methyl 3-(1,1-dioxido-4-phenyltetrahydro-2*H*-1,2-thiazin-2-yl)-5-nitrobenzoate (B123) (110 mg, 60%) as a yellow oil. $[M+H+NH_3]^+$ = 408.3, RT = 3.24 min

Ester 124

Methyl 3-amino-5-(1,1-dioxido-4-phenyltetrahydro-2*H*-1,2-thiazin-2-yl)benzoate (B124)

Methyl 3-amino-5-(1,1-dioxido-4-phenyltetrahydro-2*H*-1,2-thiazin-2-yl)benzoate (B124) was obtained from methyl 3-(1,1-dioxido-4-phenyltetrahydro-2*H*-1,2-thiazin-2-yl)-5-nitrobenzoate (B123) in an analogous manner to the process described for Description 16 (D16). $[M+H]^+$ = 361.3, RT = 2.91 min

Ester 125

Methyl 3-(1,1-dioxido-4-phenyltetrahydro-2*H*-1,2-thiazin-2-yl)-5-(ethylamino)benzoate (B125)

Methyl 3-(1,1-dioxido-4-phenyltetrahydro-2*H*-1,2-thiazin-2-yl)-5-(ethylamino)benzoate (B125) was obtained from methyl 3-amino-5-(1,1-dioxido-4-phenyltetrahydro-2*H*-1,2-thiazin-2-yl)benzoate (B124) in an analogous manner to the process described for Ester 35 (B35) using acetaldehyde instead of propionaldehyde. $[M+H]^+$ = 389.4, RT = 3.23 min

Ester 126

Methyl 3-cyclopentyl-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)benzoate (B126)

Methyl 3-cyclopentyl-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)benzoate (B126) was obtained from methyl 3-(1-cyclopenten-1-yl)-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)benzoate, methyl 3-(2-cyclopenten-1-yl)-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)benzoate and methyl 3-(3-cyclopenten-1-yl)-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)benzoate (D265) in an analogous manner to the process described for Ester 107 (B107).

Ester 127

Methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-[(1-methylethyl)amino]benzoate (B127)

Methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-[(1-methylethyl)amino]benzoate (B127) was obtained from methyl 3-amino-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)benzoate (D194) in an analogous manner to the process described for Ester 35 (B35) using acetone instead of propionaldehyde. $[M+H]^+$ = 327.2, RT = 2.82 min.

Ester 128

1,1-Dimethylethyl 3-[ethyl(methyl)amino]-5-(2-oxo-1-pyrrolidinyl)benzoate (B128)

1,1-Dimethylethyl 3-[ethyl(methyl)amino]-5-(2-oxo-1-pyrrolidinyl)benzoate (B128) was obtained from 1,1-dimethylethyl 3-(methylamino)-5-(2-oxo-1-pyrrolidinyl)benzoate (B32) in an analogous manner to the process described in Ester 35 (B35) using acetaldehyde instead of propionaldehyde. $[M+H]^+$ = 319.4, RT = 3.17 min.

The following compounds have been obtained from their corresponding precursors in an analogous manner to the process described for Ester 35 (B35) using acetaldehyde instead of propionaldehyde and the appropriate precursor indicated in the below table.

Ester	Precursor	$[M+H]^+$	RT (min)
Methyl 3-(ethylamino)-4-methyl-5-(2-oxo-1-pyrrolidinyl) benzoate (B129)	D184	277.1	2.63
Methyl 3-(1,1-dioxido-2-isothiazolidinyl)-5-(ethylamino)-4-methylbenzoate (B130)	D186	313.1	2.79
Methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-(ethylamino)-4-methylbenzoate (B131)	D188	327.1	2.93
Methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-(ethylamino)-4-(methyloxy) benzoate (B132)	D187	343.1	2.90
Methyl 3-(ethylamino)-4-(methyloxy)-5-(2-oxo-1-pyrrolidinyl) benzoate (B133)	D183	293.1	2.64
Methyl 3-(1,1-dioxido-2-isothiazolidinyl)-5-(ethylamino)-4-(methyloxy) benzoate (B134)	D185	329.1	2.79

Ester 135

Methyl 3-(diethylamino)-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-4-methylbenzoate (B135)

Methyl 3-(diethylamino)-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-4-methylbenzoate (B135) was obtained as a by-product during the synthesis of methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-(ethylamino)-4-methylbenzoate (B131) from methyl 3-amino-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-4-methylbenzoate (D188).

$[M+H]^+$ = 355.1, RT = 2.95 min.

Ester 136

Methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-4-(methyloxy)-5-[(1*E/Z*)-1-propen-1-yl]benzoate (B136)

To a solution of methyl 3-[[(4-chlorobutyl)sulfonyl]amino]-4-(methyloxy)-5-[(1*E/Z*)-1-propen-1-yl]benzoate (D170) (650 mg, 1.72 mmol, 1 equiv) in EtOH (50 ml) was added NEt_3 (500 µl, 3.6 mmol, 2.1 equiv) and the resulting solution was refluxed for 6 h then cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in AcOEt and the organic phase was washed with a 2N aqueous HCl solution and a saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*Iso*-hexane/AcOEt: 3/1) gave methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-4-(methyloxy)-5-[(1*E/Z*)-1-propen-1-yl]benzoate (B136) (450 mg, 77%) as a pale yellow oil. $[M+H]^+$ = 340.0, RT = 3.14 min.

Ester 138

Methyl 3-(1,1-dioxido-2-isothiazolidinyl)-5-(2-oxo-1-pyrrolidinyl)benzoate (B138)

Methyl 3-(1,1-dioxido-2-isothiazolidinyl)-5-(2-oxo-1-pyrrolidinyl)benzoate (B138) was obtained from methyl 3-[(4-chlorobutanoyl)amino]-5-(1,1-dioxido-2-isothiazolidinyl)benzoate (D195) in an analogous manner to the process described for Ester 27 (B27). $[M+H]^+$ = 339.0, RT = 2.41 min.

Ester 140

Methyl 1-ethyl-4-(2-oxo-1-pyrrolidinyl)-1*H*-indole-6-carboxylate (B140)

To a solution of methyl 4-(2-oxo-1-pyrrolidinyl)-1*H*-indole-6-carboxylate (B154) (500 mg, 1.94 mmol, 1 equiv) in DMF (10 ml) at room temperature was added NaH (60% dispersion in mineral oil, 84 mg, 2.1 mmol, 1.1 equiv) and the resulting mixture was stirred 15 min. Ethyl iodide (200 µl, 2.5 mmol, 1.3 equiv) was added and the resulting solution was stirred for 30 min then concentrated *in vacuo*. The residue was dissolved in AcOEt and the organic phase was washed with a 2N aqueous HCl solution, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (AcOEt/*iso*-hexane: 1/4 to 1/1) gave methyl 1-ethyl-4-(2-oxo-1-pyrrolidinyl)-1*H*-indole-6-carboxylate (B140) (400 mg, 72%) as an off-white solid. $[M+H]^+$ = 287.0, RT = 2.73 min.

The following compounds have been obtained from their corresponding precursors in an analogous manner to the process described for Description 2 (D2):

Ester	Precursor	$[M+H]^+$	RT (min)
Ethyl 3-ethyl-7-(2-oxo-1-pyrrolidinyl)-1*H*-indole-5-carboxylate (B141)	D225		
Methyl 1-ethyl-4-(2-oxo-1-pyrrolidinyl)-1*H*-benzimidazole-6-carboxylate (B149)	D227		
Methyl 1-ethyl-4-(2-oxo-1-pyrrolidinyl)-1*H*-indazole-6-carboxylate (B152)	D229	288.4	2.20
Methyl 4-(2-oxo-1-pyrrolidinyl)-1*H*-indole-6-carboxylate (B154)	D228	259.0	2.22
Ethyl 3-methyl-7-(2-oxo-1-pyrrolidinyl)-1*H*-indole-5-carboxylate (B160)	D224		
Ethyl 3-(1-methylethyl)-7-(2-oxo-1-pyrrolidinyl)-1*H*-indole-5-carboxylate (B161)	D226		
Methyl 4-ethyl-8-(2-oxo-1-pyrrolidinyl)-1,2,3,4-tetrahydro-6-quinoxalinecarboxylate (B171)	D230	304.3	2.52

Ester 142

Ethyl 3-ethyl-1-methyl-7-(2-oxo-1-pyrrolidinyl)-1*H*-indole-5-carboxylate (B142)

To a solution of ethyl 3-ethyl-7-(2-oxo-1-pyrrolidinyl)-1*H*-indole-5-carboxylate (B141) (658 mg, 2.3 mmol, 1 equiv) in DMF (10 ml) at room temperature was added NaH (60% dispersion in mineral oil, 120 mg, 3.0 mmol, 1.3 equiv) and the resulting mixture was stirred 15 min at this temperature. Ethyl iodide (187 µl, 3.0 mmol, 1.3 equiv) was added and the resulting solution was stirred for 30 min then concentrated *in vacuo*. The residue was dissolved in AcOEt and the organic phase was washed with H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. The

residue was triturated with *iso*-hexane to give ethyl 3-ethyl-1-methyl-7-(2-oxo-1-pyrrolidinyl)-1*H*-indole-5-carboxylate (620 mg, 90%) as a yellow solid which was used in the next step without further purification.

Ester 143

Methyl 4-(1,1-dioxido-2-isothiazolidinyl)-1-ethyl-1*H*-indole-6-carboxylate (B143)

To a solution of methyl 4-[[(3-chloropropyl)sulfonyl]amino]-1-ethyl-1*H*-indole-6-carboxylate (D241) (900 mg, 2.5 mmol, 1 equiv) in EtOH (100 ml) was added NEt_3 (1 ml, 7.3 mmol, 3 equiv) and the resulting solution was refluxed for 1.5 h then cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in AcOEt and the organic phase was washed with a 2N aqueous HCl solution, dried over $MgSO_4$ and concentrated *in vacuo* to give methyl 4-(1,1-dioxido-2-isothiazolidinyl)-1-ethyl-1*H*-indole-6-carboxylate (B143) (386 mg, 48%) as a brown oil which was used in the next step without further purification.

Ester 144

Ethyl 7-(1,1-dioxido-2-isothiazolidinyl)-3-ethyl-1*H*-indole-5-carboxylate (B144)

Ethyl 7-(1,1-dioxido-2-isothiazolidinyl)-3-ethyl-1*H*-indole-5-carboxylate (B144) was obtained from ethyl 7-[[(3-chloropropyl)sulfonyl]amino]-3-ethyl-1*H*-indole-5-carboxylate (D243) in an analogous manner to the process described for methyl 4-(1,1-dioxido-2-isothiazolidinyl)-1-ethyl-1*H*-indole-6-carboxylate (B143). $[M+H]^+$ = 337.1, RT = 3.23 min

Ester 145

Methyl 4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-1-ethyl-2,3-dihydro-1*H*-indole-6-carboxylate (B145)

To a solution of methyl 1-acetyl-4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2,3-dihydro-1*H*-indole-6-carboxylate (D235) (300 mg, 0.85 mmol, 1 equiv) in THF (20 ml) at room temperature was added BH_3 (1.5 M in THF, 2 ml, 3 mmol, 3.5 equiv) and the resulting mixture was stirred at room temperature for 15 h. EtOH (5 ml) was added and the resulting mixture was concentrated *in vacuo* after 5 min. The residue was partitioned between a 2N aqueous HCl solution (20 ml) and CH_2Cl_2 (20 ml) and the biphasic mixture was vigorously stirred for 3 h. The two layers were separated and the organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (AcOEt/*iso*-hexane: 1/2) gave methyl 4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-1-ethyl-2,3-dihydro-1*H*-indole-6-carboxylate (B145) (200 mg, 70%) as a very pale yellow solid. $[M+H]^+$ = 339.2, RT = 2.92 min.

Ester 146

Ethyl 7-(1,1-dioxido-2-isothiazolidinyl)-3-ethyl-1-methyl-1*H*-indole-5-carboxylate (B146)

Ethyl 7-(1,1-dioxido-2-isothiazolidinyl)-3-ethyl-1-methyl-1*H*-indole-5-carboxylate (B146) was prepared from ethyl 7-(1,1-dioxido-2-isothiazolidinyl)-3-ethyl-1*H*-indole-5-carboxylate (B144) in an analogous manner to the process described for Ester 142 (B142).

Ester 147

Methyl 4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-1-ethyl-1*H*-indole-6-carboxylate (B147)

To a solution of methyl 4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-1*H*-indole-6-carboxylate (D231) (180 mg, 0.58 mmol, 1 equiv) in DMF (3 ml) at room temperature was added NaH (60% dispersion in mineral oil, 24 mg, 0.6 mmol, 1 equiv) and the resulting mixture was stirred 15 min at this temperature. Ethyl iodide (64 µl, 0.8 mmol, 1.4 equiv) was added and the resulting solution was stirred for 1 h then concentrated *in vacuo*. The residue was dissolved in AcOEt and the organic phase was washed with a 2N aqueous HCl solution, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel gave methyl 4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-1-ethyl-1*H*-indole-6-carboxylate (B147) (110 mg, 51%) as a yellow solid which was used in the next step without further purification. $[M+H]^+$ = 337.0 ,RT = 2.82 min.

Ester 148

Ethyl 7-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-3-ethyl-1*H*-indole-5-carboxylate (B148)

To a solution of ethyl 7-[[(4-chlorobutyl)sulfonyl]amino]-3-ethyl-1*H*-indole-5-carboxylate (D242) (230 mg, 0.59 mmol, 1 equiv) in EtOH (10 ml) was added NEt_3 (249 µl, 1.76 mmol, 3 equiv) and the resulting solution was stirred at 70°C for 3 h. NEt_3 (1 ml, excess) was added and the solution was stirred at the same temperature for 15 h then cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in AcOEt and the organic phase was washed with a 2N aqueous HCl solution, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (AcOEt/*iso*-hexane: 3/7) gave ethyl 7-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-3-ethyl-1*H*-indole-5-carboxylate (B148) (150 mg, 72%) as a colorless oil. $[M-H]^-$ = 349.3, RT = 3.10 min.

Ester 150

Methyl 4-(1,1-dioxido-2-isothiazolidinyl)-1-ethyl-1*H*-benzimidazole-6-carboxylate (B150)

Methyl 4-(1,1-dioxido-2-isothiazolidinyl)-1-ethyl-1*H*-benzimidazole-6-carboxylate (B150) was obtained from methyl 4-[bis[(3-chloropropyl)sulfonyl]amino]-1-ethyl-1*H*-benzimidazole-6-carboxylate (D239) in an analogous manner to the process described for methyl 4-(1,1-dioxido-2-isothiazolidinyl)-1-ethyl-1*H*-indazole-6-carboxylate (B153)
$[M+H]^+$ = 324.5, RT = 2.10 min.

Ester 151

Methyl 4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-1-ethyl-1*H*-benzimidazole-6-carboxylate (B151)

To a solution of methyl 4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-1*H*-benzimidazole-6-carboxylate (D253) (230 mg, 0.74 mmol, 1 equiv) in DMF (10 ml) at room temperature was added NaH (60% dispersion in mineral oil, 33 mg, 0.82 mmol, 1.1 equiv) and the resulting mixture was stirred 5 min at this temperature. Ethyl iodide (66 µl, 0.82 mmol, 1.1 equiv) was added and the resulting solution was stirred for 30 min at 60°C then cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between AcOEt and a

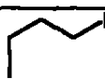
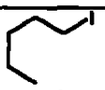
5% aqueous citric acid solution. The two layers were separated and the aqueous phase saturated with NaCl and extracted twice with AcOEt. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give methyl 4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-1-ethyl-1*H*-benzimidazole-6-carboxylate (B151) (400 mg, 160%) as a pale yellow viscous oil which was used in the next step without further purification. $[M+H]^+$ = 338.1, RT = 2.43 min.

Ester 153

Methyl 4-(1,1-dioxido-2-isothiazolidinyl)-1-ethyl-1*H*-indazole-6-carboxylate (B153)

To a solution of methyl 4-[bis[(3-chloropropyl)sulfonyl]amino]-1-ethyl-1*H*-indazole-6-carboxylate (D237) (1.5 g, 3 mmol, 1 equiv) in EtOH (20 ml) was added NEt_3 (920 µl, 6.6 mmol, 2.2 equiv) and the resulting solution was refluxed for 3 h then cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in AcOEt and the organic phase was washed with a 2N aqueous HCl solution, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with AcOEt/*iso*-hexane to give methyl 4-(1,1-dioxido-2-isothiazolidinyl)-1-ethyl-1*H*-indazole-6-carboxylate (B153) as a light brown solid which was used in the next step without further purification. $[M+H]^+$ = 324.5, RT = 2.35 min.

The following compounds have been obtained from Ester 154 (B154) in an analogous manner to the process described for Ester 140 (B140) using the appropriate alkylating reagent:

Ester	Alkylating reagent	[M+H]+	RT (min)
Methyl 1-methyl-4-(2-oxo-1-pyrrolidinyl)-1*H*-indole-6-carboxylate (B156)		273.0	2.52
Methyl 1-butyl-4-(2-oxo-1-pyrrolidinyl)-1*H*-indole-6-carboxylate (B157)		315.1	3.10
Methyl 4-(2-oxo-1-pyrrolidinyl)-1-pentyl-1*H*-indole-6-carboxylate (B158)			

Ester 159

Methyl 3-methyl-7-(2-oxo-1-pyrrolidinyl)-1-benzofuran-5-carboxylate (B159)

Methyl 3-methyl-7-(2-oxo-1-pyrrolidinyl)-1-benzofuran-5-carboxylate (B159) was obtained from methyl 3-iodo-5-(2-oxo-1-pyrrolidinyl)-4-(2-propen-1-yloxy)benzoate (D259) in an analogous manner to the process described for Ester 163 (B163).
$[M+H]^+$ = 274.0, RT = 2.97 min.

Ester 162

Ethyl 1-methyl-3-(1-methylethyl)-7-(2-oxo-1-pyrrolidinyl)-1*H*-indole-5-carboxylate (B162)

Ethyl 1-methyl-3-(1-methylethyl)-7-(2-oxo-1-pyrrolidinyl)-1*H*-indole-5-carboxylate (B162) has been obtained from ethyl 3-(1-methylethyl)-7-(2-oxo-1-pyrrolidinyl)-1*H*-indole-5-carboxylate (B161) using an analogous procedure to the process described for ethyl 3-ethyl-1-methyl-7-(2-oxo-1-pyrrolidinyl)-1*H*-indole-5-carboxylate (B142).

Ester 163

Methyl 3-ethyl-7-(2-oxo-1-pyrrolidinyl)-1-benzofuran-5-carboxylate (B163)

To a solution of methyl 4-[(2*E/Z*)-2-buten-1-yloxy]-3-iodo-5-(2-oxo-1-pyrrolidinyl)benzoate (D258) (1.4 g, 3.37 mmol, 1 equiv) in DMF (20 ml) at room temperature under nitrogen were added $Pd(OAc)_2$ (38 mg, 0.17 mmol, 0.05 equiv), NaCOOH (688 mg, 10.1 mmol, 3 equiv), Na_2CO_3 (893 mg, 8.4 mmol, 2.5 equiv) and NBu_4Cl (845 mg, 3.71 mmol, 1.1 equiv). The resulting suspension was stirred under nitrogen at 120°C for 1 h then cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between AcOEt and H_2O and the two phases were separated. The organic phase was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt : 1/1) gave methyl 3-ethyl-7-(2-oxo-1-pyrrolidinyl)-1-benzofuran-5-carboxylate (B163) (250 mg, 26%) as a white solid. $[M+H]^+$ = 288.1, RT = 3.02 min.

Ester 164

Methyl 4-(ethyloxy)-3-[ethyl(propanoyl)amino]-5-(1-methylethyl)benzoate (B164)

Methyl 4-(ethyloxy)-3-[ethyl(propanoyl)amino]-5-(1-methylethyl)benzoate (B164) was obtained from methyl 4-methyl-8-(2-oxo-1-pyrrolidinyl)-2*H*-chromene-6-carboxylate and methyl 4-(ethyloxy)-3-[ethyl(propanoyl)amino]-5-(1-methylethenyl)benzoate (D261) in an analogous manner to the process described for 3-(2-oxo-piperidin-1-yl)-5-propyl-benzoic acid *tert*-butyl ester (B116).

Ester 165

Ethyl 3-ethyl-7-(2-oxo-1-piperidinyl)-1*H*-indole-5-carboxylate (B165)

To a solution of ethyl 3-ethyl-7-iodo-1*H*-indole-5-carboxylate (D190) (1 g, 2.91 mmol, 1 equiv) in toluene (10 ml) were added 2-piperidinone (346 mg, 3.50 mmol, 1.2 equiv), K_3PO_4 (1.24 g, 5.83 mmol, 2 equiv), CuI (56 mg, 0.29 mmol, 0.1 equiv) and dimethyl ethylene diamine (62 µl, 0.58 mmol, 0.2 equiv) and the resulting mixture was stirred at 100°C for 15 h then cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between AcOEt and H_2O and the layers were separated. The organic phase was dried under $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (AcOEt/*iso*-hexane: 1/0) gave ethyl 3-ethyl-7-(2-oxo-1-piperidinyl)-1*H*-indole-5-carboxylate (B165) (250 mg, 27%) as an off-white solid.
$[M+H]^+$ = 315.4, RT = 2.98 min.

Ester 166

Ethyl 3-ethyl-7-(2-oxo-4-phenyl-1-pyrrolidinyl)-1*H*-indole-5-carboxylate (B166)

Ethyl 3-ethyl-7-(2-oxo-4-phenyl-1-pyrrolidinyl)-1*H*-indole-5-carboxylate (B166) was obtained from ethyl 3-ethyl-7-iodo-1*H*-indole-5-carboxylate (D166) in an analogous manner to the process described for 1,1-dimethylethyl 3-bromo-5-(2-oxo-5-phenyl-1-piperidinyl)benzoate (D190) using 4-phenyl-2-pyrrolidinone (Koelsch *J. Am. Chem. Soc.* 1943, (65), p 2093) instead of 5-phenyl-2-piperidinone. $[M+H]^+$ = 377.2, RT = 3.60 min.

Ester 167

Methyl 1-ethyl-4-(2-oxo-1-pyrrolidinyl)-1*H*-1,2,3-benzotriazole-6-carboxylate (B167)
To a solution of ethyl methyl 4-(2-oxo-1-pyrrolidinyl)-1*H*-1,2,3-benzotriazole-6-carboxylate (D249) (400 mg, 1.54 mmol, 1 equiv) in DMF (10 ml) at room temperature was added NaH (60% dispersion in mineral oil, 68 mg, 1.69 mmol, 1.1 equiv) and the resulting mixture was stirred 5 min at this temperature. Ethyl iodide (135 µl, 1.69 mmol, 1.1 equiv) was added and the resulting solution was stirred for 2 h then concentrated *in vacuo*. The residue was dissolved in AcOEt and the organic phase was washed with H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (AcOEt/*iso*-hexane: 100/0) gave methyl 1-ethyl-4-(2-oxo-1-pyrrolidinyl)-1*H*-1,2,3-benzotriazole-6-carboxylate (270 mg, 61%) as a pale yellow oil.
$[M+H]^+$ = 289.3, RT = 2.47 min.

Ester 168
Methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-(ethyloxy)benzoate (B168)
Methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-(ethyloxy)benzoate (B168) was obtained from methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-hydroxybenzoate (D268) in an analogous manner to the process described for Ester 18 (B18) from Description 41 (D41).

Ester 169
Methyl 3-cyclopentyl-5-(1,1-dioxido-2-isothiazolidinyl)benzoate (B169)
Methyl 3-cyclopentyl-5-(1,1-dioxido-2-isothiazolidinyl)benzoate (B169) was obtained from methyl 3-(3-cyclopenten-1-yl)-5-(1,1-dioxido-2-isothiazolidinyl)benzoate, methyl 3-(2-cyclopenten-1-yl)-5-(1,1-dioxido-2-isothiazolidinyl)benzoate and methyl 3-(1-cyclopenten-1-yl)-5-(1,1-dioxido-2-isothiazolidinyl)benzoate (D264) in an analogous manner to the process described for Ester 107 (B107).

Ester 170
Methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-[(1-methylethyl)oxy]benzoate (B170)
Methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-[(1-methylethyl)oxy]benzoate (B170) was obtained from methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-hydroxybenzoate (D268) in an analogous manner to the process described for Ester 18 (B18) from Description 41 (D41) using 2-iodopropane instead of iodoethane.

Ester 172
Methyl 8-(1,1-dioxido-2-isothiazolidinyl)-4-ethyl-1,2,3,4-tetrahydro-6-quinoxalinecarboxylate (B172)
Methyl 8-(1,1-dioxido-2-isothiazolidinyl)-4-ethyl-1,2,3,4-tetrahydro-6-quinoxalinecarboxylate (B172) was obtained from methyl 8-{bis[(3-chloropropyl)sulfonyl]amino}-4-ethyl-1,2,3,4-tetrahydro-6-quinoxalinecarboxylate (D238) in an analogous manner to the process described for methyl 4-(1,1-dioxido-2-isothiazolidinyl)-1-ethyl-1*H*-indazole-6-carboxylate (B153). $[M+H]^+$ = 340.2 ,RT = 3.32 min.

Ester 175

Methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluoro-5-[(1-methylethyl)amino]benzoate (B175)

Methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluoro-5-[(1-methylethyl)amino]benzoate (B175) was obtained from Description 152 (D152) in an analogous manner to the process described for Ester 43 (B43) using acetone instead of 3-pentanone.

Ester 176

Methyl 5-cyclopentyl-3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluorobenzoate (B176)

Methyl 5-cyclopentyl-3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluorobenzoate (B176) was obtained from Description (D269) in an analogous manner to the process described for Ester B116 (B116).

Preparation of Epoxides

Epoxide K1

1,1-Dimethylethyl {(1*S*)-2-(3,5-difluorophenyl)-1-[(2*S*)-2-oxiranyl]ethyl}carbamate (K1)

1,1-Dimethylethyl {(1*S*)-2-(3,5-difluorophenyl)-1-[(2*S*)-2-oxiranyl]ethyl}carbamate (K1) was obtained from 3,5-difluoro-L-phenylalaninate (D299) according to the procedure described in Patent US 2003/0004360 A1

The following epoxides were obtained in an analogous manner to the process described for epoxide K1 using the appropriate alaninate:

Epoxide	Precursor
1,1-dimethylethyl {(1*S*)-2-(3-fluorophenyl)-1-[(2*S*)-2-oxiranyl]ethyl}carbamate (K2)	D300
1,1-dimethylethyl {(1*S*)-2-(3,4-difluorophenyl)-1-[(2*S*)-2-oxiranyl]ethyl}carbamate (K3)	D301
1,1-dimethylethyl {(1*S*)-2-(2-chlorophenyl)-1-[(2*S*)-2-oxiranyl]ethyl}carbamate (K4)	D302
1,1-dimethylethyl {(1*S*)-2-(3-chlorophenyl)-1-[(2*S*)-2-oxiranyl]ethyl}carbamate (K5)	D303
1,1-dimethylethyl {(1*S*)-2-(4-chlorophenyl)-1-[(2*S*)-2-oxiranyl]ethyl}carbamate (K6)	D304
1,1-dimethylethyl [(1*S*)-1-[(2*S*)-2-oxiranyl]-2-(2-thienyl)ethyl]carbamate (K7)	D305
1,1-dimethylethyl [(1*S*)-1-[(2*S*)-2-oxiranyl]-2-(3-thienyl)ethyl]carbamate (K8)	D306
1,1-dimethylethyl {(1*S*)-2-(2-furanyl)-1-[(2*S*)-2-oxiranyl]ethyl}carbamate (K9)	D307
1,1-dimethylethyl [(1*S*)-1-[(2*S*)-2-oxiranyl]-2-(2-pyridinyl)ethyl]carbamate (K10)	D308
1,1-dimethylethyl [(1*S*)-1-[(2*S*)-2-oxiranyl]-2-(1,3-thiazol-2-yl)ethyl]carbamate (K11)	D309
1,1-dimethylethyl [(1*S*)-1-[(2*S*)-2-oxiranyl]-2-(1*H*-pyrazol-1-yl)ethyl]carbamate (K12)	D310

1,1-dimethylethyl [(1*S*)-1-[(2*S*)-2-oxiranyl]-2-(3-pyridinyl)ethyl]carbamate (K13)	D311

Preparation of BOC-protected amines

BOC-protected amine 1 (H1)

((1S,2R)-1-Benzyl-3-cyclohexylamino-2-hydroxy-propyl)-carbamic acid *tert*-butyl ester (H1)

((S)-(S)-1-Oxiranyl-2-phenyl-ethyl)-carbamic acid *tert*-butyl ester (D101) (10 g, 38 mmol, 1 equiv) [Chirex 1819W94 Lot#9924382] was dissolved in EtOH (100 ml) and cyclohexylamine (13 ml, 114 mmol, 3 equiv) was added. The resulting mixture was heated, under an atmosphere of nitrogen, for 12 h at reflux temperature. The mixture was cooled and the solvent was removed by evaporation *in vacuo*. The resulting white solid was washed with H_2O and then with Et_2O before drying *in vacuo* to give ((1S,2R)-1-benzyl-3-cyclohexylamino-2-hydroxy-propyl)-carbamic acid *tert*-butyl ester (H1) (9.0 g, 66%). $[M+H]^+$ = 363.2

BOC-protected amines H2-H20, H24-H33 and H36 were prepared in an analogous manner to that described for BOC-protected amine H1, substituting cyclohexylamine with the amines indicated in the table below (unless amines are commercially available):

BOC-protected amine	Precursor
((1S,2R)-1-Benzyl-3-cyclobutylamino-2-hydroxy-propyl)-carbamic acid *tert*-butyl ester (H2)	-
((1S,2R)-1-Benzyl-2-hydroxy-3-isobutylamino-propyl)-carbamic acid *tert*-butyl ester (H3)	-
((1S,2R)-1-Benzyl-2-hydroxy-3-propylamino-propyl)-carbamic acid *tert*-butyl ester (H4)	-
[(1S,2R)-1-Benzyl-2-hydroxy-3-(1,1,5-trimethyl-hexylamino)-propyl]-carbamic acid *tert*-butyl ester (H5)	F5
[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl-ethylamino)-2-hydroxy-propyl]-carbamic acid *tert*-butyl ester (H6)	F6
{(1S,2R)-1-Benzyl-2-hydroxy-3-[(R)-1-(3-methoxy-phenyl)-ethylamino]-propyl}-carbamic acid *tert*-butyl ester (H7)	-
[(1S,2R)-1-Benzyl-2-hydroxy-3-(1-methyl-1-phenyl-ethylamino)-propyl]-carbamic acid *tert*-butyl ester (H8)	-
[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-methyl-butylamino)-propyl]-carbamic acid *tert*-butyl ester (H9)	-
((1S,2R)-1-Benzyl-3-*tert*-butylamino-2-hydroxy-propyl)-carbamic acid *tert*-butyl ester (H10)	-
[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethoxy-benzylamino)-propyl]-carbamic acid *tert*-butyl ester (H11)	-
[(1S,2R)-1-Benzyl-2-hydroxy-3-(2,2,3,3,3-pentafluoro-propylamino)-propyl]-carbamic acid *tert*-butyl ester (H12)	-
[(1S,2R)-1-Benzyl-3-(2,2,3,3,4,4,4-heptafluoro-butylamino)-2-hydroxy-propyl]-carbamic acid *tert*-butyl ester (H13)	-

[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-methoxy-benzylamino)-propyl]-carbamic acid *tert*-butyl ester (H14)	-
{(1S,2R)-1-Benzyl-2-hydroxy-3-[1-(3-methoxy-phenyl)-1-methyl-ethylamino]-propyl}-carbamic acid *tert*-butyl ester (H15)	F15
[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-carbamic acid *tert*-butyl ester (H16)	-
{(1S,2R)-1-Benzyl-2-hydroxy-3-[(S)-1-(3-methoxy-phenyl)-ethylamino]-propyl}-carbamic acid *tert*-butyl ester (H17)	-
{(1S,2R)-1-Benzyl-2-hydroxy-3-[(S)-1-(3-methoxy-phenyl)-ethylamino]-propyl}-carbamic acid *tert*-butyl ester (H18)	-
[(1S,2R)-1-Benzyl-2-hydroxy-3-(5-methyl-hexylamino)-propyl]-carbamic acid *tert*-butyl ester (H19)	-
[(1S,2R)-1-Benzyl-3-(1,5-dimethyl-hexylamino)-2-hydroxy-propyl]-carbamic acid *tert*-butyl ester (H20)	-
((1S,2R)-1-Benzyl-3-ethylamino-2-hydroxy-propyl)-carbamic acid *tert*-butyl ester (H24)	-
[(1S,2R)-1-Benzyl-3-(bis-trifluoromethyl-benzylamino)-2-hydroxy-propyl]-carbamic acid *tert*-butyl ester (H25)	-
((1S,2R)-1-Benzyl-3-cyclopropylamino-2-hydroxy-propyl)-carbamic acid *tert*-butyl ester (H26)	-
[(1S,2R)-1-Benzyl-2-hydroxy-3-(4-methoxy-benzylamino)-propyl]-carbamic acid *tert*-butyl ester (H27)	-
((1S,2R)-1-Benzyl-2-hydroxy-3-isopropylamino-propyl)-carbamic acid *tert*-butyl ester (H28)	-
[(1S,2R)-1-Benzyl-2-hydroxy-3-(2-methoxy-benzylamino)-propyl]-carbamic acid tert-butyl ester (H29)	-
[(1S,2R)-1-Benzyl-2-hydroxy-3-((S)-1-phenyl-ethylamino)-propyl]-carbamic acid *tert*-butyl ester (H30)	-
[(1S,2R)-1-Benzyl-2-hydroxy-3-((R)-1-phenyl-ethylamino)-propyl]-carbamic acid *tert* butyl ester (H31)	-
[(1S,2R)-1-Benzyl-2-hydroxy-3-(4-methyl-pentylamino)-propyl]-carbamic acid *tert*-butyl ester (H32)	-
[(1S,2R)-1-Benzyl-2-hydroxy-3-((R)-2-hydroxy-1-isobutylcarbamoyl-pentylamino)-propyl]-carbamic acid *tert*-butyl ester (H33)	F33
[(1S,2R)-1-Benzyl-2-hydroxy-3-((S)-1-isobutylcarbamoyl-pentylamino)-propyl]-carbamic acid *tert*-butyl ester (H36)	F36

BOC-protected amines H40-H114 were prepared in an analogous manner to that described for BOC-protected amine H1, substituting cyclohexylamine with the amines indicated in the table below (unless amines are commercially available):

BOC-protected amine	Precursor
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-({[3-	F40

(trifluoromethyl)phenyl]methyl} amino)propyl]carbamate (H40)	
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-({1-[3-(methyloxy)phenyl]cyclohexyl} amino)-1-(phenylmethyl)propyl]carbamate (H41)	F41
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-[[(1-methyl-1*H*-pyrazol-4-yl)methyl]amino}-1-(phenylmethyl)propyl]carbamate (H42)	
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-(tetrahydro-2*H*-pyran-4-ylamino)propyl]carbamate (H43)	
1,1-dimethylethyl [(1*S*,2*R*)-3-[(3,3-dimethylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H44)	
1,1-dimethylethyl {(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-[(1,1,3,3-tetramethylbutyl)amino] propyl}carbamate (H45)	
1,1-dimethylethyl [(1*S*,2*R*)-3-[(1,3-dimethylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H46)	
1,1-dimethylethyl [(1*S*,2*R*)-3-({[4-fluoro-3-(trifluoromethyl)phenyl] methyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H47)	
1,1-dimethylethyl [(1*S*,2*R*)-3-[(1,1-dimethylhexyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H48)	F48
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-({[2-methyl-5-(trifluoromethyl)phenyl] methyl}amino)-1-(phenylmethyl)propyl]carbamate (H49)	
1,1-dimethylethyl [(1*S*,2*R*)-3-[(1*S*)-2,3-dihydro-1*H*-inden-1-ylamino]-2-hydroxy-1-(phenylmethyl)propyl] carbamate (H50)	
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-[[(1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl]amino}-1-(phenylmethyl)propyl]carbamate (H51)	
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-[[6-(methyloxy)-2,3-dihydro-1*H*-inden-1-yl]amino}-1-(phenylmethyl)propyl]carbamate (H52)	F52
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-[[(1*R*,2*S*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl]amino}-1-(phenylmethyl)propyl]carbamate (H53)	
1,1-dimethylethyl [(1*S*,2*R*)-3-({1,1-dimethyl-2-[(2-methylpropyl)thio] ethyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H54)	F54
1,1-dimethylethyl [(1*S*,2*R*)-3-[[1,1-dimethyl-2-(phenyloxy)ethyl] amino}-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H55)	F55
1,1-dimethylethyl [(1*S*,2*R*)-3-({1,1-dimethyl-2-[(phenylmethyl)oxy] ethyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H56)	F56
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-[[3-(methyloxy)phenyl] amino}-1-(phenylmethyl)propyl] carbamate (H57)	
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-({2-[3-(trifluoromethyl)phenyl]ethyl}amino)propyl]carbamate (H58)	
1,1-dimethylethyl [(1*S*,2*R*)-3-[(1,1-dimethyl-2-phenylethyl)amino]-2-hydroxy-1-(phenylmethyl)propyl] carbamate (H59)	
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-[[2-(1-naphthalenyl) ethyl]amino}-1-(phenylmethyl) propyl]carbamate (H60)	
1,1-dimethylethyl [(1*S*,2*R*)-3-({1,1-dimethyl-2-[3-(methyloxy)phenyl] ethyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H61)	F61

H5
116

1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-(phenylamino)-1-(phenylmethyl)propyl]carbamate (H62)	
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-({1-[3-(methyloxy) phenyl]cyclopropyl}amino)-1-(phenylmethyl)propyl]carbamate (H63)	F63
1,1-dimethylethyl [(1*S*,2*R*)-3-[(cyclohexylmethyl)amino]-2-hydroxy-1-(phenylmethyl)propyl] carbamate (H64)	
1,1-dimethylethyl {(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]propyl}carbamate (H65)	
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-(tetrahydro-2*H*-thiopyran-4-ylamino)propyl]carbamate (H66)	
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-[(1-methylpropyl)amino]-1-(phenylmethyl)propyl]carbamate (H67)	
1,1-dimethylethyl [(1*S*,2*R*)-3-[[4-(1,1-dimethylethyl)cyclohexyl] amino}-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H68)	
1,1-dimethylethyl [(1*S*,2*R*)-3-[(1-ethylcyclobutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H69)	F69
1,1-dimethylethyl [(1*S*,2*R*)-3-({1,1-dimethyl-2-[(2-methylpropyl)oxy] ethyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H70)	F70
1,1-dimethylethyl [(1*S*,2*R*)-3-({1,1-dimethyl-2-[(2-methyl-2-propen-1-yl)oxy]ethyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H71)	F71
1,1-dimethylethyl [(1*S*,2*R*)-3-[(1*R*)-2,3-dihydro-1*H*-inden-1-ylamino]-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H72)	
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-[[1-(4-methylpentyl)cyclopropyl]amino]-1-(phenylmethyl)propyl]carbamate (H73)	F73
1,1-dimethylethyl [(1*S*,2*R*)-3-[(1-ethylcyclopropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H74)	F74
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-[[1-(1-methylethyl)cyclopropyl] amino}-1-(phenylmethyl)propyl]carbamate (H75)	F75
1,1-dimethylethyl [(1*S*,2*R*)-3-(butylamino)-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H76)	
1,1-dimethylethyl {(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-[(1-propylcyclopropyl)amino]propyl} carbamate (H77)	F77
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-[[1-(3-methylbutyl) cyclopropyl]amino}-1-(phenylmethyl)propyl]carbamate (H78)	F78
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-[[1-(2-methylpropyl) cyclopropyl]amino}-1-(phenylmethyl)propyl]carbamate (H79)	F79
1,1-dimethylethyl [(1*S*,2*R*)-3-({1-[(3-chlorophenyl)methyl] cyclopropyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H80)	F80
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-[(1-methylcyclohexyl) amino]-1-(phenylmethyl)propyl] carbamate (H81)	F81
1,1-dimethylethyl [(1*S*,2*R*)-3-[(2*S*)-bicyclo[2.2.1]hept-2-ylamino]-2-hydroxy-1-(phenylmethyl)propyl] carbamate (H82)	
1,1-dimethylethyl [(1*S*,2*R*)-3-[(4,4-dimethylcyclohexyl)amino]-2-hydroxy-1-	F83

117

(phenylmethyl)propyl] carbamate (H83)	
1,1-dimethylethyl ((1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-{[(1*R*)-1,2,2-trimethylpropyl]amino} propyl)carbamate (H84)	
1,1-dimethylethyl ((1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-{[(1*S*)-1,2,2-trimethylpropyl]amino} propyl)carbamate (H85)	
1,1-dimethylethyl [(1*S*,2*R*)-3-[(2,2-dimethylcyclohexyl)amino]-2-hydroxy-1-(phenylmethyl)propyl] carbamate (H86)	F86
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-(pentylamino)-1-(phenylmethyl)propyl]carbamate (H87)	
1,1-dimethylethyl [(1*S*,2*R*)-3-(hexylamino)-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H88)	
1,1-dimethylethyl [(1*S*,2*R*)-3-[(3,3-dimethylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H89)	
1,1-dimethylethyl [(1*S*,2*R*)-3-[(1,1-dimethylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H90)	
1,1-dimethylethyl [(1*S*,2*R*)-3-[(cyclopropylmethyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H91)	
1,1-dimethylethyl [(1*S*,2*R*)-3-[(3,3-dimethylcyclopentyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H92)	F92
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-(methylamino)-1-(phenylmethyl)propyl]carbamate (H93)	
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-(tricyclo[3.3.1.1^{3,7}]dec-1-ylamino)propyl]carbamate (H94)	
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-(1,2,3,4-tetrahydro-1-naphthalenylamino)propyl] carbamate (H95)	
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-({2-[3-(methyloxy)phenyl]ethyl}amino)-1-(phenylmethyl)propyl]carbamate (H96)	
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-({2-[4-(methyloxy)phenyl]ethyl}amino)-1-(phenylmethyl)propyl]carbamate (H97)	
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-({2-[2-(methyloxy)phenyl]ethyl}amino)-1-(phenylmethyl)propyl]carbamate (H98)	
1,1-dimethylethyl [(1*S*,2*R*)-3-{[2-(2-chlorophenyl)ethyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H99)	
1,1-dimethylethyl [(1*S*,2*R*)-3-{[2-(3-chlorophenyl)ethyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H100)	
1,1-dimethylethyl [(1*S*,2*R*)-3-{[2-(4-chlorophenyl)ethyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H101)	
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-{[2-(4-methylphenyl)ethyl]amino}-1-(phenylmethyl)propyl]carbamate (H102)	
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-{[2-(2-methylphenyl)ethyl]amino}-1-(phenylmethyl)propyl]carbamate (H103)	
1,1-dimethylethyl [(1*S*,2*R*)-3-{[2-(3,4-dichlorophenyl)ethyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H104)	

1,1-dimethylethyl [(1*S*,2*R*)-3-{[2-(2,4-dichlorophenyl)ethyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H105)	
1,1-dimethylethyl [(1*S*,2*R*)-3-({2-[3,5-bis(methyloxy)phenyl]ethyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H106)	
1,1-dimethylethyl [(1*S*,2*R*)-3-({2-[2,3-bis(methyloxy)phenyl] ethyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H107)	
1,1-dimethylethyl {(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-[(phenylmethyl)amino]propyl} carbamate (H108)	
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-[(2-phenylethyl)amino]-1-(phenylmethyl)propyl]carbamate (H109)	
1,1-dimethylethyl [(1*S*,2*R*)-3-[(1-ethylcyclohexyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H110)	F110
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-[(1-methylcyclopentyl)amino]-1-(phenylmethyl)propyl]carbamate (H111)	F111
1,1-dimethylethyl {(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-[(1-propylcyclopentyl)amino]propyl} carbamate (H112)	F112
1,1-dimethylethyl {(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-[(1-propylcyclohexyl)amino]propyl} carbamate (H113)	F113
1,1-dimethylethyl [(1*S*,2*R*)-3-{[2-(3-chlorophenyl)-1,1-dimethylethyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H114)	F114

The following BOC-protected amines H115-H147 were prepared in an analogous manner to that described for BOC-protected amine H1, using the appropriate epoxide and the appropriate amine indicated in the table below (only non commercial amines are given):

Boc-protected amine	Epoxide	Amine
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-({[3-(methyloxy)phenyl] methyl}amino)-1-(3-pyridinylmethyl)propyl]carbamate (H115)	K13	
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-({[3-(methyloxy)phenyl] methyl}amino)-1-(1,3-thiazol-2-ylmethyl)propyl]carbamate (H116)	K11	
1,1-dimethylethyl [(1*S*,2*R*)-3-(cyclohexylamino)-2-hydroxy-1-(1,3-thiazol-2-ylmethyl)propyl]carbamate (H117)	K11	
1,1-dimethylethyl [(1*S*,2*R*)-3-[(1,5-dimethylhexyl)amino]-2-hydroxy-1-(1,3-thiazol-2-ylmethyl)propyl]carbamate (H118)	K11	
1,1-dimethylethyl [(1*S*,2*R*)-1-(2-furanylmethyl)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino) propyl]carbamate (H119)	K9	
1,1-dimethylethyl [(1*S*,2*R*)-3-(cyclohexylamino)-1-(2-furanylmethyl)-2-hydroxypropyl]carbamate (H120)	K9	
1,1-dimethylethyl [(1*S*,2*R*)-3-[(1,5-dimethylhexyl)amino]-1-(2-furanylmethyl)-2-hydroxypropyl]carbamate (H121)	K9	
1,1-dimethylethyl {(1*S*,2*R*)-1-(2-furanylmethyl)-2-hydroxy-3-[(1,1,5-trimethylhexyl)amino]propyl} carbamate (H122)	K9	F5
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-({[3-(methyloxy)phenyl]	K10	

methyl]amino)-1-(2-pyridinylmethyl)propyl]carbamate (H123)		
1,1-dimethylethyl [(1*S*,2*R*)-1-[(4-chlorophenyl)methyl]-3-(cyclohexylamino)-2-hydroxypropyl]carbamate (H124)	K6	
1,1-dimethylethyl [(1*S*,2*R*)-1-[(4-chlorophenyl)methyl]-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl} amino)propyl]carbamate (H125)	K6	
1,1-dimethylethyl [(1*S*,2*R*)-1-[(3,5-difluorophenyl)methyl]-2-hydroxy-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]carbamate (H126)	K1	
1,1-dimethylethyl [(1*S*,2*R*)-1-[(3,5-difluorophenyl)methyl]-2-hydroxy-3-({[3-(methyloxy)phenyl] methyl}amino)propyl]carbamate (H127)	K1	
1,1-dimethylethyl {(1*S*,2*R*)-1-[(3,5-difluorophenyl)methyl]-3-[(1,5-dimethylhexyl)amino]-2-hydroxypropyl}carbamate (H128)	K1	
1,1-dimethylethyl {(1*S*,2*R*)-3-(cyclohexylamino)-1-[(3,5-difluorophenyl)methyl]-2-hydroxypropyl}carbamate (H129)	K1	
1,1-dimethylethyl {(1*S*,2*R*)-1-[(3,5-difluorophenyl)methyl]-2-hydroxy-3-[(1,1,5-trimethylhexyl)amino]propyl} carbamate (H130)	K1	F5
1,1-dimethylethyl [(1*S*,2*R*)-1-[(3,4-difluorophenyl)methyl]-2-hydroxy-3-({[3-(methyloxy)phenyl] methyl}amino)propyl]carbamate (H131)	K3	
1,1-dimethylethyl {(1*S*,2*R*)-3-(cyclohexylamino)-1-[(3,4-difluorophenyl)methyl]-2-hydroxypropyl}carbamate (H132)	K3	
1,1-dimethylethyl {(1*S*,2*R*)-1-[(3,4-difluorophenyl)methyl]-2-hydroxy-3-[(1,1,5-trimethylhexyl)amino] propyl}carbamate (H133)	K3	F5
1,1-dimethylethyl [(1*S*,2*R*)-1-[(3-chlorophenyl)methyl]-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl} amino)propyl]carbamate (H134)	K5	
1,1-dimethylethyl [(1*S*,2*R*)-1-[(3-chlorophenyl)methyl]-3-(cyclohexylamino)-2-hydroxypropyl]carbamate (H135)	K5	
1,1-dimethylethyl [(1*S*,2*R*)-1-[(2-chlorophenyl)methyl]-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl} amino)propyl]carbamate (H136)	K4	
1,1-dimethylethyl [(1*S*,2*R*)-1-[(2-chlorophenyl)methyl]-3-(cyclohexylamino)-2-hydroxypropyl]carbamate (H137)	K4	
1,1-dimethylethyl {(1*S*,2*R*)-1-[(2-chlorophenyl)methyl]-3-[(1,5-dimethylhexyl)amino]-2-hydroxypropyl}carbamate (H138)	K4	
1,1-dimethylethyl {(1*S*,2*R*)-1-[(3-chlorophenyl)methyl]-3-[(1,5-dimethylhexyl)amino]-2-hydroxypropyl}carbamate (H139)	K5	
1,1-dimethylethyl [(1*S*,2*R*)-1-[(3-fluorophenyl)methyl]-2-hydroxy-3-({[3-(methyloxy)phenyl] methyl}amino)propyl]carbamate (H140)	K2	
1,1-dimethylethyl {(1*S*,2*R*)-3-[(1,5-dimethylhexyl)amino]-1-[(3-fluorophenyl)methyl]-2-hydroxypropyl}carbamate (H141)	K2	
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-({[3-(methyloxy)phenyl] methyl}amino)-1-(2-thienylmethyl)propyl]carbamate (H142)	K7	

1,1-dimethylethyl [(1*S*,2*R*)-3-[(1,5-dimethylhexyl)amino]-2-hydroxy-1-(2-thienylmethyl)propyl]carbamate (H143)	K7	
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-({[3-(methyloxy)phenyl] methyl}amino)-1-(1*H*-pyrazol-1-ylmethyl)propyl]carbamate (H144)	K12	
1,1-dimethylethyl [(1*S*,2*R*)-3-[(1,5-dimethylhexyl)amino]-2-hydroxy-1-(1*H*-pyrazol-1-ylmethyl)propyl]carbamate (H145)	K12	
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-({[3-(methyloxy)phenyl] methyl}amino)-1-(3-thienylmethyl)propyl]carbamate (H146)	K8	
1,1-dimethylethyl [(1*S*,2*R*)-3-[(1,5-dimethylhexyl)amino]-2-hydroxy-1-(3-thienylmethyl)propyl]carbamate (H147)	K8	

BOC-protected amines H148-H156 were prepared in an analogous manner to that described for BOC-protected amine H1, substituting cyclohexylamine with the amines indicated in the table below (if amines are not commercially available):

BOC-protected amine	Precursor
1,1-dimethylethyl {(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-[(1-propylcyclobutyl)amino]propyl} carbamate (H148)	F148
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-[[1-(1-methylethyl)cyclobutyl]amino]-1-(phenylmethyl)propyl]carbamate (H149)	F149
1,1-dimethylethyl [(1*S*,2*R*)-3-({1-[(3-chlorophenyl) methyl]cyclobutyl} amino)-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H150)	F150
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-(tricyclo[3.3.1.1^{3,7}]dec-2-ylamino)propyl]carbamate (H151)	
1,1-dimethylethyl [(1*S*,2*R*)-3-[(1*r*,4*R*)-bicyclo[2.2.1]hept-1-ylamino]-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H152)	
1,1-dimethylethyl [(1*S*,2*R*)-3-(bicyclo[2.2.2]oct-1-ylamino)-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H153)	
1,1-dimethylethyl [(1*S*,2*R*)-3-[[(1-ethyl-1*H*-pyrazol-4-yl)methyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H154)	
1,1-dimethylethyl [(1*S*,2*R*)-3-[(4,4-difluorocyclohexyl)amino]-2-hydroxy-1-(phenylmethyl)propyl] carbamate (H155)	F155
1,1-dimethylethyl [(1*S*,2*R*)-3-({[3,4-bis(methyloxy)phenyl] methyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H156)	

BOC-protected amine H157

1,1-Dimethylethyl [(1*S*,2*R*)-3-[[(3-ethyl-5-isoxazolyl)methyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H157)

1,1-dimethylethyl [(1*S*,2*R*)-3-[[(3-ethyl-5-isoxazolyl)methyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H157) was prepared from Description F157 in an analogous manner to the process described for BOC-protected amine H1.

Preparation of Acids

Acid 1

121

3-Methylsulfanyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A1)

To a solution of 3-methylsulfanyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B1) (115 mg, 0.433 mmol, 1 equiv) in MeOH (8 ml) was added 2N aqueous NaOH solution (0.65 ml, 1.3 mmol, 3 equiv). The resulting mixture was stirred for 4 h, 2N aqueous NaOH solution (1 ml, mmol, equiv) was added and the resulting solution was stirred for 16 h then concentrated *in vacuo*. The residue was diluted with H_2O and extracted with Et_2O. The aqueous layer was acidified using 2N aqueous HCl solution and the white precipitate formed was extracted twice with AcOEt. The combined organic solutions were dried over Na_2SO_4 and concentrated *in vacuo* to give 3-methylsulfanyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A1) (109 mg, 100%) as a white solid. $[M+H]^+$ = 252.0, RT = 2.61 min

Acid 2

3-Ethylsulfanyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A2)

Acid 2 was prepared from 125 mg (0.426 mmol) of 3-methylsulfanyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B2) in an analogous manner to that described for Acid 1 which yielded 11 mg (98%) of 3-methylsulfanyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A2) as a white solid. $[M+H]^+$ = 266.1, RT = 2.82 min

Acid 3

3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-methylsulfanyl-benzoic acid (A3)

To a solution of 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-methylsulfanyl-benzoic acid methyl ester (B3) (144 mg, 0.48 mmol, 1 equiv) in MeOH (10 ml) was added 2N aqueous NaOH solution (2.4 ml, 4.8 mmol, 10 equiv). The resulting mixture was stirred at room temperature for 3.5 h and at 40°C for 1 h, then cooled to room temperature and concentrated *in vacuo*. The residue was diluted with H_2O and extracted with Et_2O. The aqueous layer was acidified with 2N aqueous HCl solution and the white precipitate formed was extracted twice with AcOEt. The combined organic solutions were dried over Na_2SO_4 and concentrated *in vacuo* to give 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-methylsulfanyl-benzoic acid (A3) (136 mg, 100%) as a white solid. $[M+H]^+$ = 288.0, RT = 2.63 min

Acid 4

3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-ethylsulfanyl-benzoic acid (A4)

To a solution of 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-ethylsulfanyl-benzoic acid ethyl ester (B4) (145 mg, 0.44 mmol, 1 equiv) in MeOH (5 ml) was added 2N aqueous NaOH solution (2.2 ml, 4.4 mmol, 10 equiv). The resulting mixture was stirred at room temperature for 3 h then concentrated *in vacuo*. The residue was diluted with H_2O and extracted with Et_2O. The aqueous layer was acidified with 2N aqueous HCl solution and the white precipitate formed extracted twice with AcOEt. The combined organic solutions were dried over Na_2SO_4 and concentrated *in vacuo* to give 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-ethylsulfanyl-benzoic acid (A4) (133 mg, 100%) as a white solid. $[M+H]^+$ = 302.0, RT = 2.83 min

Acid 5

3-Methanesulfonyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A5)

To a solution of 3-methylsulfanyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A1) (59 mg, 0.235 mmol, 1 equiv) in MeOH/H_2O (3:1, 24 ml) was added oxone (578 mg, 0.94 mol, 4 equiv). The resulting mixture was stirred at room temperature for 50 min and then concentrated *in vacuo*. The residue was partitioned between AcOEt and H_2O and the layers separated. The organic layer was washed with H_2O and brine, dried over Na_2SO_4 and concentrated *in vacuo* to give a solid which was triturated with Et_2O to give 3-methanesulfonyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A5) (57 mg, 86%) as a white solid. $[M+H]^+$ = 284.0, RT = 2.05 min

Acid 6

3-Ethanesulfonyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A6)

Acid 6 was prepared from 59 mg (0.22 mmol) of 3-ethylsulfanyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A2) in an analogous manner to that described for Acid 5 which yielded 59 mg (89%) of 3-ethanesulfonyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A6) as a white solid. $[M+H]^+$ = 298.0, Rt = 2.08 min

Acid 7

3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-methanesulfonyl-benzoic acid (A7)

Acid 7 was prepared from 78 mg (0.27 mmol) of 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-methylsulfanyl-benzoic acid (A3) in an analogous manner to that described for Acid 6 which yielded 78 mg (90%) of 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-methanesulfonyl-benzoic acid (A7) as a white solid. $[M-H]^-$ = 318.0, RT = 2.07 min

Acid 8

3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-ethanesulfonyl-benzoic acid (A8)

Acid 8 was prepared from 72 mg (0.24 mmol) of 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-ethylsulfanyl-benzoic acid (A4) 73 mg (91%) in an analogous manner to that described in Acid 7 which yielded 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-ethanesulfonyl-benzoic acid A8 as a white solid. $[M-H]^-$ = 332.0, RT = 2.14 min

Acids A9-A15 were prepared from the corresponding ester indicated in the below table using a procedure analogous to that described in either A113 or A114 (indicated in the below table).

Acid	Procedure	Ester
3-Methoxy-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A9)	A113	B9
3-Propoxy-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A10)	A113	B10
3-Ethoxy-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A11)	A113	B11
3-Isopropoxy-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A12)	A113	B12
3-Pentoxy-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A13)	A113	B13
3-(2-Methoxy-ethoxy)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A14)	A113	B14
3-(3-Hydroxy-propoxy)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A15)	A113	B15

Acid 16

3-(2-Hydroxy-ethoxy)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A16)

Acid 16 was prepared in accordance with an analogous procedure to that described for Ester 15 from 3-(2-benzyloxy-ethoxy)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (D40).

Acids A17-A22 and A24-A27 were prepared from the corresponding ester indicated in the below table using a procedure analogous to that described in either A113 or A114 (indicated in the below table).

Acid	Procedure	Ester
3-(3-Methoxy-propoxy)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A17)	A113	B17
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-ethoxy- benzoic acid (A18)	A113	B18
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-isopropoxy-benzoic acid (A19)	A113	B19
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-methoxy-benzoic acid (A20)	A113	B20
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-propoxy-benzoic acid (A21)	A113	B21
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-pentoxy-benzoic acid (A22)	A113	B22
3,5-Bis-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A24)	A113	B24
4-Chloro-3,5-bis-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A25)	A113	B25
4-Methoxy-3,5-bis-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A26)	A113	B26
3-Nitro-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A27)	A113	B27

Acid 27 (Alternative Procedure)

3-Nitro-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A27)

A flask was charged under nitrogen with 3-bromo-5-nitro-benzoic acid (D5) (12.3 g, 50 mmol, 1 equiv), Cs_2CO_3 (24.4 g, 75 mmol, 1.5 equiv), tris(dibenzylideneacetone)dipalladium(0) (229 mg, 0.25 mmol, 0.005 equiv), Xantphos (433 mg, 0.75 mmol, 0.015 equiv) and dioxan (120 ml). 2-Pyrrolidin-2-one (5.7 ml, 75 mmol, 1.5 equiv) was then added *via syringe* and the resulting mixture was stirred at reflux for 60 h then cooled to room temperature and concentrated *in vacuo*. The residue was diluted with H_2O and 1N aqueous NaOH solution and extracted twice with Et_2O. The aqueous phase was then acidified to pH 1 and extracted three times with AcOEt. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give 3-nitro-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A27) (9.3 g, 75%) as a pale brown solid.

Acids A28-A74 were prepared from the corresponding ester indicated in the below table using a procedure analogous to that described in either A113 or A114 (indicated in the below table).

Acid	Procedure	Ester
3-(2-Oxo-pyrrolidin-1-yl)-5-piperidin-1-yl-benzoic acid (A28)	A113	B28
3-Morpholin-4-yl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A29)	A113	B29
3-(2-Oxo-pyrrolidin-1-yl)-5-phenylamino-benzoic acid (A30)	A113	B30
3-Ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A31)	A114	B31
3-Methylamino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A32)	A114	B32
3-Diethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A33)	A113	B33
3-Dimethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A34)	A113	B34
3-(2-Oxo-pyrrolidin-1-yl)-5-propylamino-benzoic acid (A35)	A113	B35

3-Isobutylamino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A36)	A113	B36
3-Benzylamino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A37)	A113	B37
3-(3-Methyl-butylamino)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A38)	A113	B38
3- Pentylamino-5- (2-oxo-pyrrolidin-1-yl) - benzoic acid (A39)	A113	B39
3- Butylamino-5- (2-oxo-pyrrolidin-1-yl) - benzoic acid (A40)	A113	B40
3-(2,2-Dimethyl-propylamino)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A41)	A113	B41
3-(Cyclopropylmethyl-amino)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A42)	A113	B42
3-(1-Ethyl-propylamino)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A43)	A113	B43
3-Isopropylamino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A44)	A113	B44
3-Cyclopentylamino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A45)	A113	B45
3-Cyclohexylamino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A46)	A113	B46
3-(Acetyl-methyl-amino)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A47)	A113	B47
3-(Acetyl-propyl-amino)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A48)	A114	B48
3-(Acetyl-isopropyl-amino)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A49)	A114	B49
3-Acetylamino-5-(2-oxo-pyrrolidin- 1-yl)-benzoic acid (A50)	A113	B50
3-(Methanesulfonyl-methyl-amino)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A51)	A113	B51
3-(Methanesulfonyl-propyl-amino)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A52)	A114	B52
3-Methanesulfonylamino-5-(2-oxo-pyrrolidin-1-yl)- benzoic acid (A53)	A113	B53
3-(2-Oxo-piperidin-1-yl)-5-pyrrolidin-1-yl-benzoic acid (A54)	A114	B54
3-(2-Oxo-piperidin-1-yl)-5-piperidin-1-yl-benzoic acid (A55)	A114	B55
3-Morpholin-4-yl-5-(2-oxo-piperidin-1-yl)-benzoic acid (A56)	A114	B56
3-Methylamino-5-(2-oxo-piperidin-1-yl)-benzoic acid (A57)	A114	B57
3-Propylamino-5-(2-oxo-piperidin-1-yl)-benzoic acid (A58)	A113	B58
3-Ethylamino-5-(2-oxo-piperidin-1-yl)-benzoic acid (A59)	A114	B59
3-Diethylamino-5-(2-oxo-piperidin-1-yl)-benzoic acid (A60)	A113	B60
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-morpholin-4-yl-benzoic acid (A61)	A114	B61
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-methylamino-benzoic acid (A62)	A114	B62
3-Diethylamino-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid (A63)	A113	B63
3-Benzylamino-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid (A64)	A113	B64
3-Butylamino-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid (A65)	A113	B65
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-(3-methyl-butylamino)-benzoic acid (A66)	A113	B66
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-phenethylamino-benzoic acid . (A67)	A113	B67
3-Pentylamino-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid (A68)	A113	B68
3-Propylamino-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid (A69)	A113	B69

3-Ethylamino-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid (A70)	A113	B70
3-(Cyclopropylmethyl-amino)-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid (A71)	A113	B71
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-isopropylamino-benzoic acid (A72)	A113	B72
3-(1,1-Dioxo-1λ^6-[1,2]thiazinan-2-yl)-5-ethylamino-benzoic acid (A73)	A114	B73
3-tert-Butoxy-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A74)	A113	B74

Acids A75-A85 were prepared from the corresponding ester indicated in the below table using a procedure analogous to that described in either A113 or A114 (indicated in the below table).

Acid	Procedure	Ester
3-Methoxy-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A75)	A114	B74
3-Hydroxymethyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A76)	A113	B76
5-(2-Oxo-pyrrolidin-1-yl)-*N*-propyl-isophthalamic acid (A77)	A113	B77
N,N-Dimethyl-5-(2-oxo-pyrrolidin-1-yl)-isophthalamic acid (A78)	A113	B78
N-Methyl-5-(2-oxo-pyrrolidin-1-yl)-isophthalamic acid (A79)	A113	B79
5-(2-Oxo-pyrrolidin-1-yl)-*N,N*-dipropyl-isophthalamic acid (A80)	A113	B80
5-(2-Oxo-piperidin-1-yl)-*N,N*-dipropyl-isophthalamic acid (A81)	A113	B81
3-Nitro-5-(2-oxo-piperidin-1-yl)-benzoic acid (A82)	A113	B82
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-fluoromethyl-benzoic acid (A83)	A113	B83
3-Dimethylaminomethyl-5-(dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid (A84)	A113	B84
3-Azidomethyl-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid (A85)	A113	B85

Acid 86

3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-methoxymethyl-benzoic acid (A86)

A suspension of 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-methanesulfonyloxymethyl-benzoic acid methyl ester (D85) (200 mg, 0.55 mmol, 1 equiv) in MeOH (100 ml) was treated with 2N aqueous NaOH solution (10 ml). The resulting mixture was stirred for 4 h at room temperature and then concentrated *in vacuo*. The residue was dissolved in AcOEt (100 ml) and the resulting solution was washed with 2N aqueous HCl solution (50 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with Et_2O to give 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-methoxymethyl-benzoic acid (A86) (140 mg, 89%) as a white solid.

Acid 87

3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-ethoxymethyl-benzoic acid (A87)

A suspension of 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-methanesulfonyloxymethyl-benzoic acid methyl ester (D85) (200 mg, 0.55 mmol, 1 equiv) in EtOH (100 ml) was treated with 2N aqueous NaOH solution (10 ml). The resulting mixture was stirred for 4 h at room temperature and then concentrated *in vacuo*. The residue was dissolved in AcOEt (100 ml) and the resulting solution was washed with 2N aqueous HCl solution (50 ml), dried over $MgSO_4$ and

concentrated *in vacuo*. The residue was triturated with Et_2O to give 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-ethoxymethyl-benzoic acid (A87) (100 mg, 61%) as a white solid.

Acids A88-95 and A100-A102 were prepared from the corresponding ester indicated in the below table using a procedure analogous to that described in either A113 or A114 (indicated in the below table).

Acid	Procedure	Ester
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-vinyl-benzoic acid (A88)	A113	B88
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-(Z/E)-propenyl-benzoic acid (A89)	A113	B89
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-(Z/E)-butenyl-benzoic acid (A90)	A113	B90
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-(2-methyl-propenyl)-benzoic acid (A91)	A113	B91
5-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-isophthalamic acid (A92)	A113	B92
3-Cyano-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid (A93)	A113	B93
5-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-*N,N*-dipropyl-isophthalamic acid (A94)	A113	B94
5-(1,1-Dioxo-1λ^6-[1,2]thiazinan-2-yl)-*N,N*-dipropyl-isophthalamic acid (A95)	A113	B95
2-Fluoro-3-(2-oxo-pyrrolidin-1-yl)-5-trifluoromethyl-benzoic acid (A100)	A113	B100
3-(2-Oxo-pyrrolidin-1-yl)- (2-methyl-propenyl)-5-benzoic acid (A101)	A113	B101
3-(2-Oxo-pyrrolidin-1-yl)-5-((E)-styryl)-benzoic acid (A102)	A113	B102

The following compounds were prepared from the corresponding alkene in an analogous manner to the process described for 3-(2-oxo-piperidin-1-yl)-5-propyl-benzoic acid *tert*-butyl ester (B116):

Acid	Alkene	$[M+H]^+$	RT (min)
3-(1,1-Dioxo-1λ^6-[1,2]thiazinan-2-yl)-5-phenethyl-benzoic acid methyl ester (A103)	A102	310.0	3.12
3-Isobutyl-5-(2-Oxo-pyrrolidin-1-yl)-benzoic acid (A105)	A101	262.1	2.98

Acids A104, A106-A109 and A111-A112 were prepared from the corresponding ester indicated in the below table using a procedure analogous to that described in either A113 or A114 (indicated in the below table).

Acid	Procedure	Ester
3-Isopropyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A104)	A113	B104
3-(2-Oxo-pyrrolidin-1-yl)-5-propyl-benzoic acid (A106)	A113	B106
3-Cyclopentyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A107)	A113	B107

3-Cyclohexyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A108)	A113	B108
3-Ethynyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A109)	A114	B109
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-ethynyl-benzoic acid (A111)	A114	B111
3-(1,1-Dioxo-1λ^6-[1,2]thiazinan-2-yl)-5-propyl-benzoic acid (A112)	A114	B112

Acid 113

3-(2-Oxo-pyrrolidin-1-yl)-5-pyrrolidin-1-yl-benzoic acid (A113)

To a solution 3-(2-oxo-pyrrolidin-1-yl)-5-pyrrolidin-1-yl-benzoic acid methyl ester (B113) (85 mg, 0.29 mmol, 1 equiv) in THF (5 ml) was added 1N aqueous NaOH solution (0.60 ml, 0.6 mmol, 2 equiv). The resulting mixture was stirred for 14 h then concentrated *in vacuo*. The residue was diluted with H_2O and extracted with Et_2O. The aqueous layer was acidified using 2N aqueous HCl solution and the white precipitate formed was extracted twice with AcOEt. The combined organic solutions were dried over $MgSO_4$ and concentrated *in vacuo* to give 3-(2-oxo-pyrrolidin-1-yl)-5-pyrrolidin-1-yl-benzoic acid (A113) (77 mg, 95%) as a white solid. $[M+H]^+$ = 275.0, RT = 2.72 min

Acid 114

3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-pyrrolidin-1-yl-benzoic acid (A114)

A solution of 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-pyrrolidin-1-yl-benzoic acid *tert*-butyl ester (B114) (106 mg, 0.29 mmol, 1 equiv) in DCM/TFA (1/1, 4 ml) was stirred at room temperature for 2 h then concentrated *in vacuo*. Traces of solvent were removed by azeotroping with toluene. The residue was triturated with Et_2O to give 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-pyrrolidin-1-yl-benzoic acid (A114) (86 mg, 96%) as a pale brown solid. $[M+H]^+$ = 311.1, RT = 2.75 min

Acid 115

3-(4-Methyl-piperazin-1-yl)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A115)

To a solution 3-(4-methyl-piperazin-1-yl)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B115) (296 mg, 0.93 mmol, 1 equiv) in THF (10 ml) was added 1N aqueous NaOH solution (1.8 ml, 1.8 mmol, 2 equiv). The resulting mixture was stirred for 14 h then concentrated *in vacuo*. The residual solid was extracted thoroughly with MeOH and the extracts were concentrated *in vacuo* to give 3-(4-methyl-piperazin-1-yl)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A115) (390 mg, 136%) as an off white solid. $[M+H]^+$ = 304.0, RT = 1.64 min

Acid 116

3-(2-Oxo-piperidin-1-yl)-5-propyl-benzoic acid (A116):

Acid 116 was prepared from Ester 116 in an analogous manner to the process described for Acid 114.

A117-A136, A136-A154 and A156-A176 were prepared from esters B117-B136, B136-B154 and B156-B176, respectively using a procedure analogous to that described in either A113 or A114 (indicated in the below table).

Acid	Procedure	[M+H]+	RT (min)

128

3-(1,1-Dioxido-6,7-dihydro-1,2-thiazepin-2(3*H*)-yl)-5-propylbenzoic acid (A117)	A113	308.0 ([M-H]⁻)	2.66
5-(Ethylamino)-2-fluoro-3-(2-oxo-1-pyrrolidinyl) benzoic acid (A118)	A113	267.2	1.62
3-(1,1-Dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-(ethylamino)-2-fluorobenzoic acid (A119)	A113	317.2	2.23
2-Fluoro-3-(2-oxo-1-pyrrolidinyl)-5-propylbenzoic acid (A120)	A113	266.2	2.71
3-(2-Oxo-5-phenyl-1-piperidinyl)-5-propylbenzoic acid (A121)	A114	338.2	3.37
3-(1,1-Dioxido-2-isothiazolidinyl)-5-(ethylamino)-2-fluorobenzoic acid (A122)	A113	303.1	1.98
3-(1,1-Dioxido-4-phenyltetrahydro-2*H*-1,2-thiazin-2-yl)-5-nitrobenzoic acid (A123)	A113	394.1	3.47
3-Amino-5-(1,1-dioxido-4-phenyltetrahydro-2*H*-1,2-thiazin-2-yl)benzoic acid (A124)	A113	347.2	2.83
3-(1,1-Dioxido-4-phenyltetrahydro-2*H*-1,2-thiazin-2-yl)-5-(ethylamino)benzoic acid (A125)	A113	375.2	3.17
3-Cyclopentyl-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)benzoic acid (A126)	A113	324.0	0.88
3-(1,1-Dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-[(1-methylethyl)amino]benzoic acid (A127)	A113	313.2	2.38
3-[Ethyl(methyl)amino]-5-(2-oxo-1-pyrrolidinyl)benzoic acid (A128)	A114	263.3	2.15
3-(Ethylamino)-4-methyl-5-(2-oxo-1-pyrrolidinyl)benzoic acid (A129)	A113	263.1	2.30
3-(1,1-Dioxido-2-isothiazolidinyl)-5-(ethylamino)-4-methylbenzoic acid (A130)	A113	299.0	2.44
3-(1,1-Dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-(ethylamino)-4-methylbenzoic acid (A131)	A113	313.1	2.59
3-(1,1-Dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-(ethylamino)-4-(methyloxy)benzoic acid (A132)	A113	329.1	2.57
3-(Ethylamino)-4-(methyloxy)-5-(2-oxo-1-pyrrolidinyl)benzoic acid (A133)	A113	279.1	2.34
3-(1,1-Dioxido-2-isothiazolidinyl)-5-(ethylamino)-4-(methyloxy)benzoic acid (A134)	A113	315.1	2.45
3-(Diethylamino)-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-4-methylbenzoic acid (A135)	A113	341.1	2.05
3-(1,1-Dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-4-(methyloxy)-5-[(1*E/Z*)-1-propen-1-yl]benzoic acid (A136)	A113	326.0	2.87
3-(1,1-Dioxido-2-isothiazolidinyl)-5-(2-oxo-1-	A113	325.3	2.10

pyrrolidinyl)benzoic acid (A138)			
3-(1,1-Dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-(ethylamino)-2-(methyloxy)benzoic acid (A139)	A113	329.2	2.02
1-Ethyl-4-(2-oxo-1-pyrrolidinyl)-1*H*-indole-6-carboxylic acid (A140)	A113	273.0	2.53
3-Ethyl-7-(2-oxo-1-pyrrolidinyl)-1*H*-indole-5-carboxylic acid (A141)	A113	273.1	2.68
3-Ethyl-1-methyl-7-(2-oxo-1-pyrrolidinyl)-1*H*-indole-5-carboxylic acid (A142)	A113	287.4	2.43
4-(1,1-Dioxido-2-isothiazolidinyl)-1-ethyl-1*H*-indole-6-carboxylic acid (A143)	A113	309.3	2.40
7-(1,1-Dioxido-2-isothiazolidinyl)-3-ethyl-1*H*-indole-5-carboxylic acid (A144)	A113	309.0	2.79
4-(1,1-Dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-1-ethyl-2,3-dihydro-1*H*-indole-6-carboxylic acid (A145)	A113	325.3	2.69
7-(1,1-Dioxido-2-isothiazolidinyl)-3-ethyl-1-methyl-1*H*-indole-5-carboxylic acid (A146)	A113		
4-(1,1-Dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-1-ethyl-1*H*-indole-6-carboxylic acid (A147)	A113		
7-(1,1-Dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-3-ethyl-1*H*-indole-5-carboxylic acid (A148)	A113	340.4	2.68
1-Ethyl-4-(2-oxo-1-pyrrolidinyl)-1*H*-benzimidazole-6-carboxylic acid (A149)	A113	274.4	1.55
4-(1,1-Dioxido-2-isothiazolidinyl)-1-ethyl-1*H*-benzimidazole-6-carboxylic acid (A150)	A113	310.2	1.98
4-(1,1-Dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-1-ethyl-1*H*-benzimidazole-6-carboxylic acid (A151)	A113	340.4	2.68
1-Ethyl-4-(2-oxo-1-pyrrolidinyl)-1*H*-indazole-6-carboxylic acid (A152)	A113	274.2	2.10
4-(1,1-Dioxido-2-isothiazolidinyl)-1-ethyl-1*H*-indazole-6-carboxylic acid (A153)	A113	310.3	2.15
4-(2-Oxo-1-pyrrolidinyl)-1*H*-indole-6-carboxylic acid (A154)	A113		
1-Methyl-4-(2-oxo-1-pyrrolidinyl)-1*H*-indole-6-carboxylic acid (A156)	A113	259.4	2.20
1-Butyl-4-(2-oxo-1-pyrrolidinyl)-1*H*-indole-6-carboxylic acid (A157)	A113	301.0	2.88
4-(2-Oxo-1-pyrrolidinyl)-1-pentyl-1*H*-indole-6-carboxylic acid (A158)	A113	315.1	3.06
3-Methyl-7-(2-oxo-1-pyrrolidinyl)-1-benzofuran-5-carboxylic acid (A159)	A113	260.0	2.59
3-Methyl-7-(2-oxo-1-pyrrolidinyl)-1*H*-indole-5-	A113	259.1	2.48

carboxylic acid (A160)			
3-(1-Methylethyl)-7-(2-oxo-1-pyrrolidinyl)-1*H*-indole-5-carboxylic acid (A161)	A113	287.1	2.82
1-Methyl-3-(1-methylethyl)-7-(2-oxo-1-pyrrolidinyl)-1*H*-indole-5-carboxylic acid (A162)	A113	301.2	2.84
3-Ethyl-7-(2-oxo-1-pyrrolidinyl)-1-benzofuran-5-carboxylic acid (A163)	A113	274.1	2.81
4-Methyl-8-(2-oxo-1-pyrrolidinyl)-3,4-dihydro-2*H*-chromene-6-carboxylic acid (A164)	A113		
3-Ethyl-7-(2-oxo-1-piperidinyl)-1*H*-indole-5-carboxylic acid (A165)	A113	287.4	2.56
3-Ethyl-7-(2-oxo-4-phenyl-1-pyrrolidinyl)-1*H*-indole-5-carboxylic acid (A166)	A113	349.2	3.21
1-Ethyl-4-(2-oxo-1-pyrrolidinyl)-1*H*-1,2,3-benzotriazole-6-carboxylic acid (A167)	A113	275.2	2.38
3-(1,1-Dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-[(1-methylethyl)oxy]benzoic acid (A168)	A113	314.15	0.77
3-Cyclopentyl-5-(1,1-dioxido-2-isothiazolidinyl)benzoic acid (A169)	A113	310.0	0.83
3-(1,1-Dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-(ethyloxy)benzoic acid (A170)	A113	300.12	0.73
4-Ethyl-8-(2-oxo-1-pyrrolidinyl)-1,2,3,4-tetrahydro-6-quinoxalinecarboxylic acid (A171)	A113	290.5	2.00
8-(1,1-Dioxido-2-isothiazolidinyl)-4-ethyl-1,2,3,4-tetrahydro-6-quinoxalinecarboxylic acid (A172)	A113	326.2	2.00
3-(1,1-Dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluoro-5-propylbenzoic acid (A173)	A113	316.1	2.49
3-(1,1-Dioxido-2-isothiazolidinyl)-2-fluoro-5-propylbenzoic acid (A174)	A113	302.1	2.48
3-(1,1-Dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluoro-5-[(1-methylethyl)amino]benzoic acid (A175)	A113	316.2	2.30
5-Cyclopentyl-3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluorobenzoic acid (A176)	A113	342.2	2.89

Acid 137

3-(1,1-Dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-4-(methyloxy)-5-propylbenzoic acid (A137)

3-(1,1-Dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-4-(methyloxy)-5-propylbenzoic acid (A137) was prepared from 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-4-(methyloxy)-5-[(1*E*)-1-propen-1-yl]benzoic acid (A136) in an analogous manner to the process described for 3-(2-oxo-piperidin-1-yl)-5-propyl-benzoic acid *tert*-butyl ester (B116).

Acid 155

4-(1,1-Dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-1*H*-indole-6-carboxylic acid (A155)

To a solution of methyl 4-amino-1*H*-indole-6-carboxylate (D201) (1.0 g, 5.3 mmol, 1 equiv) in CH_2Cl_2 (50 ml) were added pyridine (0.55 g, 6.5 mmol, 1.2 equiv), 4-chloro-1-butanesulfonyl chloride (1.14 g, 6 mmol, 1.1 equiv) and DMAP (300 mg, 2.45 mmol, 0.5 equiv) and the resulting mixture was stirred at room temperature for 5h. NEt_3 (1 ml, 7.2 mmol, 1.3 equiv) was added and the resulting solution stirred for 2 h then diluted with AcOEt, washed with a 2N aqueous solution, a saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was dissolved in MeOH (20 ml) and treated with a 2N aqueous NaOH solution (10 ml, 20 mmol, excess). The resulting solution was stirred at room temperature for 15 h then most of the MeOH was removed *in vacuo*. The residue was partitioned between AcOEt and a 2N aqueous HCl solution. The two layers were separated and the organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (CH_2Cl_2/MeOH: 9/1) gave 4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-1*H*-indole-6-carboxylic acid (A155) (320 mg, 20%) as a pale pink solid. $[M+H]^+$ = 295.0, RT = 1.90 min.

Preparation of Amines

Amine 1 (C1)

(2R,3S)-3-Amino-1-cyclohexylamino-4-phenyl-butan-2-ol *di*-hydrogen chloride (C1)

((1S,2R)-1-Benzyl-3-cyclohexylamino-2-hydroxy-propyl)-carbamic acid *tert*-butyl ester (BOC-protected amine 1 (H1)) (9 g, 25 mmol, 1 equiv) was dissolved in MeOH (70 ml) and then a 4M solution of HCl in dioxane (60 ml, excess) was added. The resulting mixture was stirred for 3 h at room temperature and then the solvents were removed by evaporation *in vacuo*. The resulting residue was washed with AcOEt and then with Et_2O before drying *in vacuo* to give the title compound (C1) as a white solid (7.4g, 88%).

$[M+H]^+$ 335.31.

Amines C2-C20, C24-C33 and C36 were prepared from their corresponding BOC-protected amines (H2-H20, H24-H33 and H36, respectively) in an analogous manner to that described in C1.

For amines C8-C19, C25-C26 and C29-C32, the 4M HCl in dioxane was replaced with 3 equivalents of p-toluene sulphonic acid to yield the tosic acid salts.

Amine	$[M+H]^+$	RT (min)
(2R,3S)-3-Amino-1-cyclobutylamino-4-phenyl-butan-2-ol *di*-hydrochloride (C2)	235.1	0.32
(2R,3S)-3-Amino-1-isobutylamino-4-phenyl-butan-2-ol *di*-hydrochloride (C3)	237.1	0.66
(2R,3S)-3-Amino-4-phenyl-1-propylamino-butan-2-ol *di*-hydrochloride (C4)	223.1	0.43
(2R,3S)-3-Amino-4-phenyl-1-(1,1,5-trimethyl-hexylamino)-butan-2-ol *di*-hydrochloride (C5)	307.2	2.22
(S)-2-((2R,3S)-3-Amino-2-hydroxy-4-phenyl-butylamino)-*N*-cyclohexyl-propionamide *di*-hydrochloride (C6)	F899	-
(2R,3S)-3-Amino-1-[(R)-1-(3-methoxy-phenyl)-ethylamino]-4-phenyl-	-	-

butan-2-ol *di*-hydrochloride (C7)		
(2R,3S)-3-Amino-1-(1-methyl-1-phenyl-ethylamino)-4-phenyl-butan-2-ol *di*-tosylate (C8)	-	-
(2R,3S)-3-Amino-1-(3-methyl-butylamino)-4-phenyl-butan-2-ol *di*-tosylate (C9)	-	-
(2R,3S)-3-Amino-1-*tert*-butylamino-4-phenyl-butan-2-ol *di*-tosylate (C10)	-	-
(2R,3S)-3-Amino-4-phenyl-1-(3-trifluoromethoxy-benzylamino)-butan-2-ol *di*-tosylate (C11)	-	-
(2R,3S)-3-Amino-1-(2,2,3,3,3-pentafluoro-propylamino)-4-phenyl-butan-2-ol *di*-tosylate (C12)	-	-
(2R,3S)-3-Amino-1-(2,2,3,3,4,4,4-heptafluoro-butylamino)-4-phenyl-butan-2-ol *di*-tosylate (C13)	362	2.9
(2R,3S)-3-Amino-1-(3-methoxy-benzylamino)-4-phenyl-butan-2-ol *di*-tosylate (C14)	-	-
(2R,3S)-3-Amino-1-[1-(3-methoxy-phenyl)-1-methyl-ethylamino]-4-phenyl-butan-2-ol *di*-tosylate (C15)	329.1	2.05
(2R,3S)-3-Amino-4-phenyl-1-[3-(2,2,2-trifluoro-ethyl)-benzylamino]-butan-2-ol *di*-tosylate (C16)	-	-
(2R,3S)-3-Amino-1-[(S)-1-(3-methoxy-phenyl)-ethylamino]-4-phenyl-butan-2-ol *di*-tosylate (C17)	-	-
(2R,3S)-3-Amino-1-[(S)-1-(3-methoxy-phenyl)-ethylamino]-4-phenyl-butan-2-ol *di*-tosylate (C18)	-	-
(2R,3S)-3-Amino-1-(5-methyl-hexylamino)-4-phenyl-butan-2-ol *di*-tosylate (C19)	-	-
(2R,3S)-3-Amino-1-(1,5-dimethyl-hexylamino)-4-phenyl-butan-2-ol *di*-hydrochloride (C20)	293.1	2.04
(2R,3S)-3-Amino-1-ethylamino-4-phenyl-butan-2-ol *di*-hydrochloride (C24)	-	-
(2R,3S)-3-Amino-1-(bis-trifluoromethyl-benzylamino)-4-phenyl-butan-2-ol *di*-tosylate (C25)	-	-
(2R,3S)-3-Amino-1-cyclopropylamino-4-phenyl-butan-2-ol *di*-tosylate (C26)	-	-
(2R,3S)-3-Amino-1-(4-methoxy-benzylamino)-4-phenyl-butan-2-ol *di*-hydrochloride (C27)	-	-
(2R,3S)-3-Amino-1-isopropylamino-4-phenyl-butan-2-ol *di*-hydrochloride (C28)	-	-
(2R,3S)-3-Amino-1-(2-methoxy-benzylamino)-4-phenyl-butan-2-ol *di*-tosylate (C29)	301.1	1.7
(2R,3S)-3-Amino-4-phenyl-1-((S)-1-phenyl-ethylamino)-butan-2-ol *di*-tosylate (C30)	-	-
(2R,3S)-3-Amino-4-phenyl-1-((R)-1-phenyl-ethylamino)-butan-2-ol *di*-tosylate (C31)	-	-

(2R,3S)-3-Amino-1-(4-methyl-pentylamino)-4-phenyl-butan-2-ol *di*-tosylate (C32)	-	-
(R)-2-((2R,3S)-3-Amino-2-hydroxy-4-phenyl-butylamino)-3-hydroxy-hexanoic acid isobutyl-amide *di*-hydrochloride (C33)	-	-
(S)-2-((2R,3S)-3-Amino-2-hydroxy-4-phenyl-butylamino)-hexanoic acid isobutyl-amide *di*-hydrochloride (C36)	-	-

Amines C40-C114 were prepared from their corresponding BOC-protected amines H40-H114, respectively) in an analogous manner to that described in C1.

Amine	$[M+H]^+$	RT (min)
(2*R*,3*S*)-3-amino-1-({1-methyl-1-[3-(trifluoromethyl)phenyl]ethyl} amino)-4-phenyl-2-butanol *di*-tosylate (C40)	367.2	2.44
(2*R*,3*S*)-3-amino-1-({1-[3-(methyloxy)phenyl]cyclohexyl}amino)-4-phenyl-2-butanol *di*-hydrochloride (C41)		
(2*R*,3*S*)-3-amino-1-{[(1-methyl-1*H*-pyrazol-4-yl)methyl]amino}-4-phenyl-2-butanol *di*-tosylate (C42)		
(2*R*,3*S*)-3-amino-4-phenyl-1-(tetrahydro-2*H*-pyran-4-ylamino)-2-butanol *di*-tosylate (C43)		
(2*R*,3*S*)-3-amino-1-[(3,3-dimethylbutyl)amino]-4-phenyl-2-butanol *di*-tosylate (C44)	265.3	1.52
(2*R*,3*S*)-3-amino-4-phenyl-1-[(1,1,3,3-tetramethylbutyl)amino]-2-butanol *di*-tosylate (C45)	293.3	1.76
(2*R*,3*S*)-3-amino-1-[(1,3-dimethylbutyl)amino]-4-phenyl-2-butanol *di*-tosylate (C46)	265.3	1.53
(2*R*,3*S*)-3-amino-1-({[4-fluoro-3-(trifluoromethyl)phenyl]methyl} amino)-4-phenyl-2-butanol *di*-tosylate (C47)	357.3	1.79
(2*R*,3*S*)-3-amino-1-[(1,1-dimethylhexyl)amino]-4-phenyl-2-butanol *di*-tosylate (C48)	293.2	2.06
(2*R*,3*S*)-3-amino-1-({[2-methyl-5-(trifluoromethyl)phenyl]methyl} amino)-4-phenyl-2-butanol *di*-tosylate (C49)	353.1	2.09
(2*R*,3*S*)-3-amino-1-[(1*S*)-2,3-dihydro-1*H*-inden-1-ylamino]-4-phenyl-2-butanol *di*-tosylate (C50)		
(1*S*,2*R*)-1-{[(2*R*,3*S*)-3-amino-2-hydroxy-4-phenylbutyl]amino}-2,3-dihydro-1*H*-inden-2-ol *di*-tosylate (C51)	313.1	1.83
(2*R*,3*S*)-3-amino-1-{[6-(methyloxy)-2,3-dihydro-1*H*-inden-1-yl]amino}-4-phenyl-2-butanol *di*-tosylate (C52)	327.5	1.82
(1*R*,2*S*)-1-{[(2*R*,3*S*)-3-amino-2-hydroxy-4-phenylbutyl]amino}-2,3-dihydro-1*H*-inden-2-ol *di*-tosylate (C53)	313.4	1.56
(2*R*,3*S*)-3-amino-1-({1,1-dimethyl-2-[(2-methylpropyl)thio]ethyl}amino)-4-phenyl-2-butanol *di*-tosylate (C54)		
(2*R*,3*S*)-3-amino-1-{[1,1-dimethyl-2-(phenyloxy)ethyl]amino}-4-phenyl-2-butanol *di*-tosylate (C55)		
(2*R*,3*S*)-3-amino-1-({1,1-dimethyl-2-[(phenylmethyl)oxy]ethyl}amino)-	343.5	1.92

4-phenyl-2-butanol *di*-tosylate (C56)		
(2*R*,3*S*)-3-amino-1-{[3-(methyloxy)phenyl]amino}-4-phenyl-2-butanol *di*-tosylate (C57)	287.4	2.11
(2*R*,3*S*)-3-amino-4-phenyl-1-({2-[3-(trifluoromethyl)phenyl]ethyl}amino)-2-butanol *di*-tosylate (C58)	353.4	2.00
(2*R*,3*S*)-3-amino-1-[(1,1-dimethyl-2-phenylethyl)amino]-4-phenyl-2-butanol *di*-tosylate (C59)	313.5	1.98
(2*R*,3*S*)-3-amino-1-{[2-(1-naphthalenyl)ethyl]amino}-4-phenyl-2-butanol *di*-tosylate (C60)	335.4	2.04
(2*R*,3*S*)-3-amino-1-({1,1-dimethyl-2-[3-(methyloxy)phenyl]ethyl}amino)-4-phenyl-2-butanol *di*-tosylate (C61)	343.3	1.93
(2*R*,3*S*)-3-amino-4-phenyl-1-(phenylamino)-2-butanol *di*-tosylate (C62)	257.4	2.06
(2*R*,3*S*)-3-amino-1-({1-[3-(methyloxy)phenyl]cyclopropyl}amino)-4-phenyl-2-butanol *di*-tosylate (C63)	327.5	1.90
(2*R*,3*S*)-3-amino-1-[(cyclohexylmethyl)amino]-4-phenyl-2-butanol *di*-tosylate (C64)		
(2*R*,3*S*)-3-amino-4-phenyl-1-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]-2-butanol *di*-tosylate (C65)		
(2*R*,3*S*)-3-amino-4-phenyl-1-(tetrahydro-2*H*-thiopyran-4-ylamino)-2-butanol (C66)		
(2*R*,3*S*)-3-amino-1-[(1-methylpropyl)amino]-4-phenyl-2-butanol *di*-tosylate (C67)	-	
(2*R*,3*S*)-3-amino-1-{[4-(1,1-dimethylethyl)cyclohexyl]amino}-4-phenyl-2-butanol *di*-tosylate (C68)	-	
(2*R*,3*S*)-3-amino-1-[(1-ethylcyclobutyl)amino]-4-phenyl-2-butanol *di*-hydrochloride (C69)	-	
(2*R*,3*S*)-3-amino-1-({1,1-dimethyl-2-[(2-methylpropyl)oxy]ethyl}amino)-4-phenyl-2-butanol *di*-tosylate (C70)	-	
(2*R*,3*S*)-3-amino-1-({1,1-dimethyl-2-[(2-methyl-2-propen-1-yl)oxy]ethyl}amino)-4-phenyl-2-butanol *di*-tosylate (C71)		
(2*R*,3*S*)-3-amino-1-[(1*R*)-2,3-dihydro-1*H*-inden-1-ylamino]-4-phenyl-2-butanol *di*-tosylate (C72)	577.2	2.67
(2*R*,3*S*)-3-amino-1-{[1-(4-methylpentyl)cyclopropyl]amino}-4-phenyl-2-butanol *di*-hydrochloride (C73)		
(2*R*,3*S*)-3-amino-1-[(1-ethylcyclopropyl)amino]-4-phenyl-2-butanol *di*-hydrochloride (C74)		
(2*R*,3*S*)-3-amino-1-[(1-ethylcyclopropyl)amino]-4-phenyl-2-butanol *di*-hydrochloride (C75)		
(2*R*,3*S*)-3-amino-1-(butylamino)-4-phenyl-2-butanol *di*-hydrochloride (C76)		
(2*R*,3*S*)-3-amino-4-phenyl-1-[(1-propylcyclopropyl)amino]-2-butanol *di*-hydrochloride (C77)		

(2*R*,3*S*)-3-amino-1-[[1-(3-methylbutyl)cyclopropyl]amino]-4-phenyl-2-butanol *di*-hydrochloride (C78)		
(2*R*,3*S*)-3-amino-1-[[1-(2-methylpropyl)cyclopropyl]amino]-4-phenyl-2-butanol *di*-hydrochloride (C79)		
(2*R*,3*S*)-3-amino-1-({1-[(3-chlorophenyl)methyl]cyclopropyl}amino)-4-phenyl-2-butanol *di*-hydrochloride (C80)		
(2*R*,3*S*)-3-amino-1-[(1-methylcyclohexyl)amino]-4-phenyl-2-butanol *di*-hydrochloride (C81)		
(2*R*,3*S*)-3-amino-1-[(2*S*)-bicyclo[2.2.1]hept-2-ylamino]-4-phenyl-2-butanol *di*-hydrochloride (C82)		
(2*R*,3*S*)-3-amino-1-[(4,4-dimethylcyclohexyl)amino]-4-phenyl-2-butanol *di*-hydrochloride (C83)		
(2*R*,3*S*)-3-amino-4-phenyl-1-[[(1*R*)-1,2,2-trimethylpropyl]amino]-2-butanol *di*-hydrochloride (C84)		
(2*R*,3*S*)-3-amino-4-phenyl-1-[[(1*S*)-1,2,2-trimethylpropyl]amino]-2-butanol *di*-hydrochloride (C85)		
(2*R*,3*S*)-3-amino-1-[(2,2-dimethylcyclohexyl)amino]-4-phenyl-2-butanol *di*-hydrochloride (C86)		
(2*R*,3*S*)-3-amino-1-(pentylamino)-4-phenyl-2-butanol (C87)		
(2*R*,3*S*)-3-amino-1-(hexylamino)-4-phenyl-2-butanol *di*-hydrochloride (C88)		
(2*R*,3*S*)-3-amino-1-[(3,3-dimethylbutyl)amino]-4-phenyl-2-butanol *di*-hydrochloride (C89)		
(2*R*,3*S*)-3-amino-1-[(1,1-dimethylpropyl)amino]-4-phenyl-2-butanol *di*-hydrochloride (C90)		
(2*R*,3*S*)-3-amino-1-[(cyclopropylmethyl)amino]-4-phenyl-2-butanol *di*-hydrochloride (C91)		
(2*R*,3*S*)-3-amino-1-[(3,3-dimethylcyclopentyl)amino]-4-phenyl-2-butanol *di*-hydrochloride (C92)		
(2*R*,3*S*)-3-amino-1-(methylamino)-4-phenyl-2-butanol *di*-hydrochloride (C93)		
(2*R*,3*S*)-3-amino-4-phenyl-1-(tricyclo[3.3.1.1^{3,7}]dec-1-ylamino)-2-butanol *di*-hydrochloride (C94)		
(2*R*,3*S*)-3-amino-4-phenyl-1-(1,2,3,4-tetrahydro-1-naphthalenylamino)-2-butanol *di*-hydrochloride (C95)		
(2*R*,3*S*)-3-amino-1-({2-[3-(methyloxy)phenyl]ethyl}amino)-4-phenyl-2-butanol *di*-hydrochloride (C96)		
(2*R*,3*S*)-3-amino-1-({2-[4-(methyloxy)phenyl]ethyl}amino)-4-phenyl-2-butanol *di*-hydrochloride (C97)		
(2*R*,3*S*)-3-amino-1-({2-[2-(methyloxy)phenyl]ethyl}amino)-4-phenyl-2-butanol *di*-hydrochloride (C98)		
(2*R*,3*S*)-3-amino-1-[[2-(2-chlorophenyl)ethyl]amino]-4-phenyl-2-butanol *di*-hydrochloride (C99)		

(2*R*,3*S*)-3-amino-1-[[2-(3-chlorophenyl)ethyl]amino]-4-phenyl-2-butanol *di*-hydrochloride (C100)		
(2*R*,3*S*)-3-amino-1-[[2-(4-chlorophenyl)ethyl]amino]-4-phenyl-2-butanol *di*-hydrochloride (C101)		
(2*R*,3*S*)-3-amino-1-[[2-(4-methylphenyl)ethyl]amino]-4-phenyl-2-butanol *di*-hydrochloride (C102)		
(2*R*,3*S*)-3-amino-1-[[2-(2-methylphenyl)ethyl]amino]-4-phenyl-2-butanol *di*-hydrochloride (C103)		
(2*R*,3*S*)-3-amino-1-[[2-(3,4-dichlorophenyl)ethyl]amino]-4-phenyl-2-butanol *di*-hydrochloride (C104)		
(2*R*,3*S*)-3-amino-1-[[2-(2,4-dichlorophenyl)ethyl]amino]-4-phenyl-2-butanol *di*-hydrochloride (C105)		
(2*R*,3*S*)-3-amino-1-({2-[3,5-bis(methyloxy)phenyl]ethyl}amino)-4-phenyl-2-butanol *di*-hydrochloride (C106)		
(2*R*,3*S*)-3-amino-1-({2-[2,3-bis(methyloxy)phenyl]ethyl}amino)-4-phenyl-2-butanol *di*-hydrochloride (C107)		
(2*R*,3*S*)-3-amino-4-phenyl-1-[(phenylmethyl)amino]-2-butanol *di*-hydrochloride (C108)		
(2*R*,3*S*)-3-amino-4-phenyl-1-[(2-phenylethyl)amino]-2-butanol *di*-hydrochloride (C109)		
(2*R*,3*S*)-3-amino-1-[(1-ethylcyclohexyl)amino]-4-phenyl-2-butanol *di*-hydrochloride (C110)		
(2*R*,3*S*)-3-amino-1-[(1-methylcyclopentyl)amino]-4-phenyl-2-butanol *di*-hydrochloride (C111)		
(2*R*,3*S*)-3-amino-4-phenyl-1-[(1-propylcyclopentyl)amino]-2-butanol *di*-hydrochloride (C112)		
(2*R*,3*S*)-3-amino-4-phenyl-1-[(1-propylcyclohexyl)amino]-2-butanol *di*-hydrochloride (C113)		
(2*R*,3*S*)-3-amino-1-[[2-(3-chlorophenyl)-1,1-dimethylethyl]amino]-4-phenyl-2-butanol *di*-hydrochloride (C114)		

Amines C115-C147 were prepared from their corresponding BOC-protected amines H115-H147, respectively in an analogous manner to that described in C1.

Amine	$[M+H]^+$	RT (min)
(2*R*,3*S*)-3-amino-1-({[3-(methyloxy)phenyl]methyl}amino)-4-(3-pyridinyl)-2-butanol *tri*-hydrochloride (C115)		
(2*R*,3*S*)-3-amino-1-({[3-(methyloxy)phenyl]methyl}amino)-4-(1,3-thiazol-2-yl)-2-butanol *di*-hydrochloride (C116)		
(2*R*,3*S*)-3-amino-1-(cyclohexylamino)-4-(1,3-thiazol-2-yl)-2-butanol *di*-hydrochloride (C117)		
(2*R*,3*S*)-3-amino-1-[(1,5-dimethylhexyl)amino]-4-(1,3-thiazol-2-yl)-2-butanol *di*-hydrochloride (C118)		
(2*R*,3*S*)-3-amino-4-(2-furanyl)-1-({[3-		

137
137

(methyloxy)phenyl]methyl}amino)-2-butanol *di*-hydrochloride (C119)		
(2*R*,3*S*)-3-amino-1-(cyclohexylamino)-4-(2-furanyl)-2-butanol *di*-hydrochloride (C120)		
(2*R*,3*S*)-3-amino-1-[(1,5-dimethylhexyl)amino]-4-(2-furanyl)-2-butanol *di*-hydrochloride (C121)		
(2*R*,3*S*)-3-amino-4-(2-furanyl)-1-[(1,1,5-trimethylhexyl)amino]-2-butanol *di*-hydrochloride (C122)		
(2*R*,3*S*)-3-amino-1-({[3-(methyloxy)phenyl]methyl}amino)-4-(2-pyridinyl)-2-butanol *tri*-hydrochloride (C123)		
(2*R*,3*S*)-3-amino-4-(4-chlorophenyl)-1-(cyclohexylamino)-2-butanol *di*-hydrochloride (C124)		
(2*R*,3*S*)-3-amino-4-(4-chlorophenyl)-1-({[3-(methyloxy)phenyl]methyl}amino)-2-butanol *di*-hydrochloride (C125)		
(2*R*,3*S*)-3-amino-4-(3,5-difluorophenyl)-1-({[3-(trifluoromethyl) phenyl]methyl} amino)-2-butanol *di*-hydrochloride (C126)		
(2*R*,3*S*)-3-amino-4-(3,5-difluorophenyl)-1-({[3-(methyloxy)phenyl]methyl}amino)-2-butanol *di*-hydrochloride (C127)		
(2*R*,3*S*)-3-amino-4-(3,5-difluorophenyl)-1-[(1,5-dimethylhexyl)amino]-2-butanol *di*-hydrochloride (C128)		
(2*R*,3*S*)-3-amino-1-(cyclohexylamino)-4-(3,5-difluorophenyl)-2-butanol *di*-hydrochloride (C129)		
(2*R*,3*S*)-3-amino-4-(3,5-difluorophenyl)-1-[(1,1,5-trimethylhexyl)amino]-2-butanol *di*-hydrochloride (C130)		
(2*R*,3*S*)-3-amino-4-(3,4-difluorophenyl)-1-({[3-(methyloxy)phenyl]methyl}amino)-2-butanol *di*-hydrochloride (C131)		
(2*R*,3*S*)-3-amino-1-(cyclohexylamino)-4-(3,4-difluorophenyl)-2-butanol *di*-hydrochloride (C132)		
(2*R*,3*S*)-3-amino-4-(3,4-difluorophenyl)-1-[(1,1,5-trimethylhexyl)amino]-2-butanol *di*-hydrochloride (C133)		
(2*R*,3*S*)-3-amino-4-(3-chlorophenyl)-1-({[3-(methyloxy)phenyl]methyl}amino)-2-butanol *di*-hydrochloride (C134)		
(2*R*,3*S*)-3-amino-4-(3-chlorophenyl)-1-(cyclohexylamino)-2-butanol *di*-hydrochloride (C135)		
(2*R*,3*S*)-3-amino-4-(2-chlorophenyl)-1-({[3-(methyloxy)phenyl]methyl}amino)-2-butanol *di*-hydrochloride (C136)		
(2*R*,3*S*)-3-amino-4-(2-chlorophenyl)-1-(cyclohexylamino)-2-butanol		

di-hydrochloride (C137)		
(2*R*,3*S*)-3-amino-4-(2-chlorophenyl)-1-[(1,5-dimethylhexyl)amino]-2-butanol *di*-hydrochloride (C138)		
(2*R*,3*S*)-3-amino-4-(3-chlorophenyl)-1-[(1,5-dimethylhexyl)amino]-2-butanol *di*-hydrochloride (C139)		
(2*R*,3*S*)-3-amino-4-(3-fluorophenyl)-1-({[3-(methyloxy)phenyl]methyl}amino)-2-butanol *di*-hydrochloride (C140)		
(2*R*,3*S*)-3-amino-1-[(1,5-dimethylhexyl)amino]-4-(3-fluorophenyl)-2-butanol *di*-hydrochloride (C141)		
(2*R*,3*S*)-3-amino-1-({[3-(methyloxy)phenyl]methyl}amino)-4-(2-thienyl)-2-butanol *di*-hydrochloride (C142)		
(2*R*,3*S*)-3-amino-1-[(1,5-dimethylhexyl)amino]-4-(2-thienyl)-2-butanol *di*-hydrochloride (C143)		
(2*R*,3*S*)-3-amino-1-({[3-(methyloxy)phenyl]methyl}amino)-4-(1*H*-pyrazol-1-yl)-2-butanol *di*-hydrochloride (C144)		
(2*R*,3*S*)-3-amino-1-[(1,5-dimethylhexyl)amino]-4-(1*H*-pyrazol-1-yl)-2-butanol *di*-hydrochloride (C145)		
(2*R*,3*S*)-3-amino-1-({[3-(methyloxy)phenyl]methyl}amino)-4-(3-thienyl)-2-butanol *di*-hydrochloride (C146)		
(2*R*,3*S*)-3-amino-1-[(1,5-dimethylhexyl)amino]-4-(3-thienyl)-2-butanol *di*-hydrochloride (C147)		

Amines C148-C156 were prepared from their corresponding BOC-protected amines H148-H156, respectively) in an analogous manner to that described in C1

Amine	$[M+H]^+$	RT (min)
(2*R*,3*S*)-3-amino-4-phenyl-1-[(1-propylcyclobutyl)amino]-2-butanol *di*-hydrochloride (C148)		
(2*R*,3*S*)-3-amino-1-{[1-(1-methylethyl)cyclobutyl]amino}-4-phenyl-2-butanol *di*-hydrochloride (C149)		
(2*R*,3*S*)-3-amino-1-({1-[(3-chlorophenyl)methyl]cyclobutyl}amino)-4-phenyl-2-butanol *di*-hydrochloride (C150)		
(2*R*,3*S*)-3-amino-4-phenyl-1-(tricyclo[3.3.1.1^{3,7}]dec-2-ylamino)-2-butanol *di*-hydrochloride (C151)		
(2*R*,3*S*)-3-amino-1-[(1*r*,4*R*)-bicyclo[2.2.1]hept-1-ylamino]-4-phenyl-2-butanol *di*-hydrochloride (C152)		
(2*R*,3*S*)-3-amino-1-(bicyclo[2.2.2]oct-1-ylamino)-4-phenyl-2-butanol *di*-hydrochloride (C153)		
(2*R*,3*S*)-3-amino-1-[[(1-ethyl-1*H*-pyrazol-4-yl)methyl]amino]-4-phenyl-2-butanol *di*-hydrochloride (C154)	289.5	1.13
(2*R*,3*S*)-3-amino-1-[(4,4-difluorocyclohexyl)amino]-4-phenyl-2-butanol *di*-hydrochloride (C155)	299.3	1.65

(2*R*,3*S*)-3-amino-1-({[3,4-bis(methyloxy)phenyl]methyl}amino)-4-phenyl-2-butanol *di*-tosylate (C156)		

Amine 157

(2*R*,3*S*)-3-Amino-1-[[(3-ethyl-5-isoxazolyl)methyl]amino]-4-phenyl-2-butanol *di*-hydrochloride (C157)

(2*R*,3*S*)-3-Amino-1-[[(3-ethyl-5-isoxazolyl)methyl]amino]-4-phenyl-2-butanol *di*-hydrochloride (C157) was obtained from BOC-protected amine H157 in an analogous manner to the process described for amine C1.

Examples

Example 1

N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-5-(2-oxopyrrolidin-1-yl)-N',N'-dipropylisophthalamide (E1)

To a solution of 5-(2-oxo-pyrrolidin-1-yl)-*N*,*N*-dipropyl-isophthalamic acid (A80) (66 mg, 0.2 mmol, 1 equiv) in DMF (5 ml) at room temperature was added EDAC.HCl (46 mg, 0.24 mmol, 1.2 equiv), HOBT (37 mg, 0.24 mmol, 1.2 equiv), 4-ethylmorpholine (153 µ, 1.2 mmol, 6 equiv) and (S)-2-((2R,3S)-3-amino-2-hydroxy-4-phenyl-butylamino)-*N*-cyclohexyl-propionamide *di*-hydrochloride (C8) (82 mg, 0.2 mmol, 1 equiv). The resulting mixture was stirred for 3 h then concentrated *in vacuo*. The residue was diluted in CH_2Cl_2 and the organic phases washed with a saturated $NaHCO_3$ aqueous solution, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by preparative LC/MS gave N-[(1S,2R)-1-benzyl-3-((S)-1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-5-(2-oxopyrrolidin-1-yl)-N',N'-dipropylisophthalamide (E1) (78 mg, 60%) as a white foam.

$[M+H]^+$ = 648.3

RT = 2.70.

Examples 2-62

Examples 2-62 were prepared in an analogous manner to Example 1 from the appropriate acid and amines indicated in the below table:

Example	Acid	Amine	$[M+H]^+$	RT (min)
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-5-(2-oxopyrrolidin-1-yl)-N',N'-dipropylisophthalamide (E2)	A80	C8	648.3	2.7
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-5-(2-oxopyrrolidin-1-yl)-isophthalamic acid methyl ester (E3)	A75	C8	579.2	2.47

N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-5-(2-oxopyrrolidin-1-yl)-isophthalamic acid tert-butyl ester (E4)	A74	C6	621.2	2.74
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-5-(2-oxopyrrolidin-1-yl)-N'-propylisophthalamide (E5)	A77	C6	606.2	2.45
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-N',N'-dimethyl-5-(2-oxopyrrolidin-1-yl)-isophthalamide (E6)	A78	C6	592.2	2.31
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-N'-methyl-5-(2-oxopyrrolidin-1-yl)-isophthalamide (E7)	A79	C6	578.2	2.29
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-hydroxymethyl-5-(2-oxopyrrolidin-1-yl)benzamide (E8)	A76	C6	551.2	2.28
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-methoxybenzylamino)-propyl]-3-(2-oxopyrrolidin-1-yl)-5-((E)-styryl)benzamide (E9)	A102	C14	590.2	2.83
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-methoxybenzylamino)-propyl]-3-(2-oxopyrrolidin-1-yl)-5-phenethylbenzamide (E10)	A103	C14	592.2	2.80
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-methoxybenzylamino)-propyl]-3-cyclopentyl-5-(2-oxopyrrolidin-1-yl)benzamide (E11)	A107	C14	556.3	2.75
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-cyclopentyl-5-(2-oxopyrrolidin-1-yl)benzamide (E12)	A107	C6	589.3	2.78
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-cyclohexyl-5-(2-oxopyrrolidin-1-yl)benzamide (E13)	A108	C6	603.3	2.86
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-methoxybenzylamino)-propyl]-3-cyclohexyl-5-(2-oxopyrrolidin-1-yl)benzamide (E14)	A108	C14	570.3	2.84
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-methoxybenzylamino) propyl]-3-(2-oxopyrrolidin-1-yl)-5-propyl-benzamide (E15)	A108	C14	530.2	2.64

141

N-(1-Benzyl-3-cyclohexylamino-2-hydroxypropyl)-3-(2-oxopyrrolidin-1-yl)-5-propylbenzamide (E16)	A106	C1	492.2	2.61
N-[1-Benzyl-2-hydroxy-3-(3-methoxybenzylamino)propyl]-3-(2-methyl-propenyl)-5-(2-oxopyrrolidin-1-yl)benzamide (E17)	A101	C14	542.3	2.69
N-[1-Benzyl-2-hydroxy-3-(3-methoxybenzylamino)propyl]-3-isobutyl-5-(2-oxopyrrolidin-1-yl)benzamide (E18)	A105	C14	544.3	2.73
N-(1-Benzyl-3-cyclohexylamino-2-hydroxypropyl)-3-isopropyl-5-(2-oxopyrrolidin-1-yl)benzamide (E19)	A104	C1	492.3	2.60
N-(1-Benzyl-3-cyclohexylamino-2-hydroxypropyl)-3-isobutyl-5-(2-oxopyrrolidin-1-yl)benzamide (E20)	A105	C1	506.3	2.71
N-(1-Benzyl-3-cyclohexylamino-2-hydroxypropyl)-3-cyclopentyl-5-(2-oxopyrrolidin-1-yl)benzamide (E21)	A107	C16	518.4	2.77
N-[1-Benzyl-2-hydroxy-3-(3-trifluoromethylbenzylamino) propyl]-3-cyclopentyl-5-(2-oxopyrrolidin-1-yl)benzamide (E22)	A107	C16	594.4	2.97
N-[1-Benzyl-2-hydroxy-3-(3-trifluoromethylbenzylamino) propyl]-3-(2-oxopyrrolidin-1-yl)-5-propylbenzamide (E23)	A106	C16	568.3	2.69
N-[1-Benzyl-3-(1,5-dimethylhexylamino)-2-hydroxypropyl]-3-(2-oxopyrrolidin-1-yl)-5-propylbenzamide formate salt (E24)	A106	C20	522.4	2.87
N-[1-Benzyl-2-hydroxy-3-(3-trifluoromethylbenzylamino)propyl]-3-ethynyl-5-(2-oxopyrrolidin-1-yl)benzamide (E25)	A109	C16	550.3	2.47
N-[1-Benzyl-3-(1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-3-(2-oxopyrrolidin-1-yl)-5-propylbenzamide (E26)	A106	C6	563.4	2.70
N-[1-Benzyl-2-hydroxy-3-(3-trifluoromethylbenzylamino) propyl]-2-fluoro-3-(2-oxopyrrolidin-1-yl)-5-trifluoromethyl-benzamide formate salt (E27)	A100	C16	612.0	2.76
formic acid - 5-cyclopentyl-3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluoro-*N*-[(1*S*,2*R*)-2-hydroxy-1-	A176	C16	662.5	3.00

(phenylmethyl)-3-({[3-trifluoromethyl)phenyl]methyl}amino) propyl]benzamide (1:1) (E26)				
formic acid - 5-cyclopentyl-3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluoro-*N*-[(1*S*,2*R*)-2-hydroxy-3-({1-methyl-1-[3-(methyloxy)phenyl]ethyl}amino)-1-(phenylmethyl)propyl]benzamide (1:1) (E29)	A176	C15	652.5	2.92
formic acid - 5-cyclopentyl-3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-*N*-[(1*S*,2*R*)-3-[[(1-ethyl-1*H*-pyrazol-4-yl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-2-fluorobenzamide (1:1) (E30)	A176	C154	612.5	2.62
formic acid - 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluoro-*N*-[(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl]methyl}amino)propyl]-5-[(1-methylethyl)amino]benzamide (1:1) (E31)	A175	C16	651.5	2.78
formic acid - 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluoro-*N*-[(1*S*,2*R*)-2-hydroxy-3-({1-methyl-1-[3-(methyloxy)phenyl]ethyl}amino)-1-(phenylmethyl)propyl]-5-[(1-methylethyl)amino]benzamide (1:1) (E32)	A175	C15	641.5	2.65
formic acid - 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-*N*-[(1*S*,2*R*)-3-[[(1-ethyl-1*H*-pyrazol-4-yl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-2-fluoro-5-[(1-methylethyl)amino]benzamide (1:1) (E33)	A175	C154	601.5	2.34
formic acid - 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluoro-*N*-[(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-[(1,1,5-trimethylhexyl)amino]propyl}-5-[(1-methylethyl)amino]benzamide (1:1) (E34)	A175	C5	619.6	2.94
formic acid - 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluoro-*N*-[(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-(tetrahydro-2*H*-pyran-4-ylamino)propyl]-5-[(1-methylethyl)amino]benzamide (1:1) (E35)	A175	C43	577.5	2.27
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3,5-bis-(2-oxopyrrolidin-1-yl)benzamide (E36)	A24	C8	604.2	2.02
3-Acetylamino-N-[(1S,2R)-1-benzyl-3-((S)-1-cyclohexylcarbamoylethylamino) -2-hydroxypropyl]-5-(2-oxopyrrolidin-1-yl)benzamide (E37)	A50	C8	578.1	2.38
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-methanesulfonylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E38)	A53	C8	614.1	2.42

N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-isopropylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E39)	A44	C6	578.2	2.59
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(2-oxopyrrolidin-1-yl)-5-propylaminobenzamide (E40)	A35	C6	578.3	2.62
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoylethyl amino)-2-hydroxypropyl]-3-cyclopentylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E41)	A45	C6	604.2	2.69
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoylethyl amino)-2-hydroxypropyl]-3-diethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E42)	A33	C6	592.2	2.69
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-morpholin-4-yl-5-(2-oxopyrrolidin-1-yl)benzamide (E43)	A29	C6	606.2	2.43
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(4-methylpiperazin-1-yl)-5-(2-oxopyrrolidin-1-yl)benzamide (E44)	A115	C6	619.2	2.05
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(2-oxopyrrolidin-1-yl)-5-piperidin-1-ylbenzamide (E45)	A28	C6	604.2	2.64
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(2-oxopyrrolidin-1-yl)-5-pyrrolidin-1-ylbenzamide (E46)	A113	C6	590.2	2.65
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(2-oxopyrrolidin-1-yl)-5-phenylaminobenzamide (E47)	A30	C6	612.2	2.70
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-4-methoxy-3,5-bis-(2-oxopyrrolidin-1-yl)benzamide (E48)	A26	C6	634.2	2.36
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-4-chloro-3,5-bis-(2-oxopyrrolidin-1-yl)benzamide (E49)	A25	C6	638.1	2.41
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E50)	A31	C6	564.2	2.48

3-Benzylamino-N-[(1S,2R)-1-benzyl-3-((S)-1-cyclohexylcarbamoylethylamino) -2-hydroxypropyl]-5-(2-oxopyrrolidin-1-yl)benzamide (E51)	A37	C6	626.2	2.70
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(3-methylbutylamino)-5-(2-oxopyrrolidin-1-yl)benzamide (E52)	A38	C6	606.2	2.79
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-cyclohexylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E53)	A46	C6	618.2	2.77
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(2-oxopyrrolidin-1-yl)-5-pentylaminobenzamide (E54)	A39	C6	606.2	2.77
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(1-ethylpropylamino)-5-(2-oxopyrrolidin-1-yl)benzamide (E55)	A43	C6	606.2	2.77
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-butylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E56)	A40	C6	592.2	2.7
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(2,2-dimethylpropylamino)-5-(2-oxopyrrolidin-1-yl)benzamide (E57)	A41	C6	604.2	2.78
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(cyclopropylmethylamino)-5-(2-oxopyrrolidin-1-yl)-benzamide (E58)	A42	C6	590.2	2.60
3-(Acetylpropylamino)-N-[(1S,2R)-1-benzyl-3-((S)-1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-5-(2-oxopyrrolidin-1-yl)benzamide (E59)	A48	C6	620.2	2.47
N-[(1S,2R)-1-Benzyl-3-(1,5-dimethylhexylamino)-2-hydroxypropyl]-3-isopropylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E60)	A44	C20	537.3	2.69
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-nitro-5-(2-oxopyrrolidin-1-yl)benzamide formate salt (E61)	A27	C6	566.1	2.56
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-nitro-5-(2-oxopyrrolidin-1-yl)benzamide (E62)	A27	C6	566.1	2.56

Example 63

145

3-Amino-N-[(1S,2R)-1-benzyl-3-((S)-1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-5-(2-oxopyrrolidin-1-yl)benzamide (E63)

A mixture of *N*-[(1S,2R)-1-benzyl-3-((S)-1-cyclohexylcarbamoyl-ethylamino)-2-hydroxy-propyl]-3-nitro-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E62) (40 mg, 0.07 mmol, 1 equiv), 10% Pd on charcoal (50% wet, 10 mg, 12.5% w/w), NH_4COOH (55 mg, 0.90 mmol, 13 equiv), EtOH (5 ml) and H_2O (2.5 ml) was stirred at 50°C for 2 h, cooled to room temperature and the catalyst was filtered off through a pad of celite. Most of the EtOH was removed *in vacuo* and the residue was partitioned between AcOEt and saturated aqueous $NaHCO_3$ solution. The aqueous phase was extracted with AcOEt. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with Et_2O to give 3-amino-*N*-[(1S,2R)-1-benzyl-3-((S)-1-cyclohexylcarbamoyl-ethylamino)-2-hydroxypropyl]-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E63) (15mg, 38%) as a pale yellow solid.

$[M+H]^+$ = 536.1

RT = 2.27 min

Examples 64-65

Examples 64-65 were prepared in an analogous manner to Example 1 from the appropriate acid and amines indicated in the below table:

Example	Acid	Amine	$[M+H]^+$	RT (min)
3-(Acetylisopropylamino)-N-[(1S,2R)-1-benzyl-3-((S)-1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-5-(2-oxo-pyrrolidin-1-yl)benzamide (E64)	A49	C8	620.2	2.44
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(methanesulfonyl propylamino)-5-(2-oxopyrrolidin-1-yl)-benzamide (E65)	A52	C8	656.2	2.56

Example 66

N-((1S,2R)-3-Amino-1-benzyl-2-hydroxypropyl)-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E66)

Example 66 (E66) was prepared in an analogous manner to Example 182 from [(2R,3S)-3-({1-[3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-phenyl]-methanoyl}-amino)-2-hydroxy-4-phenyl-butyl]-carbamic acid benzyl ester (D106).

Examples 67-87

Examples 67-87 were prepared in an analogous manner to Example 1 from the appropriate acid and amines indicated in the below table:

Example	Acid	Amine	$[M+H]^+$	RT (min)

N-((1S,2R)-1-Benzyl-3-cyclopropylamino-2-hydroxypropyl)-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E67)	A31	C26	451.2	2.23
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-methoxybenzylamino)-propyl]-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide formate salt (E68)	A31	C14	531.2	2.41
N-((1S,2R)-1-Benzyl-3-cyclohexylamino-2-hydroxypropyl)-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide formate salt (E69)	A31	C24	493.2	2.39
N-((1S,2R)-1-Benzyl-3-ethylamino-2-hydroxypropyl)-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide formate salt (E70)	A31	C24	439.2	2.20
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(4-methoxybenzylamino)-propyl]-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E71)	A31	C27	531.2	2.41
N-((1S,2R)-1-Benzyl-2-hydroxy-3-isopropylaminopropyl)-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E72)	A31	C28	453.2	2.20
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethylbenzylamino)-propyl]-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E73)	A31	C16	569.2	2.54
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(2,2,3,3,3-pentafluoro-propylamino)-propyl]-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E74)	A31	C12	543.1	2.92
N-[(1S,2R)-1-Benzyl-3-(2,2,3,3,4,4,4-heptafluorobutylamino)-2-hydroxypropyl]-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E75)	A31	C13	593.1	3.13
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(R)-1-phenylethylamino)propyl]-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E76)	A31	C31	515.2	2.38
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-((S)-1-phenylethylamino)propyl]-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E77)	A31	C30	515.2	2.38
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(2-methoxybenzylamino)-propyl]-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E78)	A31	C29	531.2	2.37

N-[(1S,2R)-1-Benzyl-3-(3,5-bis-trifluoromethylbenzyl amino)-2-hydroxypropyl]-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E79)	A31	C25	637.1	2.74
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-[(R)-1-(3-methoxyphenyl)-ethylamino]-propyl]-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E80)	A31	C7	545.2	2.41
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-[(S)-1-(3-methoxyphenyl)-ethylamino]-propyl]-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E81)	A31	C17	545.2	2.43
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-3-isobutylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E82)	A36	C8	592.2	2.66
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-3-dimethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E83)	A34	C8	564.2	2.47
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(1-methyl-1-phenylethylamino)-propyl]-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E84)	A31	C8	529.3	2.44
N-((1S,2R)-1-Benzyl-3-tert-butylamino-2-hydroxypropyl)-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E85)	A31	C10	467.3	2.25
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethoxybenzylamino)-propyl]-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E86)	A31	C11	585.3	2.61
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-methylbutylamino)-propyl]-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E87)	A31	C9	481.3	2.38

Example 88

N-((1S,2R)-3-Amino-1-benzyl-2-hydroxypropyl)-3-isopropylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E88)

Example 88 was prepared in an analogous manner to Example 182 from [(2R,3S)-3-({1-[3-Isopropylamino-5-(2-oxo-pyrrolidin-1-yl)-phenyl]-methanoyl}-amino)-2-hydroxy-4-phenyl-butyl]-carbamic acid benzyl ester (D107).

$[M+H]^+$ = 425.2, RT = 2.20 min

Examples 89-102

Examples 89-102 were prepared in an analogous manner to Example 1 from the appropriate acid and amines indicated in the below table:

148

Example	Acid	Amine	$[M+H]^+$	RT (min)
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-methylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E89)	A32	C6	550.3	2.37
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(methanesulfonyl methylamino)-5-(2-oxopyrrolidin-1-yl)-benzamide (E90)	A51	C6	628.2	2.41
3-(Acetylmethylamino)-N-[(1S,2R)-1-benzyl-3-((S)-1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-5-(2-oxopyrrolidin-1-yl)-benzamide (E91)	A47	C6	592.2	2.31
N-((1S,2R)-1-Benzyl-3-cyclopentylamino-2-hydroxypropyl)-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E92)	A31	C18	479.2	2.31
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(4-methylpentylamino)-propyl]-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E93)	A31	C32	495.3	2.51
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(5-methylhexylamino)-propyl]-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E94)	A31	C19	509.3	2.62
N-[(1S,2R)-1-Benzyl-3-(1,5-dimethyl-hexylamino)-2-hydroxypropyl]-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide formate salt (E95)	A31	C20	523.3	2.68
N-((1S,2R)-1-Benzyl-3-cyclohexylamino-2-hydroxypropyl)-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E96)	A31	C7	493.2	2.38
N-(1-Benzyl-3-cyclobutylamino-2-hydroxypropyl)-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E97)	A31	C2	465.4	2.29
N-(1-Benzyl-3-cycloheptylamino-2-hydroxypropyl)-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E98)	A31	C33	507.3	2.52
N-(1-Benzyl-2-hydroxy-3-isobutylaminopropyl)-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E99)	A31	C3	424.2	2.35

N-[1-Benzyl-2-hydroxy-3-(1,1,5-trimethylhexylamino)propyl]-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E100)	A31	C5	537.3	2.80
N-(1-Benzyl-2-hydroxy-3-propylaminopropyl)-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E101)	A31	C4	453.2	2.29
N-[1-Benzyl-2-hydroxy-3-[1-(3-methoxyphenyl)-1-methylethylamino]propyl]-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide formate salt (E102)	A31	C15	559.2	2.59

Examples 103-170

Examples 103-170 were prepared by reductive amination using N-((1S,2R)-3-amino-1-benzyl-2-hydroxypropyl)-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E66) in an analogous procedure to that described for E183.

Example	$[M+H]^+$	RT (min)
N-[(1S,2R)-1-Benzyl-3-(3,4-dichloro-benzylamino)-2-hydroxy-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E103)		
N-((1S,2R)-1-Benzyl-3-benzylamino-2-hydroxy-propyl)-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E104)		
N-[(1S,2R)-1-Benzyl-3-(4-fluoro-benzylamino)-2-hydroxy-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E105)		
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(4-trifluoromethyl-benzylamino)-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E106)		
N-[(1S,2R)-1-Benzyl-3-[(furan-2-ylmethyl)-amino]-2-hydroxy-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E107)		
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-[(quinolin-4-ylmethyl)-amino]-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E108)		
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-hydroxy-benzylamino)-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E109)		
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-[(thiophen-2-ylmethyl)-amino]-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E110)		
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-[(thiophen-3-ylmethyl)-amino]-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E111)		
N-[(1S,2R)-1-Benzyl-3-(3-chloro-4-methoxy-benzylamino)-2-hydroxy-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E112)		

N-[(1S,2R)-1-Benzyl-3-(2,3-dichloro-benzylamino)-2-hydroxy-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E113)		
N-[(1S,2R)-3-(4-Acetylamino-benzylamino)-1-benzyl-2-hydroxy-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E114)		
N-[(1S,2R)-1-Benzyl-3-(4-cyano-benzylamino)-2-hydroxy-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E115)		
N-((1S,2R)-1-Benzyl-2-hydroxy-3-phenethylamino-propyl)-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E116)		
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-[(1*H*-indol-3-ylmethyl)-amino]-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E117)		
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-phenyl-butylamino)-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E118)		
N-[(1S,2R)-3-[(1*H*-Benzoimidazol-5-ylmethyl)-amino]-1-benzyl-2-hydroxy-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E119)		
N-[(1S,2R)-1-Benzyl-3-[(E)-3-(4-fluoro-phenyl)-allylamino]-2-hydroxy-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E120)		
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(4-isopropoxy-benzylamino)-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E121)		
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-((E)-3-*p*-tolyl-allylamino)-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E122)		
N-[(1S,2R)-1-Benzyl-3-[(2-ethyl-5-methyl-3*H*-imidazol-4-ylmethyl)-amino]-2-hydroxy-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E123)		
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(2-methyl-3-phenyl-propylamino)-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E124)		
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-methoxy-4-nitro-benzylamino)-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E125)		
N-[(1S,2R)-1-Benzyl-3-(5-cyano-2-methoxy-benzylamino)-2-hydroxy-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E126)		
N-[(1S,2R)-1-Benzyl-3-[(cyclohex-3-enylmethyl)-amino]-2-hydroxy-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E127)		
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(2-phenyl-propylamino)-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E128)		
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-methylsulfanyl-propylamino)-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E129)		
N-[(1S,2R)-1-Benzyl-3-(3-cyano-benzylamino)-2-hydroxy-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E130)		

N-[(1S,2R)-1-Benzyl-2-hydroxy-3-[(5-methyl-thiophen-2-ylmethyl)-amino]-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E131)		
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(2-methoxy-5-methyl-benzylamino)-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E132)		
N-[(1S,2R)-3-[(Benzofuran-2-ylmethyl)-amino]-1-benzyl-2-hydroxy-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E133)		
N-[(1S,2R)-1-Benzyl-3-(3-fluoro-benzylamino)-2-hydroxy-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E134)		
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(2-*p*-tolyl-ethylamino)-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E135)		
N-[(1S,2R)-1-Benzyl-3-(dimethylamino-dimethyl-propylamino)-2-hydroxy-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E136)		
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-[(1*H*-Indol-5-ylmethyl)-amino]-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E137)		
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-[(2-methyl-thiazol-4-ylmethyl)-amino]-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E138)		
N-[(1S,2R)-1-Benzyl-3-(2-benzyloxy-ethylamino)-2-hydroxy-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E139)		
N-[(1S,2R)-1-Benzyl-3-(3,4-dimethoxy-benzylamino)-2-hydroxy-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E140)		
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-nitro-benzylamino)-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E141)		
N-[(1S,2R)-1-Benzyl-3-(3-chloro-benzylamino)-2-hydroxy-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E142)		
N-[(1S,2R)-1-Benzyl-3-(3-ethoxy-benzylamino)-2-hydroxy-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E143)		
N-[(1S,2R)-1-Benzyl-3-[(5-chloro-thiophen-2-ylmethyl)-amino]-2-hydroxy-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E144)		
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-[(thiazol-2-ylmethyl)-amino]-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E145)		
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-[(pyridin-3-ylmethyl)-amino]-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E146)		
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(4-hydroxy-3-methoxy-benzylamino)-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E147)		
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-hydroxymethyl-benzylamino)-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E148)		

N-[(1S,2R)-1-Benzyl-2-hydroxy-3-[3-(4-methoxy-phenyl)-propylamino]-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E149)		
N-[(1S,2R)-1-Benzyl-3-(4-dimethylaminomethyl-benzylamino)-2-hydroxy-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E150)		
N-[(1S,2R)-1-Benzyl-3-(3,4-difluoro-benzylamino)-2-hydroxy-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E151)		
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-[(5-methoxymethyl-furan-2-ylmethyl)-amino]-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E152)		
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-propoxy-benzylamino)-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E153)		
N-[(1S,2R)-1-Benzyl-3-(4-cyano-3-methoxy-benzylamino)-2-hydroxy-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E154)		
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-imidazol-1-yl-benzylamino)-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E155)		
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-pyrimidin-5-yl-benzylamino)-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E156)		
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-[(6-methoxy-pyridin-3-ylmethyl)-amino]-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E157)		
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-[(6-methoxy-pyridin-2-ylmethyl)-amino]-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E158)		
N-[(1S,2R)-1-Benzyl-3-(3-*tert*-butoxymethyl-benzylamino)-2-hydroxy-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E159)		
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-prop-2-ynyloxy-benzylamino)-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E160)		
N-[(1S,2R)-3-(3-Acetylamino-benzylamino)-1-benzyl-2-hydroxy-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E161)		
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-[3-(3-methoxy-phenyl)-propylamino]-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E162)		
N-[(1S,2R)-1-Benzyl-3-[3-(4-chloro-phenyl)-propylamino]-2-hydroxy-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E163)		
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-*p*-tolyl-propylamino)-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E164)		
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-[3-(2*H*-tetrazol-5-yl)-benzylamino]-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E165)		
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-[3-(1*H*-pyrazol-3-yl)-benzylamino]-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E166)		

N-[(1S,2R)-1-Benzyl-2-hydroxy-3-[3-(1*H*-imidazol-2-yl)-benzylamino]-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E167)		
N-[(1S,2R)-1-Benzyl-3-(4-fluoro-3-methoxy-benzylamino)-2-hydroxy-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E168)		
N-[(1S,2R)-1-Benzyl-3-[2,2-dimethyl-3-(2-oxo-pyrrolidin-1-yl)-propylamino]-2-hydroxy-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E169)		
N-[(1S,2R)-3-[(Benzothiazol-6-ylmethyl)-amino]-1-benzyl-2-hydroxy-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E170)		

Examples 171-181

Examples 171-181 were prepared in an analogous manner to Example 1 from the appropriate acid and amines indicated in the below table:

Example	Acid	Amine	$[M+H]^+$	RT (min)
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(2-oxopyrrolidin-1-yl)-5-propoxybenzamide formate salt (E171)	A10	C6	579.4	2.34
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-methoxy-5-(2-oxopyrrolidin-1-yl)benzamide (E172)	A9	C6	551.2	2.09
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-isopropoxy-5-(2-oxopyrrolidin-1-yl)benzamide (E173)	A12	C6	579.2	2.68
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(3-hydroxypropoxy)-5-(2-oxopyrrolidin-1-yl)benzamide (E174)	A15	C6	595.2	2.40
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(3-methoxypropoxy)-5-(2-oxopyrrolidin-1-yl)benzamide (E175)	A17	C6	609.2	2.59
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(2-hydroxyethoxy)-5-(2-oxopyrrolidin-1-yl)benzamide (E176)	A16	C6	581.1	2.36
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(2-methoxyethoxy)-5-(2-oxopyrrolidin-1-yl)benzamide (E177)	A14	C6	595.2	2.50
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(2-oxopyrrolidin-1-yl)-5-pentyloxybenzamide (E178)	A13	C6	607.2	2.87
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-((S)-1-isobutyl carbamoyl-pentylamino)-propyl]-3-isopropoxy-5-(2-oxopyrrolidin-1-yl)benzamide (E179)	A12	C36	595.2	2.75

N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-methoxybenzylamino)propyl]-3-isopropoxy-5-(2-oxopyrrolidin-1-yl)benzamide (E180)	A12	C14	548.1	2.59
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-ethoxy-5-(2-oxopyrrolidin-1-yl)benzamide (E181)	A11	C6	585.2	2.54

Example 182

N-((1S,2R)-3-Amino-1-benzyl-2-hydroxypropyl)-3-(2-oxopyrrolidin-1-yl)-5-pentyloxybenzamide (E182)

A mixture of [(2R,3S)-2-hydroxy-3-({1-[3-(2-oxo-pyrrolidin-1-yl)-5-pentyloxy-phenyl]-methanoyl}-amino)-4-phenyl-butyl]-carbamic acid benzyl ester (D105) (820 mg, 1.4 mmol, 1 equiv), 10% palladium on charcoal (50% wet, 100 mg, 6% w/w), NH_4CO_2H (800 mg, 12.7 mmol, 9 equiv), EtOH (25 ml) and H_2O (10 ml) was stirred at 60°C for 1 h. The mixture was then cooled to room temperature and the catalyst was filtered off through a pad of celite. Most of the EtOH was removed *in vacuo* and the residue was partitioned between AcOEt and H_2O. The aqueous phase was extracted with AcOEt. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give *N*-((1S,2R)-3-amino-1-benzyl-2-hydroxy-propyl)-3-(2-oxo-pyrrolidin-1-yl)-5-pentyloxy-benzamide (420 mg, 66%) as a white solid.
$[M+H]^+$ = 454.0, RT = 2.63 min

Example 183

N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(1-propylbutylamino)-propyl]-3-(2-oxopyrrolidin-1-yl)-5-pentyloxybenzamide (E183)

To a solution of *N*-((1S,2R)-3-amino-1-benzyl-2-hydroxy-propyl)-3-(2-oxo-pyrrolidin-1-yl)-5-pentyloxy-benzamide (E182) (30 mg, 0.066 mmol, 1equiv) in $(CH_2Cl)_2$ (5 ml) were added sodium triacetoxyborohydride (20 mg, 0.094 mmol, 1.4 equiv), 4-heptanone (10 µl, 0.070 mmol, 1.1 equiv) and CH_3COOH (4 µl, 0.070 mmol, 1,1 equiv). The resulting mixture was stirred at room temperature for 92 hours, diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/ethyl acetate : 3/2) gave *N*-[(1S,2R)-1-benzyl-2-hydroxy-3-(1-propyl-butylamino)-propyl]-3-(2-oxo-pyrrolidin-1-yl)-5-pentyloxy-benzamide (4.2 mg, 11%) as a colourless oil. $[M+H]^+$ = 552.2, RT = 2.98 min

Examples 184-192

The following compounds were prepared in an analogous manner to Example 183 from 3-pentoxy-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A13) and the appropriate aldehyde or ketone:

Example	$[M+H]^+$	RT (min)
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-methoxybenzylamino)-propyl]-3-(2-oxopyrrolidin-1-yl)-5- pentyloxybenzamide (E184)	574.2	2.87
N-((1S,2R)-1-Benzyl-3-benzylamino-2-hydroxypropyl)-3-(2-oxopyrrolidin-1-yl)-5-pentyloxybenzamide (E185)	544.1	2.83

N-((1S,2R)-1-Benzyl-3-ethylamino-2-hydroxypropyl)-3-(2-oxopyrrolidin-1-yl)-5-pentyloxy-benzamide (E186)	482.2	2.70
N-((1S,2R)-1-Benzyl-2-hydroxy-3-phenethylaminopropyl)-3-(2-oxopyrrolidin-1-yl)-5-pentyloxybenzamide (E187)	558.2	2.91
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(2-phenylpropylamino)-propyl]-3-(2-oxopyrrolidin-1-yl)-5-pentyloxybenzamide (E188)	572.2	2.95
N-((1S,2R)-1-Benzyl-3-cyclohexylamino-2-hydroxypropyl)-3-(2-oxopyrrolidin-1-yl)-5-pentyloxybenzamide (E189)	536.2	2.84
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(1-methylpiperidin-4-ylamino)-propyl]-3-(2-oxopyrrolidin-1-yl)-5-pentyloxybenzamide (E190)	551.2	2.43
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-methylbutylamino)-propyl]-3-(2-oxopyrrolidin-1-yl)-5-pentyloxybenzamide (E191)	524.2	2.87
N-[(1S,2R)-1-Benzyl-3-(1-ethylpropylamino)-2-hydroxypropyl]-3-(2-oxopyrrolidin-1-yl)-5-pentyloxybenzamide (E192)	594.3	3.09

Examples 193-204

Examples 193-204 were prepared in an analogous manner to Example 1 from the appropriate acid and amines indicated in the below table:

Example	Acid	Amine	$[M+H]^+$	RT (min)
N-[(1S,2R)-1-Benzyl-3-(1,5-dimethylhexylamino)-2-hydroxy-propyl]-3-isopropoxy-5-(2-oxopyrrolidin-1-yl)benzamide (E193)	A11	C20	538.3	2.81
N-[1-Benzyl-2-hydroxy-3-(3-trifluoromethylbenzylamino)propyl]-3-ethoxy-5-(2-oxopyrrolidin-1-yl)benzamide (E194)	A11	C16	570.3	2.64
N-[1-Benzyl-3-(1,5-dimethylhexylamino)-2-hydroxypropyl]-3-ethoxy-5-(2-oxopyrrolidin-1-yl)benzamide formate salt (E195)	A11	C20	524.3	2.74
N-(1-Benzyl-3-cyclohexylamino-2-hydroxypropyl)-3-ethoxy-5-(2-oxopyrrolidin-1-yl)benzamide (E196)	A11	C1	494.3	2.45
N-[1-Benzyl-2-hydroxy-3-(3-methoxybenzylamino)propyl]-3-ethoxy-5-(2-oxopyrrolidin-1-yl)benzamide (E197)	A11	C14	532.3	2.50
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexyl carbamoylethylamino)-2-hydroxypropyl]-3-methanesulfonyl-5-(2-oxopyrrolidin-1-yl)benzamide (E198)	A5	C8	599.1	2.41

N-[1-Benzyl-2-hydroxy-3-(3-trifluoromethylbenzylamino)propyl]-3-methylsulfanyl-5-(2-oxopyrrolidin-1-yl)-benzamide (E199)	A1	C16	572.2	2.72
N-[1-Benzyl-2-hydroxy-3-(3-trifluoromethylbenzylamino)propyl]-3-ethylsulfanyl-5-(2-oxopyrrolidin-1-yl)benzamide (E200)	A2	C16	586.2	2.80
N-[1-Benzyl-2-hydroxy-3-(3-trifluoromethylbenzylamino)propyl]-3-ethanesulfonyl-5-(2-oxopyrrolidin-1-yl)-benzamide (E201)	A6	C16	618.2	2.70
N-[1-Benzyl-2-hydroxy-3-(3-trifluoromethylbenzylamino)propyl]-3-methanesulfonyl-5-(2-oxopyrrolidin-1-yl)-benzamide (E202)	A5	C16	604.1	2.57
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-N',N'-dipropylisophthalamide (E203)	A94	C6	684.2	2.67
3-Azidomethyl-N-[(1S,2R)-1-benzyl-3-((S)-1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)benzamide (E204)	A85	C6	612.2	2.52

Example 205

3-Aminomethyl-N-[(1S,2R)-1-benzyl-3-((S)-1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)benzamide (E205)

A mixture of 3-azidomethyl-*N*-[(1S,2R)-1-benzyl-3-((S)-1-cyclohexylcarbamoyl-ethylamino)-2-hydroxy-propyl]-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzamide (E204) (70 mg, 0.12 mmol, 1 equiv), 10% palladium on charcoal (50% wet, 20 mg, 15% w/w), NH_4COOH (65 mg, 1 mmol, 9 equiv), EtOH (5 ml) and H_2O (2.5 ml) was stirred at 50°C for 2 h, cooled to room temperature and the catalyst was filtered off through a pad of celite. Most of the EtOH was removed *in vacuo* and the residue was partitioned between AcOEt and saturated aqueous $NaHCO_3$ solution. The aqueous phase was extracted with AcOEt. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with Et_2O to give 3-aminomethyl-*N*-[(1S,2R)-1-benzyl-3-((S)-1-cyclohexylcarbamoyl-ethylamino)-2-hydroxy-propyl]-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzamide (20 mg, 30%) as a white solid.

$[M+H]^+$ = 586.2

RT = 1.98 min

Examples 206-207

Examples 206-207 were prepared in an analogous manner to Example 1 from the appropriate acid and amines indicated in the below table:

Example	Acid	Amine	$[M+H]^+$	RT (min)
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-dimethylaminomethyl-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzamide (E206)	A84	C6	614.2	1.99
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-vinyl-benzamide (E207)	A88	C6	583.1	2.53

Example 208

N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-ethyl-benzamide (E208)

Example 208 was prepared from Example 214 in an analogous manner to that described for Example 213. $[M+H]^+$ = 585.2, RT = 2.56min

Examples 209-212

Examples 209-212 were prepared in an analogous manner to Example 1 from the appropriate acid and amines indicated in the below table:

Example	Acid	Amine	$[M+H]^+$	RT (min)
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-methoxymethylbenzamide (E209)	A86	C6	601.2	2.41
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-ethoxymethylbenzamide (E210)	A87	C6	615.2	2.50
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-(Z/E)-propenylbenzamide (E211)	A89	C6	597.2	2.61
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(Z/E)-but-1-enyl-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)benzamide (E212)	A90	C6	611.2	2.70

Example 213

N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoylethylamino)-2-

hydroxypropyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-propylbenzamide (E213)

A mixture of *N*-[(1S,2R)-1-benzyl-3-((S)-1-cyclohexylcarbamoyl-ethylamino)-2-hydroxy-propyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-propenyl-benzamide (E211) (50 mg, 0.083 mmol, 1 equiv), 10% palladium on charcoal (50% wet, 15 mg, 15% w/w), NH_4COOH (50 mg, 0.79 mmol, 9 equiv) and EtOH (5 ml) was stirred at 60°C for 1 h, cooled to room temperature and the catalyst was filtered off through a pad of celite. Most of the EtOH was removed *in vacuo* and the residue was partitioned between AcOEt and saturated aqueous $NaHCO_3$ solution. The aqueous phase was extracted with AcOEt. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with Et_2O to give of *N*-[(1S,2R)-1-benzyl-3-((S)-1-cyclohexylcarbamoyl-ethylamino)-2-hydroxy-propyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-propyl-benzamide (45 mg, 90%) as a white solid.
$[M+H]^+$ = 599.2, RT = 2.63min

Example 214

N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-3-butyl-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)benzamide (E214)

Example 214 was prepared from N-[(1S,2R)-1-benzyl-3-((S)-1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-3-(Z/E)-but-1-enyl-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)benzamide (E212) in an analogous manner to that described in Example 213. $[M+H]^+$ = 613.2, RT = 2.75min

Examples 215-216

Examples 215-216 were prepared in an analogous manner to Example 1 from the appropriate acid and amines indicated in the below table:

Example	Acid	Amine	$[M+H]^+$	RT (min)
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-(2-methylpropenyl)-benzamide (E215)	A91	C6	611.2	2.70
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-fluoromethylbenzamide (E216)	A83	C6	589.2	2.44

Example 217

N-[1-Benzyl-3-(1-cyclohexylcarbamoylethylamino)-2-hydroxy-propyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-isobutylbenzamide (E217)

Example 217 was prepared from Example 215 in an analogous manner to that described in Example 213. $[M+H]^+$ = 613.3, RT = 2.72min

Examples 218-220 and 222

Examples 218-220 and 222 were prepared in an analogous manner to Example 213 from the appropriate amine indicated in the table below:

Example	Amine	$[M+H]^+$	RT (min)
N-[1-Benzyl-2-hydroxy-3-(3-trifluoromethylbenzylamino)propyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-propylbenzamide (E218)	C16	604.3	2.76
N-[1-Benzyl-3-(1,5-dimethylhexylamino)-2-hydroxypropyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-propylbenzamide formate salt (E219)	C26	558.3	2.87
N-(1-Benzyl-3-cyclohexylamino-2-hydroxypropyl)-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-propylbenzamide (E220)	C6	528.3	2.61
N-[1-Benzyl-2-hydroxy-3-(3-methoxybenzylamino)propyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-propyl-benzamide (E222)	C14	566.2	2.64

Examples 221 and 223-226

Examples 221 and 223-226 were prepared in an analogous manner to Example 1 from the appropriate acid and amines indicated in the below table:

Example	Acid	Amine	$[M+H]^+$	RT (min)
N-[1-Benzyl-3-(1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)isophthalamide (E221)	A92	C6	600.2	2.23
N-[1-Benzyl-3-(1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-3-cyano-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)benzamide (E223)	A93	C6	582.2	2.47
N-[1-Benzyl-2-hydroxy-3-(3-trifluoromethylbenzylamino)propyl]-3-cyano-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)benzamide (E224)	A93	C16	587.2	2.43
N-[1-Benzyl-2-hydroxy-3-(3-trifluoromethylbenzyl amino)propyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-ethynyl-benzamide formate salt (E225)	A111	C16	586.2	2.71
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-nitro-5-(2-oxopiperidin-1-yl)benzamide (E226)	A82	C6	580.2	2.55

Example 227

3-Amino-N-[(1S,2R)-1-benzyl-3-((S)-1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-5-(2-oxopiperidin-1-yl)benzamide (E227)

Example 227 was prepared from Example 226 in an analogous manner to the process described for Example 63. $[M+H]^+$ = 550.1, RT = 2.31min

Examples 228-251

Examples 228-251 were prepared in an analogous manner to Example 1 from the appropriate acid and amines indicated in the below table:

Example	Acid	Amine	$[M+H]^+$	RT (min)
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(2-oxopiperidin-1-yl)-5-propylaminobenzamide (E228)	A58	C8	592.2	2.59
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-diethylamino-5-(2-oxopiperidin-1-yl)benzamide (E229)	A60	C8	606.3	2.62
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-ethylamino-5-(2-oxopiperidin-1-yl)benzamide (E230)	A59	C8	578.2	2.46
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-methylamino-5-(2-oxopiperidin-1-yl)benzamide (E231)	A57	C8	564.3	2.40
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(2-oxopiperidin-1-yl)-5-piperidin-1-ylbenzamide (E232)	A55	C8	618.3	2.65
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-morpholin-4-yl-5-(2-oxopiperidin-1-yl)benzamide (E233)	A56	C8	620.3	2.43
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(2-oxopiperidin-1-yl)-5-pyrrolidin-1-yl-benzamide (E234)	A54	C8	604.3	2.64
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-isopropylaminobenzamide (E235)	A72	C8	614.2	2.58
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-((1S,2R)-2-hydroxy-1-isobutylcarbamoyl-pentylamino)-propyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-isopropylamino-benzamide (E236)	A72	C33	646.2	2.63

161

3-Benzylamino-N-[(1S,2R)-1-benzyl-3-((S)-1-cyclohexylcarbamoylethylamino)-2-hydroxy-propyl]-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)benzamide (E237)	A64	C6	662.2	2.71
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-3-butylamino-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)benzamide (E238)	A65	C6	628.2	2.71
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-(3-methylbutylamino)-benzamide (E239)	A66	C6	642.2	2.79
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-phenethylamino-benzamide (E240)	A67	C6	676.2	2.80
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-pentylaminobenzamide (E241)	A68	C6	642.2	2.79
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-propylaminobenzamide (E242)	A69	C6	614.2	2.57
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-ethylaminobenzamide (E243)	A70	C6	600.2	2.47
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-3-diethylamino-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)benzamide (E244)	A63	C6	628.2	2.63
N-[(1S,2R)-1-Benzyl-3-(1,5-dimethylhexylamino)-2-hydroxypropyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-ethylaminobenzamide (E245)	A70	C20	559.2	2.68
N-[(1S,2R)-1-Benzyl-3-(1,5-dimethylhexylamino)-2-hydroxypropyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-isopropylaminobenzamide (E246)	A72	C20	573.2	2.77

162

N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(cyclopropylmethylamino)-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)benzamide (E247)	A71	C6	626.2	2.59
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-methoxybenzylamino)propyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-ethylamino-benzamide formate salt (E248)	A70	C14	567.2	2.44
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethylbenzylamino)propyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-ethylaminobenzamide formate salt (E249)	A70	C16	605.1	2.60
N-((1S,2R)-1-Benzyl-3-cyclohexylamino-2-hydroxypropyl)-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-ethylaminobenzamide (E250)	A70	C1	529.3	2.40
N-[1-Benzyl-2-hydroxy-3-(3-trifluoromethylbenzylamino)propyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-morpholin-4-yl-benzamide formate salt (E251)	A61	C16	647.3	2.39

Example 252

***N*-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-pyrrolidin-1-yl-benzamide formate salt (E252)**

To a solution of 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-pyrrolidin-1-yl-benzoic acid (A114) (62 mg, 0.2 mmol, 1 equiv) in DMF (5 ml) at room temperature was added (2R,3S)-3-amino-4-phenyl-1-(3-trifluoromethyl-benzylamino)-butan-2-ol (C16) (82 mg, 0.2 mmol, 1 equiv), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (46 mg, 0.24 mmol, 1.2 equiv), 1-hydroxybenzotriazole hydrate (37 mg, 0.24 mmol, 1.2 equiv) and 4-ethylmorpholine (152 µl, 1.2 mmol, 6 equiv). The resulting mixture was stirred for 4 h then concentrated *in vacuo*. The residue was diluted with AcOEt and the organic phase washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by trituration with Et_2O to yield *N*-[(1S,2R)-1-benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-pyrrolidin-1-yl-benzamide as a white solid (46 mg, 36%). $[M+H]^+$ = 631.2, RT = 2.65 min

Examples 253-289

Examples 253-289 were prepared in an analogous manner to Example 1 from the appropriate acid and amines indicated in the below table:

Example	Acid	Amine	$[M+H]^+$	RT (min)

N-[1-Benzyl-2-hydroxy-3-(3-trifluoromethylbenzylamino) propyl]-3-(1,1-dioxo-1-l6-isothiazolidin-2-yl)-5-methylaminobenzamide formate salt (E253)	A62	C16	591.2	2.58
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-ethoxybenzamide (E254)	A18	C6	601.2	2.54
N-[1-Benzyl-2-hydroxy-3-(3-trifluoromethylbenzylamino)propyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-ethoxy-benzamide (E255)	A18	C16	606.2	2.66
N-[1-Benzyl-3-(1,5-dimethylhexylamino)-2-hydroxypropyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-ethoxybenzamide formate salt (E256)	A18	C20	560.3	2.74
N-[1-Benzyl-2-hydroxy-3-(3-methoxybenzylamino)propyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-ethoxybenzamide (E257)	A18	C14	568.3	2.50
N-(1-Benzyl-3-cyclohexylamino-2-hydroxypropyl)-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-ethoxybenzamide (E258)	A18	C1	530.2	2.47
N-[1-Benzyl-3-(1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-isopropoxybenzamide (E259)	A19	C6	615.4	2.68
N-[1-Benzyl-3-(1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-propoxybenzamide (E260)	A21	C6	615.4	2.69
N-[1-Benzyl-3-(1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-pentyloxybenzamide (E261)	A22	C6	643.5	2.89
N-[1-Benzyl-3-(1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-methoxybenzamide (E262)	A20	C6	587.4	2.49
N-(1-Benzyl-3-cyclopropylamino-2-hydroxypropyl)-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-ethoxybenzamide (E263)	A18	C26	488.2	2.37
N-[1-Benzyl-2-hydroxy-3-(3-trifluoromethoxybenzylamino) propyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-ethoxybenzamide (E264)	A18	C11	622.2	2.91

N-[1-Benzyl-2-hydroxy-3-(3-trifluoromethylbenzylamino)propyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-methylsulfanylbenzamide (E265)	A3	C16	608.2	2.73
N-[1-Benzyl-2-hydroxy-3-(3-trifluoromethylbenzylamino)propyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-ethylsulfanylbenzamide (E266)	A4	C16	622.2	2.82
N-[1-Benzyl-2-hydroxy-3-(3-trifluoromethylbenzylamino)propyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-ethanesulfonylbenzamide (E267)	A8	C16	654.1	2.65
N-[1-Benzyl-2-hydroxy-3-(3-trifluoromethylbenzylamino)propyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-Methanesulfonylbenzamide (E268)	A7	C16	640.2	2.62
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-5-(2-oxopiperidin-1-yl)-N',N'-dipropylisophthalamide (E269)	A81	C8	662.3	2.63
formic acid - 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluoro-*N*-[(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-[({3-[(trifluoromethyl)oxy]phenyl}methyl)amino]propyl]-5-[(1-methylethyl)amino]benzamide (1:1) (E270)	A175	C11	667.4	2.82
3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-(ethylamino)-*N*-[(1*S*,2*R*)-3-{[(3-ethyl-5-isoxazolyl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-2-fluorobenzamide (E271)	A119	C157	588.4	2.30
4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-1-ethyl-*N*-[(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-(tetrahydro-2*H*-pyran-4-ylamino)propyl]-1*H*-benzimidazole-6-carboxamide (E272)	A151	C43	570.4	1.91
8-(1,1-dioxido-2-isothiazolidinyl)-4-ethyl-*N*-[(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-(tetrahydro-2*H*-pyran-4-ylamino)propyl]-1,2,3,4-tetrahydro-6-quinoxalinecarboxamide (E273)	A172	C43	572.4	2.08
8-(1,1-dioxido-2-isothiazolidinyl)-4-ethyl-*N*-[(1*S*,2*R*)-3-{[(1-ethyl-1*H*-pyrazol-4-yl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-1,2,3,4-tetrahydro-6-quinoxalinecarboxamide (E274)	A172	C154	596.4	2.15
4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-1-ethyl-*N*-[(1*S*,2*R*)-2-hydroxy-3-[(1-methylethyl)amino]-1-(phenylmethyl)propyl]-1*H*-benzimidazole-6-carboxamide (E275)	A151	C28	528.4	1.92
8-(1,1-dioxido-2-isothiazolidinyl)-4-ethyl-*N*-[(1*S*,2*R*)-2-hydroxy-3-[(1-methylethyl)amino]-1-	A172	C28	530.4	2.11

(phenylmethyl)propyl]-1,2,3,4-tetrahydro-6-quinoxalinecarboxamide (E276)				
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-5-(1,1-dioxo-1λ^6-[1,2]thiazinan-2-yl)-N',N'-dipropylisophthalamide (E277)	A95	C8	698.2	2.68
N-[1-Benzyl-2-hydroxy-3-(3-trifluoromethylbenzylamino)propyl]-5-(1,1-dioxo-1λ^6-[1,2]thiazinan-2-yl)-N',N'-dipropylisophthalamide (E278)	A95	C16	703.3	2.87
N-(1-Benzyl-3-cyclopropylamino-2-hydroxypropyl)-5-(1,1-dioxo-1λ^6-[1,2]thiazinan-2-yl)-N',N'-dipropylisophthalamide (E279)	A95	C26	585.3	2.55
N-[1-Benzyl-2-hydroxy-3-(3-trifluoromethylbenzylamino) propyl]-3-(1,1-dioxo-1λ^6-[1,2]thiazinan-2-yl)-5-propylbenzamide (E280)	A112	C16	618.2	3.07
N-[1-Benzyl-2-hydroxy-3-(3-methoxybenzylamino)propyl]-3-(1,1-dioxo-1λ^6-[1,2]thiazinan-2-yl)-5-propylbenzamide formate salt (E281)	A112	C14	580.3	2.77
N-[1-Benzyl-3-(1,5-dimethylhexylamino)-2-hydroxypropyl]-3-(1,1-dioxo-1λ^6-[1,2]thiazinan-2-yl)-5-propylbenzamide formate salt (E282)	A112	C20	572.3	3.01
N-[1-Benzyl-3-(1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-3-(1,1-dioxo-1λ^6-[1,2]thiazinan-2-yl)-5-propylbenzamide (E283)	A112	C8	613.4	2.80
N-[1-Benzyl-2-hydroxy-3-(3-methoxybenzylamino)propyl]-5-(1,1-dioxo-1λ^6-[1,2]thiazinan-2-yl)-N',N'-dipropyl-isophthalamide (E284)	A95	C14	665.3	2.85
N-[1-Benzyl-2-hydroxy-3-(3-trifluoromethoxybenzylamino) propyl]-5-(1,1-dioxo-1λ^6-[1,2]thiazinan-2-yl)-N',N'-dipropyl-isophthalamide formate salt (E285)	A95	C11	719.2	3.02
N-[1-Benzyl-2-hydroxy-3-(3-trifluoromethylbenzylamino) propyl]-3-(1,1-dioxo-1λ^6-[1,2]thiazinan-2-yl)-5-ethylaminobenzamide formate salt (E286)	A73	C16	619.2	2.73
N-[1-Benzyl-2-hydroxy-3-(3-methoxybenzylamino)propyl]-3-(1,1-dioxo-1λ^6-[1,2]thiazinan-2-yl)-5-ethylaminobenzamide formate salt (E287)	A73	C14	581.2	2.72
N-[1-Benzyl-3-(1,5-dimethylhexylamino)-2-hydroxypropyl]-3-(1,1-dioxo-1λ^6-[1,2]thiazinan-2-yl)-5-ethylaminobenzamide formate salt (E288)	A73	C20	573.3	2.99

166

N-[1-Benzyl-3-(1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-3-(1,1-dioxo-1λ^6-[1,2]thiazinan-2-yl)-5-ethylaminobenzamide (E289)	A73	C6	614.3	2.75

Examples 290-427 (E290-E427)

The following compounds were prepared in an analogous manner to Example 183 from the appropriate amine and the appropriate aldehyde or ketone :

Example	Precursor	$[M+H]^+$	RT (min)
formic acid - N-{(1S,2R)-1-Benzyl-3-[(3,5-dichlorobenzyl)amino]-2-hydroxypropyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E290)	D120	619.3	2.69
formic acid - N-{(1S,2R)-1-Benzyl-3-[(2-fluoro-5-methoxybenzyl)amino]-2-hydroxypropyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E291)	D120	599.4	2.48
formic acid - N-{(1S,2R)-1-Benzyl-3-[(4-fluoro-3-methoxybenzyl)amino]-2-hydroxypropyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E292)	D120	599.4	2.52
formic acid - N-{(1S,2R)-1-Benzyl-3-[(3,5-dimethylbenzyl)amino]-2-hydroxypropyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E293)	D120	579.3	2.68
N-{(1S,2R)-1-Benzyl-3-[(3,5-difluorobenzyl)amino]-2-hydroxypropyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (E294)	D120	587.3	2.61
N-((1S,2R)-1-Benzyl-2-hydroxy-3-[[3-nitro-5-(trifluoromethyl)benzyl]amino}propyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (E295)	D120	664.2	2.76
N-((1S,2R)-1-Benzyl-3-[[(5-cyanopyridin-3-yl)methyl]amino}-2-hydroxypropyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (E296)	D120	577.3	2.42
formic acid - N-{(1S,2R)-1-Benzyl-3-[(3-chloro-5-methoxybenzyl)amino]-2-hydroxypropyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E297)	D120	615.3	2.70
N-{(1S,2R)-1-Benzyl-3-[(3-bromo-5-fluorobenzyl)amino]-2-hydroxypropyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (E298)	D120	649.2	2.70
5-[[((2R,3S)-3-[[3-(1,1-Dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzoyl]amino}-2-hydroxy-4-phenylbutyl)amino]methyl}-N-methylnicotinamide (E299)	D120	609.3	2.34
formic acid - N-{(1S,2R)-1-Benzyl-3-[(3-bromo-5-methoxybenzyl)amino]-2-hydroxypropyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E300)	D120	661.2	2.71

167

Methyl 5-[[((2R,3S)-3-[[3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzoyl] amino}-2-hydroxy-4-phenylbutyl)amino]methyl} nicotinate (E301)	D120	610.3	2.44
N-[(1S,2R)-1-Benzyl-3-[(3,5-di-tert-butylbenzyl)amino]-2-hydroxypropyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (E302)	D120	663.4	3.14
N-((1S,2R)-1-Benzyl-2-hydroxy-3-[[3-methyl-5-(methylsulfonyl)benzyl]amino}propyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (E303)	D120	643.3	2.53
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-[(3-methoxy-5-methylbenzyl)amino]propyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (E304)	D120	595.3	2.65
Dimethyl 5-[[((2R,3S)-3-[[3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzoyl] amino}-2-hydroxy-4-phenylbutyl)amino]methyl} isophthalate (E305)	D120	667.3	2.63
N-[(1S,2R)-1-Benzyl-3-[(3,5-diisopropoxybenzyl)amino]-2-hydroxypropyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (E306)	D120	667.4	2.91
N-[(1S,2R)-1-Benzyl-3-[[(4-bromo-2-thienyl)methyl]amino}-2-hydroxypropyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (E307)	D120	637.3	2.56
N-[(1S,2R)-1-Benzyl-3-[(2,3-dihydro-1-benzofuran-6-ylmethyl)amino]-2-hydroxypropyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (E308)	D120	593.3	2.42
formic acid - N-((1S,2R)-1-Benzyl-3-[[(4-chloro-1-methyl-1H-pyrazol-3-yl)methyl]amino}-2-hydroxypropyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E309)	D120	589.3	2.26
N-((1S,2R)-1-Benzyl-3-[[(2-bromo-1,3-thiazol-5-yl)methyl]amino}-2-hydroxypropyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (E310)	D120	638.2	2.36
N-((1S,2R)-1-Benzyl-3-[[(4-bromo-1H-pyrrol-2-yl)methyl]amino}-2-hydroxypropyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (E311)	D120	618.2	2.54
formic acid - N-((1S,2R)-1-Benzyl-3-[[(2-butyl-1H-imidazol-4-yl)methyl]amino}-2-hydroxypropyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E312)	D120	597.4	2.11
N-[(1S,2R)-1-Benzyl-3-[(3-bromobenzyl)amino]-2-hydroxypropyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (E313)	D120	631.2	2.59
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-[(3-nitrobenzyl)amino]propyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (E314)	D120	596.3	2.45
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-[(3-thienylmethyl) amino]propyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (E315)	D120	557.3	2.36
N-((1S,2R)-1-Benzyl-3-[[(4-bromo-1-methyl-1H-pyrazol-3-	D120	635.3	2.33

yl)methyl]amino}-2-hydroxypropyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (E316)			
N-((1S,2R)-1-Benzyl-3-[[3-fluoro-5-(trifluoromethyl)benzyl]amino}-2-hydroxypropyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (E317)	D120	637.3	2.68
formic acid - N-{(1S,2R)-1-Benzyl-2-hydroxy-3-[(3-vinylbenzyl)amino]propyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E318)	D120	577.3	2.43
formic acid - N-((1S,2R)-1-Benzyl-2-hydroxy-3-[[(4-methoxy-3-thienyl)methyl]amino}propyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E319)	D120	587.3	2.31
3-[[((2R,3S)-3-[[3-(1,1-Dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzoyl]amino}-2-hydroxy-4-phenylbutyl)amino]methyl}benzoic acid - formic acid (1:1) (E320)	D120	595.3	2.27
formic acid - N-{(1S,2R)-1-Benzyl-3-[(3,4-dimethoxybenzyl)amino]-2-hydroxypropyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E321)	D120	611.3	2.28
formic acid - N-{(1S,2R)-1-Benzyl-3-[[(5-ethyl-2-furyl)methyl]amino}-2-hydroxypropyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E322)	D120	567.4	2.34
formic acid - N-{(1S,2R)-1-Benzyl-3-[(2,3-dihydro-1,4-benzodioxin-6-ylmethyl)amino]-2-hydroxypropyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E323)	D120	609.4	2.32
formic acid - N-{(1S,2R)-1-Benzyl-3-[(3-ethoxy-4-methoxybenzyl)amino]-2-hydroxypropyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E324)	D120	625.4	2.36
formic acid - N-{(1S,2R)-1-Benzyl-3-[[(5-ethyl-2-thienyl)methyl]amino}-2-hydroxypropyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E325)	D120	585.3	2.46
formic acid - N-{(1S,2R)-1-Benzyl-3-[(3-chloro-4-fluorobenzyl)amino]-2-hydroxypropyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E326)	D120	603.3	2.49
formic acid - N-((1S,2R)-1-Benzyl-3-[[(1-ethyl-1H-pyrazol-4-yl)methyl]amino}-2-hydroxypropyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E327)	D120	569.4	2.13
formic acid - N-((1S,2R)-1-Benzyl-3-[[(1-ethyl-3-methyl-1H-pyrazol-4-yl)methyl]amino}-2-hydroxypropyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E328)	D120	583.4	2.17
formic acid - N-((1S,2R)-1-Benzyl-3-[[(2,2-dimethyl-3,4-dihydro-2H-chromen-6-yl)methyl]amino}-2-hydroxypropyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E329)	D120	635.4	2.60
formic acid - N-((1S,2R)-1-Benzyl-3-[[4-chloro-3-(trifluoromethyl)benzyl]amino}-2-hydroxypropyl)-3-(1,1-dioxido-	D120	653.3	2.69

1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E330)			
formic acid - N-((1S,2R)-1-Benzyl-2-hydroxy-3-[[(6-methylpyridin-2-yl)methyl]amino}propyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E331)	D120	566.3	2.22
formic acid - N-[(1S,2R)-1-benzyl-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E332)	D120	579.5	2.40
N-((1S,2R)-1-benzyl-3-[[(1-ethyl-1H-pyrazol-4-yl)methyl]amino}-2-hydroxypropyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)-2-fluorobenzamide (E333)	D121	587.4	2.08
formic acid - N-((1S,2R)-1-benzyl-3-[[(1-ethyl-1H-pyrazol-4-yl)methyl]amino}-2-hydroxypropyl)-3-(ethylamino)-5-(2-oxopyrrolidin-1-yl)benzamide (1:1) (E334)	E66	519.5	2.00
formic acid - N-[(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxy-4-methylbenzyl)amino]propyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E335)	D120	595.2	2.65
formic acid - N-[(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxy-2-methylbenzyl)amino]propyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E336)	D120	595.4	2.60
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-3-[(1-methylbutyl)amino]-1-(phenylmethyl)propyl] benzamide (E337)	D120	531.5	0.75
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-{(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[(1-propylbutyl)amino]propyl} benzamide hydrochloride (E338)	D120	559.5	0.88
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-3-[(1-methylpentyl)amino]-1-(phenylmethyl)propyl] benzamide hydrochloride (E339)	D120	545.5	0.84
N-[(1S,2R)-3-[(1,4-dimethylpentyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E340)	D120	559.5	0.88
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-3-[(3-methylbutyl)amino]-1-(phenylmethyl)propyl] benzamide hydrochloride (E341)	D120	531.5	0.81
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-(propylamino)propyl] benzamide hydrochloride E342)	D120	503.5	0.72
N-[(1S,2R)-3-[[1-(3-chlorophenyl)propyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-3-(ethylamino)-5-(2-oxo-1-pyrrolidinyl)benzamide hydrochloride (E343)	E66	563.5	0.84
N-[(1S,2R)-3-[[1-(3-chlorophenyl)propyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-3-cyclopentyl-5-(2-oxo-1-pyrrolidinyl)benzamide hydrochloride (E344)	D122	588.4	1.01

3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-3-[(4-methylpentyl)amino]-1-(phenylmethyl)propyl] benzamide hydrochloride (E345)	D120	545.5	0.85
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-3-[(5-methylhexyl)amino]-1-(phenylmethyl)propyl] benzamide hydrochloride (E346)	D120	559.6	0.89
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-3-[(1-methylpropyl)amino]-1-(phenylmethyl)propyl] benzamide hydrochloride (E347)	D120	517.5	0.74
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-3-[(1-methylhexyl)amino]-1-(phenylmethyl)propyl] benzamide hydrochloride (E348)	D120	559.6	0.89
N-[(1S,2R)-3-[[(3,5-dibromophenyl)methyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-3-[(1-methylethyl)oxy]-5-(2-oxo-1-pyrrolidinyl)benzamide (E349)	D123	672.3	0.89
N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[(phenylmethyl)amino]propyl]-3-[(1-methylethyl)oxy]-5-(2-oxo-1-pyrrolidinyl)benzamide (E350)	D123	516.5	0.78
N-[(1S,2R)-3-[[(3-bromophenyl)methyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-3-[(1-methylethyl)oxy]-5-(2-oxo-1-pyrrolidinyl)benzamide (E351)	D123	596.2	0.83
N-[(1S,2R)-3-({[3-(ethyloxy)phenyl]methyl} amino)-2-hydroxy-1-(phenylmethyl)propyl]-3-[(1-methylethyl)oxy]-5-(2-oxo-1-pyrrolidinyl)benzamide (E352)	D123	560.4	0.82
N-[(1S,2R)-3-[[(3-chlorophenyl)methyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-3-[(1-methylethyl)oxy]-5-(2-oxo-1-pyrrolidinyl)benzamide (E353)	D123	550.3	0.82
N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[({3-[(trifluoromethyl)oxy]phenyl}methyl)amino]propyl]-3-[(1-methylethyl)oxy]-5-(2-oxo-1-pyrrolidinyl)benzamide (E354)	D123	600.3	0.87
N-[(1S,2R)-3-({[3,5-bis(methyloxy)phenyl]methyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]-3-[(1-methylethyl)oxy]-5-(2-oxo-1-pyrrolidinyl)benzamide (E355)	D123	576.4	0.81
N-[(1S,2R)-3-[[(3,5-dichlorophenyl)methyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-3-[(1-methylethyl)oxy]-5-(2-oxo-1-pyrrolidinyl)benzamide (E356)	D123	584.2	0.87
N-[(1S,2R)-3-[[(3,5-difluorophenyl)methyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-3-[(1-methylethyl)oxy]-5-(2-oxo-1-pyrrolidinyl)benzamide (E357)	D123	552.3	0.80
N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-3-[(1-methylethyl)oxy]-5-(2-oxo-1-pyrrolidinyl)benzamide (E358)	D123	584.3	0.85
N-[(1S,2R)-3-({[3,5-bis(trifluoromethyl)phenyl] methyl}amino)-2-	D123	652.3	0.93

hydroxy-1-(phenylmethyl)propyl]-3-[(1-methylethyl)oxy]-5-(2-oxo-1-pyrrolidinyl)benzamide (E359)			
N-[(1S,2R)-2-hydroxy-3-[[(3-methylphenyl)methyl]amino]-1-(phenylmethyl)propyl]-3-[(1-methylethyl)oxy]-5-(2-oxo-1-pyrrolidinyl)benzamide (E360)	D123	530.4	0.82
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-5-[(1-methylethyl)oxy]benzamide hydrochloride (E361)	D124	634.3	0.88
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl} amino)-1-(phenylmethyl)propyl]-5-[(1-methylethyl)oxy]benzamide hydrochloride (E362)	D124	596.3	0.82
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[({3-[(trifluoromethyl)oxy]phenyl}methyl)amino]propyl]-5-[(1-methylethyl)oxy]benzamide hydrochloride (E363)	D124	650.3	0.89
N-[(1S,2R)-3-({[3,5-bis(trifluoromethyl)phenyl] methyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-[(1-methylethyl)oxy]benzamide hydrochloride (E364)	D124	702.3	0.98
N-[(1S,2R)-3-({[3,5-bis(methyloxy)phenyl]methyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-[(1-methylethyl)oxy]benzamide hydrochloride (E365)	D124	626.3	0.82
N-[(1S,2R)-3-[[(3,5-dibromophenyl)methyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-[(1-methylethyl)oxy]benzamide hydrochloride (E366)	D124	722.1	0.90
3-cyclopentyl-5-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl] benzamide hydrochloride (E367)	D125	644.4	0.94
3-cyclopentyl-5-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl} amino)-1-(phenylmethyl)propyl] benzamide hydrochloride (E368)	D125	606.4	0.88
3-cyclopentyl-5-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-N-{(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[({3-[(trifluoromethyl)oxy]phenyl}methyl)amino]propyl} benzamide hydrochloride (E369)	D125	660.4	0.95
N-[(1S,2R)-3-({[3,5-bis(trifluoromethyl)phenyl] methyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]-3-cyclopentyl-5-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)benzamide hydrochloride (E370)	D125	712.4	1.02

N-[(1S,2R)-3-({[3,5-bis(methyloxy)phenyl]methyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]-3-cyclopentyl-5-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)benzamide hydrochloride (E371)	D125	636.4	0.90
3-cyclopentyl-N-[(1S,2R)-3-[[(3,5-dibromophenyl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-5-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)benzamide hydrochloride (E372)	D125	732.2	0.99
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-{(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[({3-[(trifluoromethyl)oxy]phenyl}methyl)amino]propyl} benzamide hydrochloride (E373)	D120	635.3	0.83
N-[(1S,2R)-3-({[3,5-bis(trifluoromethyl)phenyl] methyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E374)	D120	667.3	0.89
N-[(1S,2R)-3-({[3,5-bis(methyloxy)phenyl]methyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E375)	D120	611.4	0.77
N-[(1S,2R)-3-[[(3,5-dibromophenyl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E376)	D120	707.2	0.85
3-(ethyloxy)-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[({3-[(trifluoromethyl)oxy]phenyl}methyl)amino]propyl]-5-(2-oxo-1-pyrrolidinyl)benzamide hydrochloride (E377)	D126	586.2	0.82
N-[(1S,2R)-3-({[3,5-bis(trifluoromethyl)phenyl] methyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]-3-(ethyloxy)-5-(2-oxo-1-pyrrolidinyl)benzamide hydrochloride (E378)	D126	638.2	0.88
N-[(1S,2R)-3-({[3,5-bis(methyloxy)phenyl]methyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]-3-(ethyloxy)-5-(2-oxo-1-pyrrolidinyl)benzamide hydrochloride (E379)	D126	582.3	0.75
N-[(1S,2R)-3-[[(3,5-dibromophenyl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-3-(ethyloxy)-5-(2-oxo-1-pyrrolidinyl)benzamide hydrochloride (E380)	D126	658.0	0.83
3-cyclopentyl-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[({3-[(trifluoromethyl)oxy]phenyl}methyl)amino]propyl]-5-(2-oxo-1-pyrrolidinyl)benzamide hydrochloride (E381)	D122	610.3	0.92
N-[(1S,2R)-3-({[3,5-bis(trifluoromethyl)phenyl] methyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]-3-cyclopentyl-5-(2-oxo-1-pyrrolidinyl)benzamide hydrochloride (E382)	D122	662.3	0.99
N-[(1S,2R)-3-({[3,5-bis(methyloxy)phenyl]methyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]-3-cyclopentyl-5-(2-oxo-1-pyrrolidinyl)benzamide hydrochloride (E383)	D122	586.3	0.86
3-cyclopentyl-N-[(1S,2R)-3-[[(3,5-dibromophenyl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-5-(2-oxo-1-	D122	662.1	0.94

pyrrolidinyl)benzamide hydrochloride (E384)			
N-[(1S,2R)-3-({[3,5-bis(methyloxy)phenyl]methyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]-3-(ethylamino)-5-(2-oxo-1-pyrrolidinyl)benzamide hydrochloride (E385)	E66	561.3	0.73
N-[(1S,2R)-3-[[(3,5-dibromophenyl)methyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-3-(ethylamino)-5-(2-oxo-1-pyrrolidinyl)benzamide hydrochloride (E386)	E66	657.1	0.80
N-[(1S,2R)-3-({[3,5-bis(trifluoromethyl)phenyl] methyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxido-2-isothiazolidinyl)-5-(ethyloxy)benzamide hydrochloride (E387)	D127	674.2	0.88
N-[(1S,2R)-3-({[3,5-bis(methyloxy)phenyl]methyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxido-2-isothiazolidinyl)-5-(ethyloxy)benzamide hydrochloride (E388)	D127	598.3	0.76
N-[(1S,2R)-3-[[(3,5-dibromophenyl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxido-2-isothiazolidinyl)-5-(ethyloxy)benzamide hydrochloride (E389)	D127	694.1	0.84
3-(1,1-dioxido-2-isothiazolidinyl)-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-5-[(1-methylethyl)oxy]benzamide hydrochloride (E390)	D128	620.2	0.84
3-(1,1-dioxido-2-isothiazolidinyl)-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl} amino)-1-(phenylmethyl)propyl]-5-[(1-methylethyl)oxy]benzamide hydrochloride (E391)	D128	582.3	0.77
3-(1,1-dioxido-2-isothiazolidinyl)-N-{(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[({3-[(trifluoromethyl)oxy]phenyl}methyl)amino]propyl}-5-[(1-methylethyl)oxy]benzamide hydrochloride (E392)	D128	636.2	0.85
N-[(1S,2R)-3-({[3,5-bis(trifluoromethyl)phenyl] methyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxido-2-isothiazolidinyl)-5-[(1-methylethyl)oxy]benzamide hydrochloride (E393)	D128	688.2	0.91
N-[(1S,2R)-3-({[3,5-bis(trifluoromethyl)phenyl] methyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxido-2-isothiazolidinyl)-5-[(1-methylethyl)oxy]benzamide hydrochloride (E394)	D128	612.2	0.80
N-[(1S,2R)-3-[[(3,5-dibromophenyl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxido-2-isothiazolidinyl)-5-[(1-methylethyl)oxy]benzamide hydrochloride (E395)	D128	708.1	0.87
3-cyclopentyl-5-(1,1-dioxido-2-isothiazolidinyl)-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl] benzamide hydrochloride (E396)	D129	630.2	0.90
3-cyclopentyl-5-(1,1-dioxido-2-isothiazolidinyl)-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl} amino)-1-(phenylmethyl)propyl] benzamide hydrochloride (E397)	D129	592.3	0.84
3-cyclopentyl-5-(1,1-dioxido-2-isothiazolidinyl)-N-{(1S,2R)-2-	D129	646.3	0.91

hydroxy-1-(phenylmethyl)-3-[({3-[(trifluoromethyl)oxy]phenyl}methyl)amino]propyl} benzamide hydrochloride (E398)			
N-[(1S,2R)-3-({[3,5-bis(trifluoromethyl)phenyl] methyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]-3-cyclopentyl-5-(1,1-dioxido-2-isothiazolidinyl)benzamide hydrochloride (E399)	D129	698.3	0.98
N-[(1S,2R)-3-({[3,5-bis(methyloxy)phenyl]methyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]-3-cyclopentyl-5-(1,1-dioxido-2-isothiazolidinyl)benzamide hydrochloride (E400)	D129	622.3	0.86
3-cyclopentyl-N-[(1S,2R)-3-{[(3,5-dibromophenyl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-5-(1,1-dioxido-2-isothiazolidinyl)benzamide hydrochloride (E401)	D129	718.1	0.94
3-(1,1-dioxido-2-isothiazolidinyl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[({3-[(trifluoromethyl)oxy] phenyl}methyl)amino]propyl}benzamide hydrochloride (E402)	D130	621.3	0.80
N-[(1S,2R)-3-({[3,5-bis(trifluoromethyl)phenyl] methyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxido-2-isothiazolidinyl)-5-(ethylamino)benzamide hydrochloride (E403)	D130	673.3	0.86
N-[(1S,2R)-3-({[3,5-bis(methyloxy)phenyl]methyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxido-2-isothiazolidinyl)-5-(ethylamino)benzamide hydrochloride (E404)	D130	597.4	0.73
N-[(1S,2R)-3-{[(3,5-dibromophenyl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxido-2-isothiazolidinyl)-5-(ethylamino)benzamide hydrochloride (E405)	D130	693.2	0.82
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethyloxy)-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl] benzamide hydrochloride (E406)	D131	620.3	0.83
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethyloxy)-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl} amino)-1-(phenylmethyl)propyl] benzamide hydrochloride (E407)	D131	582.4	0.78
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethyloxy)-N-{(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[({3-[(trifluoromethyl)oxy]phenyl}methyl)amino]propyl} benzamide hydrochloride (E408)	D131	636.3	0.86
N-[(1S,2R)-3-({[3,5-bis(trifluoromethyl)phenyl] methyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethyloxy)benzamide hydrochloride (E409)	D131	668.3	0.93
N-[(1S,2R)-3-({[3,5-bis(methyloxy)phenyl]methyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethyloxy)benzamide hydrochloride (E410)	D131	612.3	0.79
N-[(1S,2R)-3-{[(3,5-dibromophenyl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-	D131	708.1	0.88

yl)-5-(ethyloxy)benzamide hydrochloride (E411)			
N-[(1S,2R)-3-[[1-(3-chlorophenyl)propyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E412)	D120	613.3	0.92
3-cyclopentyl-5-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-N-[(1S,2R)-2-hydroxy-3-[(1-methylbutyl)amino]-1-(phenylmethyl)propyl] benzamide hydrochloride (E413)	D125	556.6	0.92
N-[(1S,2R)-1-benzyl-2-hydroxy-3-(1,2,3,4-tetrahydronaphthalen-2-ylamino)propyl]-3-cyclopentyl-5-(2-oxopyrrolidin-1-yl)benzamide hydrochloride (E414)	D122	586.5	0.9
N-[(1S,2R)-1-benzyl-3-(2,3-dihydro-1H-inden-2-ylamino)-2-hydroxypropyl]-3-cyclopentyl-5-(2-oxopyrrolidin-1-yl)benzamide hydrochloride (E415)	D122	552.6	0.9
N-[(1S,2R)-1-benzyl-3-(2,3-dihydro-1H-inden-2-ylamino)-2-hydroxypropyl]-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E416)	D120	577.5	0.8
N-[(1S,2R)-1-benzyl-2-hydroxy-3-(1,2,3,4-tetrahydronaphthalen-2-ylamino)propyl]-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E417)	D120	591.5	0.8
N-[(1S,2R)-1-benzyl-2-hydroxy-3-[(7-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)amino]propyl]-3-cyclopentyl-5-(2-oxopyrrolidin-1-yl)benzamide hydrochloride (E418)	D122	596.6	0.9
N-[(1S,2R)-1-benzyl-3-[(3,5-dichlorobenzyl)amino]-2-hydroxypropyl]-3-cyclopentyl-5-(2-oxopyrrolidin-1-yl)benzamide (E419)	D122	594.5	2.5
N-[(1S,2R)-1-benzyl-3-[(3,5-dichlorobenzyl)amino]-2-hydroxypropyl]-3-(1,1-dioxidoisothiazolidin-2-yl)-5-ethoxybenzamide (E420)	D127	606.4	2.3
N-[(1S,2R)-1-benzyl-3-[(3,5-dichlorobenzyl)amino]-2-hydroxypropyl]-3-(1,1-dioxidoisothiazolidin-2-yl)-5-isopropoxybenzamide (E421)	D128	620.4	2.3
N-[(1S,2R)-1-benzyl-3-[(3,5-dichlorobenzyl)amino]-2-hydroxypropyl]-3-cyclopentyl-5-(1,1-dioxidoisothiazolidin-2-yl)benzamide (E422)	D129	630.4	2.5
N-[(1S,2R)-1-benzyl-3-[(3,5-dichlorobenzyl)amino]-2-hydroxypropyl]-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-ethoxybenzamide (E423)	D131	620.3	2.3
N-[(1S,2R)-1-benzyl-3-[(3,5-dichlorobenzyl)amino]-2-hydroxypropyl]-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-isopropoxybenzamide (E424)	D124	634.3	2.4
N-[(1S,2R)-1-benzyl-3-[(3,5-dichlorobenzyl)amino]-2-hydroxypropyl]-3-cyclopentyl-5-(1,1-dioxido-1,2-thiazinan-2-yl)benzamide (E425)	D125	644.4	2.6

N-[(1S,2R)-1-benzyl-3-[(3,5-dichlorobenzyl)amino]-2-hydroxypropyl]-3-(ethylamino)-5-(2-oxopyrrolidin-1-yl)benzamide hydrochloride (E426)	E66	568.8	2.2
N-[(1S,2R)-1-benzyl-3-[(3,5-dichlorobenzyl)amino]-2-hydroxypropyl]-3-(1,1-dioxidoisothiazolidin-2-yl)-5-(ethylamino)benzamide hydrochloride (E427)	D130	604.9	2.2

Examples 428-570 (E428-E570)

Examples E428-E570 were prepared in an analogous manner to Example 1 from the appropriate acid and amines indicated in the below table:

Example	Acid	Amine	$[M+H]^+$	RT (min)
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-3-[[1-(4-methylpentyl)cyclopropyl] amino]-1-(phenylmethyl)propyl] benzamide hydrochloride (E428)	A73	C73	585.6	0.90
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-3-[(1-ethylcyclopropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl] benzamide hydrochloride (E429)	A73	C74	529.5	0.73
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-3-[[1-(1-methylethyl)cyclopropyl] amino]-1-(phenylmethyl)propyl] benzamide hydrochloride (E430)	A73	C75	543.4	0.77
N-[(1S,2R)-3-(butylamino)-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E431)	A73	C76	517.4	0.75
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[(1-propyl cyclopropyl)amino]propyl]benzamide hydrochloride (E432)	A73	C77	543.5	0.79
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-3-[[1-(3-methylbutyl)cyclopropyl] amino]-1-(phenylmethyl)propyl] benzamide hydrochloride (E433)	A73	C78	571.6	0.88
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-3-[[1-(2-methylpropyl)cyclopropyl]amino]-1-(phenylmethyl)propyl] benzamide hydrochloride (E434)	A73	C79	557.5	0.84
N-[(1S,2R)-3-({1-[(3-chlorophenyl)methyl] cyclopropyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E435)	A73	C80	625.4	0.90
N-[(1S,2R)-1-benzyl-2-hydroxy-3-[(1-methylcyclohexyl)amino]propyl]-3-(1,1-dioxido-1,2-thiazinan-	A73	C81	557.5	0.78

2-yl)-5-(ethylamino)benzamide hydrochloride (E436)				
N-[(1S,2R)-1-benzyl-3-[(1S,2S,4R)-bicyclo[2.2.1]hept-2-ylamino]-2-hydroxypropyl]-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E437)	A73	C82	555.4	0.78
N-[(1S,2R)-1-benzyl-3-[(4,4-dimethylcyclohexyl) amino]-2-hydroxypropyl]-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E438)	A73	C83	571.3	0.82
N-((1S,2R)-1-benzyl-2-hydroxy-3-[[(1R)-1,2,2-trimethylpropyl]amino} propyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E439)	A73	C84	545.6	0.8
N-((1S,2R)-1-benzyl-2-hydroxy-3-[[(1S)-1,2,2-trimethylpropyl]amino} propyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E440)	A73	C85	545.6	0.81
N-[(1S,2R)-1-benzyl-3-[(2,2-dimethylcyclohexyl) amino]-2-hydroxypropyl]-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E441)	A73	C86	571.6	0.83
N-[(1S,2R)-1-benzyl-2-hydroxy-3-(pentylamino)propyl]-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E442)	A73	C87	531.5	0.84
N-[(1S,2R)-1-benzyl-3-(hexylamino)-2-hydroxypropyl]-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E443)	A73	C88	545.5	0.9
N-[(1S,2R)-1-benzyl-3-[(3,3-dimethylbutyl)amino]-2-hydroxypropyl]-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E444)	A73	C89	545.5	0.86
N-[(1S,2R)-1-benzyl-3-[(1,1-dimethylpropyl)amino]-2-hydroxypropyl]-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E445)	A73	C90	531.5	0.8
N-[(1S,2R)-1-benzyl-3-[(cyclopropylmethyl) amino]-2-hydroxypropyl]-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E446)	A73	C91	515.5	0.76
N-[(1S,2R)-1-benzyl-3-[(3,3-dimethylcyclopentyl) amino]-2-hydroxypropyl]-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E447)	A73	C92	557.6	0.81
N-[(1S,2R)-1-benzyl-3-(ethylamino)-2-hydroxypropyl]-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E448)	A73	C24	489.5	0.7
N-[(1S,2R)-1-benzyl-2-hydroxy-3-(methylamino)propyl]-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E449)	A73	C93	475.5	0.68
N-[(1S,2R)-1-benzyl-3-(cyclopropylamino)-2-hydroxypropyl]-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E450)	A73	C26	501.5	0.71

N-[(1S,2R)-3-(1-adamantylamino)-1-benzyl-2-hydroxypropyl]-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E451)	A73	C94	595.6	0.85
N-[(1S,2R)-1-benzyl-2-hydroxy-3-(1,2,3,4-tetrahydronaphthalen-1-ylamino)propyl]-3-cyclopentyl-5-(2-oxopyrrolidin-1-yl)benzamide hydrochloride (E452)	A107	C95	566.5	0.91
N-[(1S,2R)-1-benzyl-2-hydroxy-3-(1,2,3,4-tetrahydronaphthalen-1-ylamino)propyl]-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E453)	A73	C95	591.5	0.81
N-((1S,2R)-1-benzyl-2-hydroxy-3-{[2-(3-methoxyphenyl)ethyl] amino}propyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E454)	A73	C96	595.6	0.79
N-((1S,2R)-1-benzyl-2-hydroxy-3-{[2-(4-methoxyphenyl)ethyl] amino}propyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E455)	A73	C97	595.6	0.78
N-((1S,2R)-1-benzyl-2-hydroxy-3-{[2-(2-methoxyphenyl)ethyl] amino}propyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E458)	A73	C98	595.4	0.79
N-((1S,2R)-1-benzyl-3-{[2-(2-chlorophenyl)ethyl]amino}-2-hydroxypropyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E457)	A73	C99	599.5	0.81
N-((1S,2R)-1-benzyl-3-{[2-(3-chlorophenyl)ethyl]amino}-2-hydroxypropyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E458)	A73	C100	599.5	0.82
N-((1S,2R)-1-benzyl-3-{[2-(4-chlorophenyl)ethyl]amino}-2-hydroxypropyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E459)	A73	C101	599.5	0.82
N-((1S,2R)-1-benzyl-2-hydroxy-3-{[2-(4-methylphenyl) ethyl]amino}propyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E460)	A73	C102	579.5	2.02
N-((1S,2R)-1-benzyl-2-hydroxy-3-{[2-(2-methylphenyl) ethyl]amino}propyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E461)	A73	C103	580.5	2.02
N-((1S,2R)-1-benzyl-3-{[2-(3,4-dichlorophenyl)ethyl] amino}-2-hydroxypropyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E462)	A73	C104	633.4	2.15
N-((1S,2R)-1-benzyl-3-{[2-(2,4-dichlorophenyl)ethyl] amino}-2-hydroxypropyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E463)	A73	C105	633.4	0.86

N-((1S,2R)-1-benzyl-3-[[2-(3,5-dimethoxyphenyl)ethyl] amino]-2-hydroxypropyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E464)	A73	C106	625.5	0.8
N-((1S,2R)-1-benzyl-3-[[2-(2,3-dimethoxyphenyl)ethyl] amino]-2-hydroxypropyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E465)	A73	C107	625.4	0.79
N-[(1S,2R)-1-benzyl-3-(benzylamino)-2-hydroxypropyl]-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E466)	A73	C108	551.5	0.75
N-((1S,2R)-1-benzyl-2-hydroxy-3-[(2-phenylethyl)amino]propyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E467)	A73	C109	565.4	0.79
N-((1S,2R)-1-benzyl-3-[(1-ethylcyclohexyl)amino]-2-hydroxypropyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E468)	A73	C110	571.6	0.82
N-((1S,2R)-1-benzyl-2-hydroxy-3-[(1-methylcyclopentyl)amino]propyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E469)	A73	C111	544.5	1.81
N-((1S,2R)-1-benzyl-2-hydroxy-3-[(1-propylcyclopentyl)amino]propyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E470)	A73	C112	571.7	0.83
N-((1S,2R)-1-benzyl-2-hydroxy-3-[(1-propylcyclohexyl)amino] propyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E471)	A73	C113	585.6	0.88
N-((1S,2R)-1-benzyl-3-[[2-(3-chlorophenyl)-1,1-dimethylethyl] amino]-2-hydroxypropyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E472)	A73	C114	627.5	0.92
3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-3-[(3-methoxybenzyl)amino]-1-(pyridin-3-ylmethyl)propyl] benzamide hydrochloride (E473)	A73	C115	582.0	1.75
3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-3-[(3-methoxybenzyl)amino]-1-(1,3-thiazol-2-ylmethyl)propyl] benzamide hydrochloride (E474)	A73	C116	588.0	1.91
N-[(1S,2R)-3-(cyclohexylamino)-2-hydroxy-1-(1,3-thiazol-2-ylmethyl)propyl]-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E475)	A73	C117	550.0	1.88
N-[(1S,2R)-3-[(1,5-dimethylhexyl)amino]-2-hydroxy-1-(1,3-thiazol-2-ylmethyl)propyl]-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E476)	A73	C118	580.1	2.21
3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)-N-[(1S,2R)-1-(2-furylmethyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]	A73	C119	571.0	2.02

propyl]benzamide hydrochloride (E477)				
N-[(1S,2R)-3-(cyclohexylamino)-1-(2-furylmethyl)-2-hydroxypropyl]-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E478)	A73	C120	533.0	2.01
N-[(1S,2R)-3-[(1,5-dimethylhexyl)amino]-1-(2-furylmethyl)-2-hydroxypropyl]-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E479)	A73	C121	583.1	2.32
3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)-N-[(1S,2R)-1-(2-furylmethyl)-2-hydroxy-3-[(1,1,5-trimethylhexyl)amino] propyl]benzamide hydrochloride (E480)	A73	C122	577.2	2.39
3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)-N-[(1S)-2-hydroxy-3-[(3-methoxybenzyl)amino]-1-(pyridin-2-ylmethyl)propyl] benzamide (E481)	A73	C123	581.9	1.84
N-[(1S,2R)-1-[(4-chlorophenyl)methyl]-3-(cyclohexylamino)-2-hydroxypropyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E482)	A73	C124	577.4	0.82
N-[(1S,2R)-1-[(4-chlorophenyl)methyl]-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E483)	A73	C125	615.4	0.82
3-cyclopentyl-N-[(1S,2R)-1-[(3,5-difluorophenyl)methyl]-2-hydroxy-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-5-(2-oxo-1-pyrrolidinyl)benzamide hydrochloride (E484)	A107	C126	630.4	0.94
N-[(1S,2R)-1-[(3,5-difluorophenyl)methyl]-2-hydroxy-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E485)	A73	C126	655.4	0.85
N-[(1S,2R)-1-[(3,5-difluorophenyl)methyl]-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E486)	A73	C127	617.3	0.8
N-[(1S,2R)-1-[(3,5-difluorophenyl)methyl]-3-[(1,5-dimethylhexyl)amino]-2-hydroxypropyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E487)	A73	C128	609.5	0.9
N-[(1S,2R)-3-(cyclohexylamino)-1-[(3,5-difluorophenyl)methyl]-2-hydroxypropyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E488)	A73	C129	579.4	0.8
N-[(1S,2R)-1-[(3,5-difluorophenyl)methyl]-2-hydroxy-3-[(1,1,5-trimethylhexyl)amino] propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E489)	A73	C130	623.6	0.93

N-[(1S,2R)-1-[(3,4-difluorophenyl)methyl]-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E490)	A73	C131	617.5	0.81
N-[(1S,2R)-3-(cyclohexylamino)-1-[(3,4-difluorophenyl)methyl]-2-hydroxypropyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E491)	A73	C132	579.5	0.79
N-[(1S,2R)-1-[(3,4-difluorophenyl)methyl]-2-hydroxy-3-[(1,1,5-trimethylhexyl)amino] propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E492)	A73	C133	623.5	0.92
N-[(1S,2R)-1-[(3-chlorophenyl)methyl]-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E493)	A73	C134	616.3	0.83
N-[(1S,2R)-1-[(3-chlorophenyl)methyl]-3-(cyclohexylamino)-2-hydroxypropyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E494)	A73	C135	578.3	0.83
N-[(1S,2R)-1-[(2-chlorophenyl)methyl]-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E495)	A73	C136	616.4	0.86
N-[(1S,2R)-1-[(2-chlorophenyl)methyl]-3-(cyclohexylamino)-2-hydroxypropyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E496)	A73	C137	578.4	0.85
N-[(1S,2R)-1-[(2-chlorophenyl)methyl]-3-[(1,5-dimethylhexyl)amino]-2-hydroxypropyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E497)	A73	C138	608.5	0.98
N-[(1S,2R)-1-[(3-chlorophenyl)methyl]-3-[(1,5-dimethylhexyl)amino]-2-hydroxypropyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E498)	A73	C139	608.5	1
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-1-[(3-fluorophenyl)methyl]-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)propyl]benzamide hydrochloride (E499)	A73	C140	599.4	0.82
N-[(1S,2R)-3-[(1,5-dimethylhexyl)amino]-1-[(3-fluorophenyl) methyl]-2-hydroxypropyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E500)	A73	C141	591.6	0.95
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}	A73	C142	587.4	0.79

amino)-1-(2-thienylmethyl)propyl] benzamide hydrochloride (E501)				
N-[(1S,2R)-3-[(1,5-dimethylhexyl)amino]-2-hydroxy-1-(2-thienylmethyl)propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E502)	A73	C143	579.5	0.92
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl} amino)-1-(1H-pyrazol-1-ylmethyl)propyl] benzamide hydrochloride (E503)	A73	C144	571.4	0.65
N-[(1S,2R)-3-[(1,5-dimethylhexyl)amino]-2-hydroxy-1-(1H-pyrazol-1-ylmethyl)propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E504)	A73	C145	563.5	0.8
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl} amino)-1-(3-thienylmethyl)propyl] benzamide hydrochloride (E505)	A73	C146	587.5	0.76
N-[(1S,2R)-3-[(1,5-dimethylhexyl)amino]-2-hydroxy-1-(3-thienylmethyl)propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E506)	A73	C147	579.5	0.85
formic acid - N-[(1S,2R)-1-benzyl-3-[(1,1-dimethylhexyl)amino]-2-hydroxypropyl]-3-(ethylamino)-5-(2-oxopyrrolidin-1-yl)benzamide (1:1) (E507)	A31	C48	523.3	2.76
formic acid - N-[(1S,2R)-1-benzyl-2-hydroxy-3-({1-methyl-1-[3-(trifluoromethyl)phenyl] ethyl}amino)propyl]-3-(ethylamino)-5-(2-oxopyrrolidin-1-yl)benzamide (1:1) (E508)	A31	C40	597.3	3.03
formic acid - N-((1S,2R)-1-benzyl-2-hydroxy-3-{[2-methyl-5-(trifluoromethyl)benzyl] amino}propyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E509)	A73	C49	633.2	2.84
formic acid - N-[(1S,2R)-1-benzyl-3-[(1S)-2,3-dihydro-1H-inden-1-ylamino]-2-hydroxypropyl]-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E510)	A73	C50	577.2	2.68
formic acid - N-((1S,2R)-1-benzyl-2-hydroxy-3-[[(1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]amino}propyl)-3-(ethylamino)-5-(2-oxopyrrolidin-1-yl)benzamide (1:1) (E511)	A31	C51	543.1	2.55
N-[(1S,2R)-1-benzyl-2-hydroxy-3-[(6-methoxy-2,3-dihydro-1H-inden-1-yl)amino]propyl]-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (E512)	A73	C52	607.5	2.55
formic acid - N-((1S,2R)-1-benzyl-2-hydroxy-3-[[(1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]amino}propyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E513)	A73	C53	593.4	2.40
N-((1S,2R)-1-benzyl-2-hydroxy-3-[[2-(isobutylthio)-1,1-dimethylethyl]amino} propyl)-3-(ethylamino)-5-(2-	A31	C54	555.4	2.62

oxopyrrolidin-1-yl)benzamide (E514)				
N-[(1S,2R)-1-benzyl-3-[(1,1-dimethyl-2-phenoxyethyl)amino]-2-hydroxypropyl]-3-(ethylamino)-5-(2-oxopyrrolidin-1-yl)benzamide (E515)	A31	C55	559.4	2.56
N-((1S,2R)-1-benzyl-3-[[2-(benzyloxy)-1,1-dimethylethyl]amino}-2-hydroxypropyl)-3-(ethylamino)-5-(2-oxopyrrolidin-1-yl)benzamide (E516)	A31	C56	573.5	2.58
N-[(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxyphenyl)amino] propyl]-3-(ethylamino)-5-(2-oxopyrrolidin-1-yl)benzamide (E517)	A31	C57	517.4	2.92
formic acid - N-[(1S,2R)-1-benzyl-2-hydroxy-3-({2-[3-(trifluoromethyl)phenyl] ethyl}amino)propyl]-3-(ethylamino)-5-(2-oxopyrrolidin-1-yl)benzamide (1:1) (E518)	A31	C58	583.4	2.62
formic acid - N-[(1S,2R)-1-benzyl-3-[(1,1-dimethyl-2-phenylethyl)amino]-2-hydroxypropyl]-3-(ethylamino)-5-(2-oxopyrrolidin-1-yl)benzamide (1:1) (E519)	A31	C59	543.5	2.55
formic acid - N-((1S,2R)-1-benzyl-2-hydroxy-3-[[2-(1-naphthyl)ethyl]amino} propyl)-3-(ethylamino)-5-(2-oxopyrrolidin-1-yl)benzamide (1:1) (E520)	A31	C60	565.5	2.63
formic acid - N-((1S,2R)-1-benzyl-2-hydroxy-3-[[2-(3-methoxyphenyl)-1,1-dimethylethyl]amino} propyl)-3-(ethylamino)-5-(2-oxopyrrolidin-1-yl)benzamide (1:1) (E521)	A31	C61	573.5	2.57
N-[(1S,2R)-3-anilino-1-benzyl-2-hydroxypropyl]-3-(ethylamino)-5-(2-oxopyrrolidin-1-yl)benzamide (E522)	A31	C62	487.4	2.90
N-((1S,2R)-1-benzyl-2-hydroxy-3-[[1-(3-methoxyphenyl) cyclopropyl]amino}propyl)-3-(ethylamino)-5-(2-oxopyrrolidin-1-yl)benzamide (E523)	A31	C63	557.4	2.47
formic acid - N-[(1S,2R)-1-benzyl-3-[(cyclohexylmethyl)amino]-2-hydroxypropyl]-3-(ethylamino)-5-(2-oxopyrrolidin-1-yl)benzamide (1:1) (E524)	A31	C64	507.5	2.48
formic acid - N-[(1S,2R)-1-benzyl-2-hydroxy-3-[(tetrahydro-2H-pyran-4-ylmethyl)amino]propyl]-3-(ethylamino)-5-(2-oxopyrrolidin-1-yl)benzamide (1:1) (E525)	A31	C65	509.4	2.15
N-[(1S,2R)-1-benzyl-2-hydroxy-3-(tetrahydro-2H-thiopyran-4-ylamino)propyl]-3-(ethylamino)-5-(2-oxopyrrolidin-1-yl)benzamide (E526)	A31	C66	511.4	2.30
formic acid - N-[(1S,2R)-1-benzyl-2-hydroxy-3-(isopropylamino)propyl]-3-ethyl-7-(2-oxopyrrolidin-1-yl)-1H-indole-5-carboxamide (1:1) (E527)	A141	C28	478.5	2.04
formic acid - N-[(1S,2R)-1-benzyl-3-(cyclohexylamino)-2-hydroxypropyl]-3-ethyl-7-(2-oxopyrrolidin-1-yl)-1H-indole-5-carboxamide (1:1) (E528)	A141	C1	517.5	2.17
formic acid - N-[(1S,2R)-1-benzyl-2-hydroxy-3-[(1,1,5-	A141	C5	561.5	2.56

trimethylhexyl)amino] propyl}-3-ethyl-7-(2-oxopyrrolidin-1-yl)-1H-indole-5-carboxamide (1:1) (E529)				
formic acid - N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino] propyl}-7-(1,1-dioxidoisothiazolidin-2-yl)-3-ethyl-1H-indole-5-carboxamide (1:1) (E530)	A144	C14	591.4	2.36
N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(1,1,5-trimethylhexyl)amino] propyl}-7-(1,1-dioxidoisothiazolidin-2-yl)-3-ethyl-1H-indole-5-carboxamide (E531)	A144	C5	597.5	2.72
formic acid - N-[(1S,2R)-1-benzyl-3-(cyclohexylamino)-2-hydroxypropyl]-7-(1,1-dioxidoisothiazolidin-2-yl)-3-ethyl-1H-indole-5-carboxamide (1:1) (E532)	A144	C1	554.5	2.33
formic acid - N-{(1S,2R)-1-benzyl-2-hydroxy-3-(isopropylamino)propyl}-7-(1,1-dioxidoisothiazolidin-2-yl)-3-ethyl-1H-indole-5-carboxamide (1:1) (E533)	A144	C28	514.4	2.14
formic acid - N-((1S,2R)-1-benzyl-2-hydroxy-3-{[1-(3-methoxyphenyl)-1-methylethyl]amino}propyl)-7-(1,1-dioxidoisothiazolidin-2-yl)-3-ethyl-1H-indole-5-carboxamide (1:1) (E534)	A144	C15	619.4	2.45
formic acid - N-[(1S,2R)-1-benzyl-2-hydroxy-3-({1-methyl-1-[3-(trifluoromethyl)phenyl] ethyl}amino)propyl]-7-(1,1-dioxidoisothiazolidin-2-yl)-3-ethyl-1H-indole-5-carboxamide (1:1) (E535)	A144	C40	657.4	2.62
N-[(1S,2R)-1-benzyl-3-(sec-butylamino)-2-hydroxypropyl]-3-(ethylamino)-5-(2-oxopyrrolidin-1-yl)benzamide (E536)	A31	C67	467.3	2.4
N-{(1S,2R)-1-benzyl-3-[(4-tert-butylcyclohexyl)amino]-2-hydroxypropyl}-3-(ethylamino)-5-(2-oxopyrrolidin-1-yl)benzamide (E537)	A31	C68	549.3	2.81
N-{(1S,2R)-1-benzyl-3-[(1S)-2,3-dihydro-1H-inden-1-ylamino]-2-hydroxypropyl}-3-(ethylamino)-5-(2-oxopyrrolidin-1-yl)benzamide (E538)	A31	C50	527.2	2.56
N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(2-isobutoxy-1,1-dimethylethyl)amino] propyl}-3-(ethylamino)-5-(2-oxopyrrolidin-1-yl)benzamide (E539)	A31	C70	539.2	2.64
N-[(1S,2R)-1-benzyl-3-({1,1-dimethyl-2-[(2-methylprop-2-en-1-yl)oxy]ethyl}amino)-2-hydroxypropyl]-3-(ethylamino)-5-(2-oxopyrrolidin-1-yl)benzamide (E540)	A31	C71	537.2	2.61
N-{(1S,2R)-1-benzyl-3-[(1R)-2,3-dihydro-1H-inden-1-ylamino]-2-hydroxypropyl}-3-(ethylamino)-5-(2-oxopyrrolidin-1-yl)benzamide (E541)	A31	C72	527.2	2.54
N-{(1S,2R)-1-benzyl-3-[(1R)-2,3-dihydro-1H-inden-1-ylamino]-2-hydroxypropyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (E542)	A73	C72	577.2	2.64

N-[(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino] propyl]-3-[ethyl(methyl)amino]-5-(2-oxopyrrolidin-1-yl)benzamide (E543)	A128	C14	548.5	2.49
N-((1S,2R)-1-benzyl-2-hydroxy-3-[[1-(3-methoxyphenyl)-1-methylethyl]amino}propyl)-3-[ethyl(methyl)amino]-5-(2-oxopyrrolidin-1-yl)benzamide (E544)	A128	C15	574.5	2.58
formic acid - N-((1S,2R)-1-benzyl-2-hydroxy-3-[[1-(3-methoxyphenyl) cyclohexyl]amino}propyl)-3-(ethylamino)-5-(2-oxopyrrolidin-1-yl)benzamide (1:1) (E545)	A31	C41	599.5	2.60
formic acid - N-((1S,2R)-1-benzyl-2-hydroxy-3-[[1-(3-methoxyphenyl) cyclohexyl]amino}propyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E546)	A73	C41	649.5	2.70
formic acid - N-((1S,2R)-1-benzyl-2-hydroxy-3-[[(1-methyl-1H-pyrazol-4-yl)methyl]amino}propyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E547)	A73	C42	555.3	2.35
formic acid - N-((1S,2R)-1-benzyl-2-hydroxy-3-[[(1-methyl-1H-pyrazol-4-yl)methyl]amino}propyl)-3-(ethylamino)-5-(2-oxopyrrolidin-1-yl)benzamide (1:1) (E548)	A31	C42	505.3	2.27
formic acid - N-[(1S,2R)-1-benzyl-3-(cyclohexylamino)-2-hydroxypropyl]-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E549)	A73	C1	543.4	2.45
formic acid - N-[(1S,2R)-1-benzyl-2-hydroxy-3-(tetrahydro-2H-pyran-4-ylamino)propyl]-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E550)	A73	C43	545.4	2.28
formic acid - N-[(1S,2R)-1-benzyl-3-(cyclohexylamino)-2-hydroxypropyl]-3-cyclopentyl-5-(1,1-dioxido-1,2-thiazinan-2-yl)benzamide (1:1) (E551)	A126	C1	568.3	2.80
formic acid - N-[(1S,2R)-1-benzyl-2-hydroxy-3-(tetrahydro-2H-pyran-4-ylamino)propyl]-3-cyclopentyl-5-(1,1-dioxido-1,2-thiazinan-2-yl)benzamide (1:1) (E552)	A126	C43	570.3	2.61
formic acid - N-[(1S,2R)-1-benzyl-3-[(3,3-dimethylbutyl) amino]-2-hydroxypropyl]-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)-2-fluorobenzamide (1:1) (E553)	A119	C44	563.4	2.53
N-[(1S,2R)-1-benzyl-2-hydroxy-3-[(1,1,3,3-tetramethylbutyl)amino] propyl]-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)-2-fluorobenzamide (E554)	A119	C45	591.4	2.63
formic acid - N-[(1S,2R)-1-benzyl-3-[(1,3-dimethylbutyl) amino]-2-hydroxypropyl]-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)-2-fluorobenzamide (1:1) (E555)	A119	C46	563.4	2.50
formic acid - N-[(1S,2R)-1-benzyl-3-(cyclohexylamino)-2-hydroxypropyl]-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(isopropylamino) benzamide (1:1) (E556)	A127	C1	557.4	2.35
formic acid - N-[(1S,2R)-1-benzyl-2-hydroxy-3-	A127	C28	517.4	2.20

(isopropylamino)propyl]-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(isopropylamino) benzamide (1:1) (E557)				
formic acid - N-[(1S,2R)-1-benzyl-2-hydroxy-3-({1-methyl-1-[3-(trifluoromethyl)phenyl] ethyl}amino)propyl]-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(isopropylamino) benzamide (1:1) (E558)	A127	C40	681.4	2.70
formic acid - N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino] propyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(isopropylamino) benzamide (1:1) (E559)	A127	C14	595.4	2.41
N-((1S,2R)-1-benzyl-2-hydroxy-3-{[3-(trifluoromethyl)benzyl] amino}propyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(isopropylamino) benzamide (E560)	A127	C16	633.4	2.66
formic acid - N-[(1S,2R)-1-benzyl-2-hydroxy-3-[(1,1,5-trimethylhexyl)amino] propyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(isopropylamino) benzamide (1:1) (E561)	A127	C5	601.5	2.80
formic acid - N-((1S,2R)-1-benzyl-3-[[4-fluoro-3-(trifluoromethyl)benzyl] amino}-2-hydroxypropyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)-2-fluorobenzamide (1:1) (E562)	A119	C47	655.4	2.50
formic acid - 3-(ethylamino)-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-5-(2-oxo-1-piperidinyl)benzamide (1:1) (E563)	A59	C14	545.2	2.79
formic acid - N-[(1S,2R)-3-[(1,5-dimethylhexyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-3-(ethylamino)-5-(2-oxo-1-piperidinyl)benzamide (1:1) (E564)	A59	C20	537.3	2.81
3-(ethylamino)-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-5-(2-oxo-1-piperidinyl)benzamide (E565)	A59	C16	583.2	2.69
formic acid - N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-3-(2-oxo-1-piperidinyl)-5-propylbenzamide (1:1) (E566)	A116	C14	544.3	2.74
formic acid - N-[(1S,2R)-3-[(1,5-dimethylhexyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-3-(2-oxo-1-piperidinyl)-5-propylbenzamide (1:1) (E567)	A116	C20	536.3	3.01
N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-3-(2-oxo-1-piperidinyl)-5-propylbenzamide (E568)	A116	C16	582.2	2.88
N-[(1S,2R)-3-{[(1S)-2-(cyclohexylamino)-1-methyl-2-oxoethyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-3-(2-oxo-1-piperidinyl)-5-propylbenzamide (E569)	A116	C8	577.3	2.76
3-(1,1-dioxido-2-isothiazolidinyl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[(1,1,5-trimethylhexyl)amino] propyl}benzamide (E570)	A70	C5	573.5	2.67

Examples 571-572 (E571-E572)

The following compounds were prepared in an analogous manner to Example 183 from the appropriate amine and the appropriate aldehyde:

Example	Precursor	[M+H]+	RT (min)
formic acid - 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-(ethylamino)-*N*-[(1*S*,2*R*)-2-hydroxy-3-({[1-(1-methylethyl)-1*H*-pyrazol-4-yl]methyl}amino)-1-(phenylmethyl)propyl]benzamide (1:1) (E571)	D120	583.5	2.24
formic acid - 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-(ethylamino)-*N*-[(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-({[1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-4-yl]methyl}amino)propyl] benzamide (1:1) (E572)	D120	623.4	2.28

Examples 573-695 (E573-E695)

Examples E573-695 were prepared in an analogous manner to Example 1 from the appropriate acid and amines indicated in the below table:

Example	Acid	Amine	$[M+H]^+$	RT (min)
formic acid - 5-(ethylamino)-2-fluoro-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-3-(2-oxo-1-pyrrolidinyl)benzamide (1:1) (E573)	A118	C14	549.3	2.42
3-(ethyloxy)-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(trifluoromethyl)phenyl] ethyl}amino)-1-(phenylmethyl)propyl]-5-(2-oxo-1-pyrrolidinyl)benzamide (E574)	A11	C40	598.4	2.76
3-(1,1-dioxido-2-isothiazolidinyl)-5-(ethyloxy)-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(trifluoromethyl)phenyl] ethyl}amino)-1-(phenylmethyl)propyl] benzamide (E575)	A18	C40	634.3	2.78
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(trifluoromethyl)phenyl] ethyl}amino)-1-(phenylmethyl)propyl] benzamide (E576)	A73	C40	647.4	2.78
1-ethyl-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(trifluoromethyl)phenyl] ethyl}amino)-1-(phenylmethyl)propyl]-4-(2-oxo-1-pyrrolidinyl)-1H-indole-6-carboxamide (E577)	A140	C40	621.4	2.75
3-(ethyloxy)-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(methyloxy)phenyl]ethyl}amino)-1-(phenylmethyl)propyl]-5-(2-oxo-1-pyrrolidinyl)benzamide (E578)	A11	C15	560.4	2.62
1-ethyl-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-	A140	C15	583.4	2.61

(methyloxy)phenyl]ethyl}amino)-1-(phenylmethyl)propyl]-4-(2-oxo-1-pyrrolidinyl)-1H-indole-6-carboxamide (E579)				
3-ethyl-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(trifluoromethyl)phenyl] ethyl}amino)-1-(phenylmethyl)propyl]-7-(2-oxo-1-pyrrolidinyl)-1H-indole-5-carboxamide (E580)	A141	C40	621.4	2.81
3-(1,1-dioxido-2-isothiazolidinyl)-5-(ethyloxy)-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(methyloxy)phenyl]ethyl}amino)-1-(phenylmethyl)propyl] benzamide (E581)	A18	C15	596.5	2.58
3-ethyl-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(methyloxy)phenyl]ethyl}amino)-1-(phenylmethyl)propyl]-7-(2-oxo-1-pyrrolidinyl)-1H-indole-5-carboxamide (E582)	A141	C15	583.5	2.62
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-2-fluoro-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl] methyl}amino)-1-(phenylmethyl)propyl] benzamide (E583)	A119	C14	599.4	2.27
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-2-fluoro-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl] benzamide (E584)	A119	C16	637.4	2.48
3-(1,1-dioxido-2-isothiazolidinyl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(trifluoromethyl)phenyl] ethyl}amino)-1-(phenylmethyl)propyl] benzamide (E585)	A70	C40	633.3	2.73
3-(1,1-dioxido-2-isothiazolidinyl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(methyloxy)phenyl]ethyl}amino)-1-(phenylmethyl)propyl] benzamide (E586)	A70	C15	595.3	2.57
5-(ethylamino)-2-fluoro-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino) propyl]-3-(2-oxo-1-pyrrolidinyl)benzamide (E587)	A118	C16	587.3	2.60
2-fluoro-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-3-(2-oxo-1-pyrrolidinyl)-5-propylbenzamide (E588)	A120	C14	548.3	2.64
2-fluoro-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-3-(2-oxo-1-pyrrolidinyl)-5-propylbenzamide (E589)	A120	C16	586.3	2.79
N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-3-(2-oxo-5-phenyl-1-piperidinyl)-5-propylbenzamide (E590)	A121	C14	620.5	3.02
N-[(1S,2R)-2-hydroxy-3-[(1-methylethyl)amino]-1-(phenylmethyl)propyl]-3-(2-oxo-5-phenyl-1-piperidinyl)-5-propylbenzamide (E591)	A121	C28	542.4	2.88
N-[(1S,2R)-3-(cyclohexylamino)-2-hydroxy-1-(phenylmethyl)propyl]-3-(2-oxo-5-phenyl-1-piperidinyl)-5-propylbenzamide (E592)	A121	C1	582.6	2.99

5-(ethylamino)-2-fluoro-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(trifluoromethyl)phenyl] ethyl}amino)-1-(phenylmethyl) propyl]-3-(2-oxo-1-pyrrolidinyl)benzamide (E593)	A118	C40	615.3	2.61
5-(ethylamino)-2-fluoro-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[(1,1,5-trimethylhexyl)amino] propyl]-3-(2-oxo-1-pyrrolidinyl)benzamide (E594)	A118	C5	555.4	2.71
N-[(1S,2R)-3-(cyclohexylamino)-2-hydroxy-1-(phenylmethyl)propyl]-5-(ethylamino)-2-fluoro-3-(2-oxo-1-pyrrolidinyl)benzamide (E595)	A118	C1	511.3	2.25
5-(ethylamino)-2-fluoro-N-[(1S,2R)-2-hydroxy-3-[(1-methylethyl)amino]-1-(phenylmethyl)propyl]-3-(2-oxo-1-pyrrolidinyl)benzamide (E596)	A118	C28	471.3	2.05
5-(ethylamino)-2-fluoro-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(methyloxy)phenyl]ethyl}amino)-1-(phenylmethyl)propyl]-3-(2-oxo-1-pyrrolidinyl)benzamide (E597)	A118	C15	577.4	2.42
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-2-fluoro-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[(1,1,5-trimethylhexyl)amino] propyl]benzamide (E598)	A119	C5	605.4	2.67
N-[(1S,2R)-3-(cyclohexylamino)-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-2-fluorobenzamide (E599)	A119	C1	561.4	2.42
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-2-fluoro-N-[(1S,2R)-2-hydroxy-3-[(1-methylethyl)amino]-1-(phenylmethyl)propyl] benzamide (E600)	A119	C28	521.3	2.20
4-(1,1-dioxido-2-isothiazolidinyl)-1-ethyl-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-1H-indazole-6-carboxamide (E601)	A153	C14	592.3	2.39
4-(1,1-dioxido-2-isothiazolidinyl)-1-ethyl-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-1H-indazole-6-carboxamide (E602)	A153	C16	630.3	2.58
4-(1,1-dioxido-2-isothiazolidinyl)-1-ethyl-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(methyloxy)phenyl]ethyl}amino)-1-(phenylmethyl)propyl]-1H-indazole-6-carboxamide (E603)	A153	C15	620.3	2.46
4-(1,1-dioxido-2-isothiazolidinyl)-1-ethyl-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(trifluoromethyl)phenyl] ethyl}amino)-1-(phenylmethyl)propyl]-1H-indazole-6-carboxamide (E604)	A153	C40	658.3	2.65
4-(1,1-dioxido-2-isothiazolidinyl)-1-ethyl-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[(1,1,5-trimethylhexyl)amino] propyl]-1H-indazole-6-carboxamide (E605)	A153	C5	598.5	2.47
N-[(1S,2R)-3-(cyclohexylamino)-2-hydroxy-1-(phenylmethyl)propyl]-4-(1,1-dioxido-2-isothiazolidinyl)-1-ethyl-1H-indazole-6-carboxamide (E606)	A153	C1	554.4	2.08

4-(1,1-dioxido-2-isothiazolidinyl)-1-ethyl-N-[(1S,2R)-2-hydroxy-3-[(1-methylethyl)amino]-1-(phenylmethyl)propyl]-1H-indazole-6-carboxamide (E607)	A153	C28	514.4	1.91
3-ethyl-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl] methyl}amino)-1-(phenylmethyl)propyl]-1-methyl-7-(2-oxo-1-pyrrolidinyl)-1H-indole-5-carboxamide (E608)	A142	C14	569.5	2.38
3-ethyl-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(methyloxy) phenyl]ethyl}amino)-1-(phenylmethyl)propyl]-1-methyl-7-(2-oxo-1-pyrrolidinyl)-1H-indole-5-carboxamide (E609)	A142	C15	597.5	2.45
3-ethyl-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(trifluoromethyl)phenyl] ethyl}amino)-1-(phenylmethyl)propyl]-1-methyl-7-(2-oxo-1-pyrrolidinyl)-1H-indole-5-carboxamide (E610)	A142	C40	635.4	2.71
N-[(1S,2R)-3-(cyclohexylamino)-2-hydroxy-1-(phenylmethyl)propyl]-3-ethyl-1-methyl-7-(2-oxo-1-pyrrolidinyl)-1H-indole-5-carboxamide (E611)	A142	C1	531.5	2.33
3-ethyl-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[(1,1,5-trimethylhexyl)amino] propyl]-1-methyl-7-(2-oxo-1-pyrrolidinyl)-1H-indole-5-carboxamide (E612)	A142	C5	575.4	2.80
3-ethyl-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[(1,1,5-trimethylhexyl)amino] propyl]-1-methyl-7-(2-oxo-1-pyrrolidinyl)-1H-indole-5-carboxamide formate salt (1:1) (E613)	A122	C5	591.5	2.60
formic acid - 3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[(1,1,5-trimethylhexyl)amino] propyl]benzamide (1:1) (E614)	A73	C5	587.6	2.61
N-[(1S,2R)-3-(cyclohexylamino)-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxido-2-isothiazolidinyl)-5-(ethylamino)-2-fluorobenzamide (E615)	A122	C1	547.5	2.08
7-(1,1-dioxido-2-isothiazolidinyl)-3-ethyl-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-1-methyl-1H-indole-5-carboxamide (E616)	A146	C14	605.5	2.49
7-(1,1-dioxido-2-isothiazolidinyl)-3-ethyl-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-1-methyl-1H-indole-5-carboxamide (E617)	A146	C16	643.4	2.68
7-(1,1-dioxido-2-isothiazolidinyl)-3-ethyl-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(methyloxy)phenyl]ethyl}amino)-1-(phenylmethyl)propyl]-1-methyl-1H-indole-5-carboxamide (E618)	A146	C15	633.4	2.57
7-(1,1-dioxido-2-isothiazolidinyl)-3-ethyl-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(trifluoromethyl)phenyl]	A146	C40	671.4	2.74

ethyl]amino)-1-(phenylmethyl)propyl]-1-methyl-1H-indole-5-carboxamide (E619)				
7-(1,1-dioxido-2-isothiazolidinyl)-3-ethyl-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[(1,1,5-trimethylhexyl)amino] propyl]-1-methyl-1H-indole-5-carboxamide (E620)	A146	C5	611.5	2.84
N-[(1S,2R)-3-(cyclohexylamino)-2-hydroxy-1-(phenylmethyl)propyl]-7-(1,1-dioxido-2-isothiazolidinyl)-3-ethyl-1-methyl-1H-indole-5-carboxamide (E621)	A146	C1	567.5	2.46
3-(ethylamino)-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-4-methyl-5-(2-oxo-1-pyrrolidinyl)benzamide (E622)	A129	C16	583.2	2.70
3-(1,1-dioxido-2-isothiazolidinyl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-4-methylbenzamide (E623)	A130	C16	619.2	2.77
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-4-methylbenzamide (E624)	A131	C16	633.2	2.84
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-4-(methyloxy)benzamide (E625)	A132	C16	649.2	2.82
3-(ethylamino)-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-4-(methyloxy)-5-(2-oxo-1-pyrrolidinyl)benzamide (E626)	A133	C16	599.2	2.71
3-(1,1-dioxido-2-isothiazolidinyl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-4-(methyloxy)benzamide (E627)	A134	C16	635.2	2.76
3-(diethylamino)-5-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-4-methylbenzamide (E628)	A135	C16	661.2	2.94
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-4-(methyloxy)-5-[(1E)-1-propen-1-yl]benzamide (E629)	A136	C16	646.1	2.95
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-4-(methyloxy)-5-propylbenzamide (E630)	A137	C16	648.2	2.99
N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-4-(2-oxo-1-pyrrolidinyl)-1H-indole-6-carboxamide (E631)	A154	C16	565.2	2.59

1-ethyl-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-4-(2-oxo-1-pyrrolidinyl)-1H-indole-6-carboxamide (E632)	A140	C16	593.2	2.83
1-ethyl-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-4-(2-oxo-1-pyrrolidinyl)-1H-indole-6-carboxamide (E633)	A140	C14	555.2	2.36
4-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-1H-indole-6-carboxamide (E634)	A155	C14	577.1	2.31
4-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-1-ethyl-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-1H-indole-6-carboxamide (E635)	A147	C14	605.4	2.60
N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-3-(1-methylethyl)-5-(2-oxo-1-pyrrolidinyl)benzamide (E636)	A104	C14	530.5	2.60
N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl] methyl}amino)-1-(phenylmethyl)propyl]-1-methyl-4-(2-oxo-1-pyrrolidinyl)-1H-indole-6-carboxamide (E637)	A156	C14	541.2	2.50
3-(1,1-dioxido-2-isothiazolidinyl)-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl) propyl]-5-(2-oxo-1-pyrrolidinyl)benzamide (E638)	A138	C14	607.2	2.43
1-butyl-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-4-(2-oxo-1-pyrrolidinyl)-1H-indole-6-carboxamide (E639)	A157	C14	583.2	2.78
N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl] methyl}amino)-1-(phenylmethyl)propyl]-4-(2-oxo-1-pyrrolidinyl)-1-pentyl-1H-indole-6-carboxamide (E640)	A158	C14	597.2	2.90
3-(1,1-dioxido-2-isothiazolidinyl)-5-(ethylamino)-2-fluoro-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl] benzamide (E641)	A122	C14	585.3	2.47
3-(1,1-dioxido-2-isothiazolidinyl)-5-(ethylamino)-2-fluoro-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl) phenyl] methyl}amino)propyl] benzamide (E642)	A122	C16	623.3	2.62
3-(1,1-dioxido-2-isothiazolidinyl)-5-(ethylamino)-2-fluoro-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(methyloxy)phenyl] ethyl}amino)-1-(phenylmethyl)propyl] benzamide (E643)	A122	C15	613.3	2.56
3-(1,1-dioxido-2-isothiazolidinyl)-5-(ethylamino)-2-fluoro-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(trifluoromethyl)phenyl] ethyl}amino)-1-(phenylmethyl)propyl] benzamide (E644)	A122	C40	651.3	2.70
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-2-fluoro-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(methyloxy)phenyl]ethyl}amino)-1-(phenylmethyl)propyl] benzamide (E645)	A119	C15	627.3	2.63

3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-2-fluoro-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(trifluoromethyl)phenyl]ethyl}amino)-1-(phenylmethyl)propyl] benzamide (E646)	A119	C40	665.3	2.77
4-(1,1-dioxido-2-isothiazolidinyl)-1-ethyl-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-1H-indole-6-carboxamide (E647)	A143	C14	591.3	2.60
4-(1,1-dioxido-2-isothiazolidinyl)-1-ethyl-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-1H-indole-6-carboxamide (E648)	A143	C16	629.3	2.75
4-(1,1-dioxido-2-isothiazolidinyl)-1-ethyl-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(methyloxy)phenyl]ethyl}amino)-1-(phenylmethyl)propyl]-1H-indole-6-carboxamide (E649)	A143	C15	619.4	2.67
4-(1,1-dioxido-2-isothiazolidinyl)-1-ethyl-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(trifluoromethyl)phenyl] ethyl}amino)-1-(phenylmethyl)propyl]-1H-indole-6-carboxamide (E650)	A143	C40	657.4	2.80
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-2-(methyloxy)benzamide (E651)	A139	C14	611.4	2.59
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-2-(methyloxy)benzamide (E652)	A139	C16	649.3	2.76
5-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-N'-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(methyloxy)phenyl]ethyl}amino)-1-(phenylmethyl)propyl]-N,N-dipropyl-1,3-benzenedicarboxamide (E653)	A95	C15	693.5	2.82
5-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-N'-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(trifluoromethyl)phenyl] ethyl}amino)-1-(phenylmethyl)propyl]-N,N-dipropyl-1,3-benzenedicarboxamide (E654)	A95	C40	731.4	2.94
1-ethyl-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-4-(2-oxo-1-pyrrolidinyl)-1H-indazole-6-carboxamide (E655)	A152	C14	556.3	2.33
1-ethyl-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-4-(2-oxo-1-pyrrolidinyl)-1H-indazole-6-carboxamide (E656)	A152	C16	594.3	2.42
1-ethyl-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(methyloxy)phenyl]ethyl}amino)-1-(phenylmethyl)propyl]-4-(2-oxo-1-pyrrolidinyl)-1H-indazole-6-carboxamide (E657)	A152	C15	584.4	2.42
1-ethyl-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-	A152	C40	622.4	2.61

(trifluoromethyl)phenyl] ethyl}amino)-1-(phenylmethyl)propyl]-4-(2-oxo-1-pyrrolidinyl)-1H-indazole-6-carboxamide (E658)				
4-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-1-ethyl-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-2,3-dihydro-1H-indole-6-carboxamide (E659)	A145	C14	607.4	2.61
4-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-1-ethyl-N-{(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[(1,1,5-trimethylhexyl)amino] propyl}-1H-indole-6-carboxamide (E660)	A147	C5	611.5	2.92
4-(1,1-dioxido-2-isothiazolidinyl)-1-ethyl-N-{(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[(1,1,5-trimethylhexyl)amino] propyl}-1H-indole-6-carboxamide (E661)	A143	C5	597.5	2.85
1-ethyl-N-{(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[(1,1,5-trimethylhexyl)amino] propyl}-4-(2-oxo-1-pyrrolidinyl)-1H-indole-6-carboxamide (E662)	A140	C5	561.5	2.83
N-[(1S,2R)-3-(cyclohexylamino)-2-hydroxy-1-(phenylmethyl)propyl]-4-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-1-ethyl-1H-indole-6-carboxamide (E663)	A147	C1	567.5	2.62
N-[(1S,2R)-3-(cyclohexylamino)-2-hydroxy-1-(phenylmethyl)propyl]-4-(1,1-dioxido-2-isothiazolidinyl)-1-ethyl-1H-indole-6-carboxamide (E664)	A143	C1	553.5	2.54
N-[(1S,2R)-3-(cyclohexylamino)-2-hydroxy-1-(phenylmethyl)propyl]-1-ethyl-4-(2-oxo-1-pyrrolidinyl)-1H-indole-6-carboxamide (E665)	A140	C1	517.4	2.51
4-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-1-ethyl-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-1H-indole-6-carboxamide (E666)	A147	C16	643.5	2.86
4-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-1-ethyl-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(methyloxy)phenyl]ethyl}amino)-1-(phenylmethyl)propyl]-1H-indole-6-carboxamide (E667)	A147	C15	633.5	2.75
4-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-1-ethyl-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(trifluoromethyl)phenyl] ethyl}amino)-1-(phenylmethyl)propyl]-1H-indole-6-carboxamide (E668)	A147	C40	671.5	2.92
7-[acetyl(ethyl)amino]-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino) propyl]-3-methyl-1-benzofuran-5-carboxamide (E669)	A159	C16	580.2	2.81
formic acid - N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-3-methyl-7-(2-	A160	C16	579.2	2.68

oxo-1-pyrrolidinyl)-1H-indole-5-carboxamide (1:1) (E670)				
N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-3-(1-methylethyl)-7-(2-oxo-1-pyrrolidinyl)-1H-indole-5-carboxamide (E671)	A161	C16	607.2	2.85
formic acid - N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-1-methyl-3-(1-methylethyl)-7-(2-oxo-1-pyrrolidinyl)-1H-indole-5-carboxamide (1:1) (E672)	A162	C16	621.2	2.89
3-ethyl-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-7-(2-oxo-1-pyrrolidinyl)-1-benzofuran-5-carboxamide (E673)	A163	C16	594.2	2.90
formic acid - N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-4-methyl-8-(2-oxo-1-pyrrolidinyl)-3,4-dihydro-2H-chromene-6-carboxamide (1:1) (E674)	A164	C16	596.2	2.81
3-ethyl-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-7-(2-oxo-1-pyrrolidinyl)-1H-indole-5-carboxamide (E675)	A141	C16	593.2	2.81
3-ethyl-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-1-methyl-7-(2-oxo-1-pyrrolidinyl)-1H-indole-5-carboxamide (E676)	A142	C16	607.2	2.83
7-(1,1-dioxido-2-isothiazolidinyl)-3-ethyl-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-1H-indole-5-carboxamide (E677)	A144	C16	629.1	2.87
N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-3-(1-methylethyl)-7-(2-oxo-1-pyrrolidinyl)-1H-indole-5-carboxamide (E678)	A161	C14	569.5	2.65
formic acid - 3-ethyl-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-7-(2-oxo-1-pyrrolidinyl)-1H-indole-5-carboxamide (1:1) (E679)	A141	C14	555.1	2.44
formic acid - 1-ethyl-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-4-(2-oxo-1-pyrrolidinyl)-1H-benzimidazole-6-carboxamide (1:1) (E680)	A149	C14	556.5	2.24
formic acid - 7-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-3-ethyl-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-1H-indole-5-carboxamide (1:1) (E681)	A148	C14	605.5	2.63
formic acid - 3-ethyl-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-7-(2-oxo-1-piperidinyl)-1H-indole-5-carboxamide (1:1) (E682)	A165	C14	569.2	2.68

3-(1,1-dioxido-4-phenyltetrahydro-2H-1,2-thiazin-2-yl)-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-5-nitrobenzamide (E683)	A123	C14	659.3	2.95
3-(1,1-dioxido-4-phenyltetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl] benzamide (E684)	A125	C14	657.4	2.85
3-amino-5-(1,1-dioxido-4-phenyltetrahydro-2H-1,2-thiazin-2-yl)-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl] benzamide (E685)	A124	C14	629.4	2.67
3-ethyl-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl] methyl}amino)-1-(phenylmethyl)propyl]-7-(2-oxo-4-phenyl-1-pyrrolidinyl)-1H-indole-5-carboxamide (E686)	A166	C14	631.4	2.92
N-[(1S,2R)-3-(cyclohexylamino)-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxido-4-phenyltetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide (E687)	A125	C1	619.4	2.89
3-(1,1-dioxido-4-phenyltetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-3-[(1-methylethyl)amino]-1-(phenylmethyl)propyl] benzamide (E688)	A125	C28	579.4	2.76
formic acid - 1-ethyl-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-4-(2-oxo-1-pyrrolidinyl)-1H-1,2,3-benzotriazole-6-carboxamide (1:1) (E689)	A167	C16	595.3	2.67
formic acid - 4-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-1-ethyl-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-1H-benzimidazole-6-carboxamide (1:1) (E690)	A151	C14	606.3	2.21
1-ethyl-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-4-(2-oxo-1-pyrrolidinyl)-1H-benzimidazole-6-carboxamide (E691)	A149	C16	594.5	2.21
1-ethyl-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(trifluoromethyl)phenyl] ethyl}amino)-1-(phenylmethyl)propyl]-4-(2-oxo-1-pyrrolidinyl)-1H-benzimidazole-6-carboxamide (E692)	A149	C40	622.5	2.24
N-[(1S,2R)-3-(cyclohexylamino)-2-hydroxy-1-(phenylmethyl)propyl]-1-ethyl-4-(2-oxo-1-pyrrolidinyl)-1H-benzimidazole-6-carboxamide (E693)	A149	C1	518.4	1.90
1-ethyl-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[(1,1,5-trimethylhexyl)amino] propyl]-4-(2-oxo-1-pyrrolidinyl)-1H-benzimidazole-6-carboxamide (E694)	A149	C5 1	562.5	2.33
formic acid - 1-ethyl-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(methyloxy)phenyl]ethyl}amino)-1-(phenylmethyl)propyl]-4-	A149	C15	584.5	2.09

(2-oxo-1-pyrrolidinyl)-1H-benzimidazole-6-carboxamide (1:1) (E695)				

Example 696

3-(1,1-dioxidotetrahydro-1,2-thiazepin-2(3H)-yl)-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-5-propylbenzamide (E696)

Example 696 was prepared from Description 313 in an analogous manner to that described for Example 213. $[M+H]^+$ = 594.4, RT = 2.77 min

Example 697

3-(1,1-dioxidotetrahydro-1,2-thiazepin-2(3H)-yl)-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl]methyl}amino)propyl]-5-propylbenzamide (E697)

Example 697 was prepared from Description 312 in an analogous manner to that described for Example 213. $[M+H]^+$ = 632.1, RT = 3.00 min

Examples 698-703 (E698-703)

The following compounds were prepared in an analogous manner to Example 183 from the appropriate amine and the appropriate aldehyde or ketone :

Example	Precursor	$[M+H]^+$	RT (min)
N-[(1S,2R)-3-[[2-(3-chlorophenyl)-1-methylethyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E698)	D120	611.3	1.01
N-[(1S,2R)-3-[[2-(3-chlorophenyl)-1-methylethyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-3-cyclopentyl-5-(1,1-dioxido tetrahydro-2H-1,2-thiazin-2-yl)benzamide hydrochloride (E699)	D125	638.4	1.00
formic acid – 3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-3-[[(5-ethyl-3-thienyl)methyl]amino]-2-hydroxy-1-(phenylmethyl)propyl] benzamide (1:1) (E700)	D120	585.5	2.57
formic acid – 3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-3-[[(4-ethyl-2-thienyl)methyl]amino]-2-hydroxy-1-(phenylmethyl)propyl] benzamide (1:1) (E701)	D120	585.5	2.45
formic acid – 3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-3-[[(1-ethyl-1H-pyrazol-3-yl)methyl]amino]-2-hydroxy-1-(phenylmethyl)propyl] benzamide (1:1) (E702)	D120	569.5	2.31
formic acid – 3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-((1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[[(1-propyl-1H-pyrazol-4-yl)methyl]amino}propyl) benzamide (1:1) (E703)	D120	583.5	2.29

Example 704

Example E704 was prepared in an analogous manner to Example 1 from the appropriate acid and amine indicated in the below table:

Example	Acid	Amine	$[M+H]^+$	RT (min)
N-[(1S,2R)-3-(bicyclo[2.2.2]oct-1-ylamino)-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E704)	A73	C153	569.5	2.02

Examples 705-709 (E705-709)

The following compounds were prepared in an analogous manner to Example 183 from the appropriate amine and the appropriate aldehyde or ketone :

Example	Precursor	$[M+H]^+$	RT (min)
formic acid - 3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-N-[(1S,2R)-3-[[(5-ethenyl-3-thienyl)methyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-5-(ethylamino)benzamide (1:1) (E705)	D120	583.5	2.55
formic acid - 3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-N-[(1S,2R)-3-[[(4-ethenyl-2-furanyl)methyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-5-(ethylamino)benzamide (1:1) (E706)	D120	567.5	2.44
formic acid - 3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[1-(2-propen-1-yl)-1H-pyrazol-4-yl]methyl}amino)propyl] benzamide (1:1) (E707)	D120	581.5	2.29
formic acid - 3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-N-[(1S,2R)-3-[[(4-ethenyl-2-thienyl)methyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-5-(ethylamino)benzamide (1:1) (E708)	D120	583.5	2.52
formic acid - 3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-3-({[1-(2-fluoroethyl)-1H-pyrazol-4-yl]methyl}amino)-2-hydroxy-1-(phenylmethyl)propyl] benzamide (1:1) (E709)	D120	587.5	2.22

Examples 710-744 (E710-744)

Examples E710-E744 were prepared in an analogous manner to Example 1 from the appropriate acid and amines indicated in the below table:

Example	Acid	Amine	$[M+H]^+$	RT (min)
3-cyclopentyl-N-[(1S,2R)-3-[[(1-ethyl-1H-pyrazol-4-yl)methyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-5-(2-oxo-1-pyrrolidinyl)benzamide (E710)	A107	C154	544.7	2.51
3-(ethyloxy)-N-[(1S,2R)-3-[[(1-ethyl-1H-pyrazol-4-yl)methyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-5-	A11	C154	520.7	2.20

(2-oxo-1-pyrrolidinyl)benzamide (E711)				
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-3-[[(1-ethyl-1H-pyrazol-4-yl)methyl]amino]-2-hydroxy-1-(phenylmethyl)propyl] benzamide (E712)	A73	C154	569.6	2.19
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-N-[(1S,2R)-3-[[(1-ethyl-1H-pyrazol-4-yl)methyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-5-propylbenzamide (E713)	A112	C154	568.6	2.46
formic acid - N-[(1S,2R)-3-[(4,4-difluorocyclohexyl)amino]-2-hydroxy-1-(phenylmethyl) propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-2-fluorobenzamide (1:1) (E714)	A119	C155	597.4	2.30
4-ethyl-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-8-(2-oxo-1-pyrrolidinyl)-1,2,3,4-tetrahydro-6-quinoxalinecarboxamide (E715)	A171	C14	572.5	2.61
4-(1,1-dioxido-2-isothiazolidinyl)-1-ethyl-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-1H-benzimidazole-6-carboxamide (E716)	A150	C14	592.4	2.21
4-(1,1-dioxido-2-isothiazolidinyl)-1-ethyl-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-1H-benzimidazole-6-carboxamide (E717)	A150	C16	630.4	2.51
4-(1,1-dioxido-2-isothiazolidinyl)-1-ethyl-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(trifluoromethyl)phenyl] ethyl}amino)-1-(phenylmethyl)propyl]-1H-benzimidazole-6-carboxamide (E718)	A150	C40	658.4	2.51
4-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-1-ethyl-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(trifluoromethyl) phenyl] ethyl}amino)-1-(phenylmethyl)propyl]-2,3-dihydro-1H-indole-6-carboxamide (E719)	A145	C40	673.5	2.90
8-(1,1-dioxido-2-isothiazolidinyl)-4-ethyl-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-1,2,3,4-tetrahydro-6-quinoxalinecarboxamide (E720)	A172	C16	646.5	2.65
formic acid - 3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-2-fluoro-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[({3-[(trifluoromethyl)oxy] phenyl}methyl)amino] propyl]benzamide (1:1) (E721)	A119	C11	653.5	2.54
formic acid - 3-(1,1-dioxido-2-isothiazolidinyl)-N-[(1S,2R)-3-[[(1-ethyl-1H-pyrazol-4-yl)methyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-fluoro-5-	A174	C154	572.4	2.37

propylbenzamide (1:1) (E722)				
3-(1,1-dioxido-2-isothiazolidinyl)-2-fluoro-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[(1,1,5-trimethylhexyl)amino] propyl]-5-propylbenzamide (E723)	A174	C5	590.5	2.92
3-(1,1-dioxido-2-isothiazolidinyl)-2-fluoro-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(methyloxy)phenyl]ethyl} amino)-1-(phenylmethyl)propyl]-5-propylbenzamide (E724)	A174	C15	612.5	2.66
3-(1,1-dioxido-2-isothiazolidinyl)-2-fluoro-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-5-propylbenzamide (E725)	A174	C16	622.4	2.68
N-[(1S,2R)-3-[(1r,4R)-bicyclo[2.2.1]hept-1-ylamino]-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E726)	A73	C152	555.1	2.23
formic acid - 3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-N-[(1S,2R)-3-[[(1-ethyl-1H-pyrazol-4-yl)methyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-fluoro-5-propylbenzamide (1:1) (E727)	A173	C154	586.4	2.50
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-2-fluoro-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-(tetrahydro-2H-pyran-4-ylamino)propyl]-5-propylbenzamide (E728)	A173	C43	562.4	2.45
formic acid - 3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-2-fluoro-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(trifluoromethyl)phenyl] ethyl}amino)-1-(phenylmethyl)propyl]-5-propylbenzamide (1:1) (E729)	A173	C40	664.5	2.97
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-2-fluoro-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-5-propylbenzamide (E730)	A173	C16	636.4	2.84
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-2-fluoro-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-5-propylbenzamide (E731)	A173	C14	598.4	2.70
2-fluoro-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-(tetrahydro-2H-pyran-4-ylamino)propyl]-3-(2-oxo-1-pyrrolidinyl)-5-propylbenzamide (E732)	A120	C43	512.5	2.32
N-[(1S,2R)-3-[[(1-ethyl-1H-pyrazol-4-yl)methyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-fluoro-3-(2-oxo-1-pyrrolidinyl)-5-propylbenzamide (E733)	A120	C154	536.5	2.36
N-[(1S,2R)-3-({[3,4-bis(methyloxy)phenyl] methyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]-2-fluoro-3-(2-oxo-1-pyrrolidinyl)-5-propylbenzamide (E734)	A120	C156	578.5	2.40

2-fluoro-N-[(1S,2R)-2-hydroxy-3-[(1-methylethyl)amino]-1-(phenylmethyl)propyl]-3-(2-oxo-1-pyrrolidinyl)-5-propylbenzamide (E735)	A120	C28	470.5	2.26
N-[(1S,2R)-3-(cyclohexylamino)-2-hydroxy-1-(phenylmethyl)propyl]-2-fluoro-3-(2-oxo-1-pyrrolidinyl)-5-propylbenzamide (E736)	A120	C1	510.5	2.44
formic acid - 2-fluoro-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[(1,1,5-trimethylhexyl)amino] propyl}-3-(2-oxo-1-pyrrolidinyl)-5-propylbenzamide (1:1) (E737)	A120	C5	554.7	3.04
formic acid - 2-fluoro-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(trifluoromethyl)phenyl] ethyl}amino)-1-(phenylmethyl)propyl]-3-(2-oxo-1-pyrrolidinyl)-5-propylbenzamide (1:1) (E738)	A120	C40	614.6	2.77
formic acid - 2-fluoro-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(methyloxy)phenyl]ethyl} amino)-1-(phenylmethyl)propyl]-3-(2-oxo-1-pyrrolidinyl)-5-propylbenzamide (1:1) (E739)	A120	C15	576.6	2.66
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-3-[(1-ethylcyclobutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl] benzamide hydrochloride (E740)	A73	C89	542.9	1.05
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-{(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[(1-propylcyclobutyl)amino] propyl}benzamide hydrochloride (E741)	A73	C148	556.9	1.08
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-3-[[1-(1-methylethyl)cyclobutyl] amino]-1-(phenylmethyl)propyl] benzamide hydrochloride (E742)	A73	C149	556.9	1.07
N-[(1S,2R)-3-({1-[(3-chlorophenyl)methyl] cyclobutyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E743)	A73	C150	639.3	1.41
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-(tricyclo[3.3.1.1~3,7~]dec-2-ylamino)propyl] benzamide hydrochloride (E744)	A73	C151	595.7	2.12

Compounds of the invention may be tested for *in vitro* biological activity in accordance with the following assays:

(i) **Asp-2 inhibitory assay**

For each compound being assayed, in a 384 well plate, is added:-

a) 1µl of a DMSO solution of the test compound (IC_{50} curve uses ten 1 in 2 serial dilutions from 500 µM).
b) 10 µl of substrate (FAM-SEVNLDAEFK-TAMRA) solution in buffer. This is prepared by diluting 2ml of a 2mM DMSO solution of the substrate into 400ml of buffer (100mM Sodium acetate pH = 4.5, 1 l Milli-Q water, 0.06% Triton X-100 (0.5 ml/l) , pH adjusted to 4.5 using glacial acetic acid). Aminomethyl fluorescein (FAM) and tetramethyl rhodamine (TAMRA) are fluorescent molecules which co-operate to emit fluorescence at 535nm upon cleavage of the SEVNLDAEFK peptide.
c) 10 µl enzyme solution. This is prepared by diluting 16ml of a 500nM enzyme solution into 384 ml of buffer (prepared as above).
Blank wells (enzyme solution replaced by buffer) are included as controls on each plate. Wells are incubated for 1h at room temperature and fluorescence read using a Tecan Ultra Fluorimeter/Spectrophotometer (485nm excitation, 535nm emission).

(II) **Cathepsin D inhibitory assay**
For each compound being assayed, in a 384 well plate, is added:-
a) 1µl of a DMSO solution of the test compound (IC_{50} curve uses ten 1 in 2 serial dilutions from 500 µM).
b) 10 µl of substrate (FAM-SEVNLDAEFK-TAMRA) solution in buffer. This is prepared by diluting 2ml of a 2mM DMSO solution of the substrate into 400ml of buffer (100mM Sodium acetate pH = 4.5, 1 l Milli-Q water, 0.06% Triton X-100 (0.5 ml/l) , pH adjusted to 4.5 using glacial acetic acid).
c) 10 µl enzyme solution. This is prepared by diluting 1.6ml of a 200 unit/ml (in 10 mM HCl) enzyme solution into 398.4 ml of buffer (prepared as above).
Blank wells (enzyme solution replaced by buffer) are included as controls on each plate. Wells are incubated for 1h at room temperature and fluorescence read using a Tecan Ultra Fluorimeter/Spectrophotometer (485nm excitation, 535nm emission).

Pharmacological Data

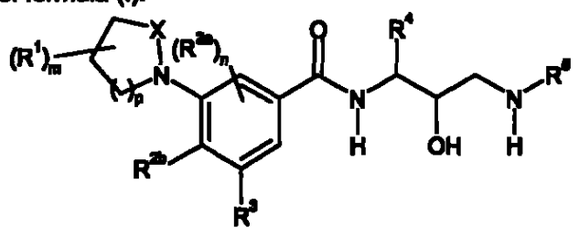
The compounds of E1-E744 were tested in Assays (I) and (II) and exhibited inhibition within the following range: 1-10000 nM (Asp-2) and 10-10000 nM (CatD). More particularly, the compounds of E12, 22, 30, 31, 33, 50, 54-56, 60, 65, 86, 102, 179, 218, 222-223, 241, 245-246, 249, 255, 266, 270, 271, 277-278, 280-289, 296, 299, 303, 313-315, 317-318, 320-322, 325, 327, 329, 332-333, 361-363, 373, 375, 406-408, 559-560, 562, 583-584, 587, 632, 641-642, 647-648, 656, 680, 690-691, 694-695, 700, 703, 708, 713, 716-718, 720-721, 725, 727, 730-731 and 733 exhibited inhibition within the following range: 1-50 nM (Asp-2) and 100-10000 nM (CatD). Yet more particularly, the compounds of E30-31, 33, 270, 562, 584, 700 and 721 exhibited inhibition within the following range: 1-10 nM (Asp-2) and 500-10000 nM (CatD).

Abbreviations

DMF	dimethylformamide
DMSO	dimethylsulfoxide
DMAP	dimethylaminophenol
DABCO	1,4-diazabicyclo [2.2.2] octane
DME	dimethyl ether
EDAC	N-ethyl-N-(3-dimethylamino propyl)carbodiimide
THF	tetrahydrofuran
DEAD	diethylacetylene dicarboxylate
DCM	dichloromethane
TFA	trifluoroacetic acid
HOBT	N-hydroxybenzotriazole
FAM	carboxyfluorescein
TAMRA	carboxytetramethylrhodamine
[ ]	single amino acid letter code relating to peptide sequence

Claims

1. A compound of formula (I):



(I)

wherein

R^1 represents C_{1-6} alkyl, C_{2-6} alkenyl, halogen, C_{1-6} alkoxy, amino, cyano, hydroxy, aryl, heteroaryl or heterocyclyl;

R^{2a} represents hydrogen, C_{1-3} alkyl, C_{1-3} alkoxy or halogen;

m and n independently represent 0, 1 or 2;

X represents CO, SO or SO_2;

p represents an integer from 1 to 3;

R^{2b} represents hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, halogen, C_{1-6} alkoxy, amino, cyano, hydroxy, aryl, heteroaryl or heterocyclyl;

R^3 represents halogen, C_{1-6} alkyl, C_{2-6} alkenyl, aryl, heteroaryl, heterocyclyl, -C_{1-6} alkyl-aryl, -C_{1-6} alkyl-heteroaryl, -C_{1-6} alkyl-heterocyclyl, -C_{2-6} alkenyl-aryl, -C_{2-6} alkenyl-heteroaryl, -C_{2-6} alkenyl-heterocyclyl, C_{3-6} cycloalkyl, -C_{1-6} alkyl-C_{3-6} cycloalkyl, cyano, azido, nitro, $-NR^7R^8$, -NR^9COR^{10}, -$NR^{11}SO_2R^{12}$, -OR^{13}, -SO_2R^{14}, -SR^{15}, -$C{\equiv}CR^{16}$, -C_{1-6} alkyl-$(CF_2)_qCF_3$, -$CONR^{17}R^{18}$, $COOR^{19}$, -C_{1-6} alkyl-$NR^{20}R^{21}$ or -C_{1-6} alkyl-N_3, or R^3 and R^{2b} together with the phenyl group to which they are attached form a naphthyl or benzofused heterocyclic or heteroaryl ring optionally substituted by one or two C_{1-6} alkyl groups;

R^4 represents $-C_{2-6}$ alkynyl, -C_{1-6} alkyl-aryl, -C_{1-6} alkyl-heteroaryl or -C_{1-6} alkyl-heterocyclyl;

R^5 represents hydrogen, -C_{1-10} alkyl, -C_{3-10} cycloalkyl, -C_{3-10} cycloalkenyl, aryl, heteroaryl, heterocyclyl, -C_{1-6} alkyl-C_{3-10} cycloalkyl, -C_{3-10} cycloalkyl-C_{1-10} alkyl, -C_{3-10} cycloalkyl-C_{1-6} alkyl-aryl, -C_{3-10} cycloalkyl-aryl, -C_{1-6} alkyl-aryl-heteroaryl, -$C(R^aR^b)$-CONH-C_{1-6} alkyl, -$C(R^cR^d)$-CONH-C_{3-10} cycloalkyl, -C_{1-6} alkyl-S-C_{1-6} alkyl, -C_{1-6} alkyl-NR^eR^f, -C_{1-6} alkyl-aryl, -C_{1-6} alkyl-heteroaryl, -C_{1-6} alkyl-heterocyclyl -C_{1-6} alkyl-C_{1-6} alkoxy-aryl, -C_{1-6} alkyl-C_{1-6} alkoxy-heteroaryl or -C_{1-6} alkyl-C_{1-6} alkoxy-heterocyclyl;

R^7, R^8, R^9, R^{10}, R^{13}, R^{14}, R^{16}, R^{19}, R^{17}, R^{18}, R^{19}, R^{20} and R^{21} independently represent hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl, aryl, heteroaryl, heterocyclyl, -C_{1-6} alkyl-C_{3-6} cycloalkyl, -C_{1-6} alkyl-aryl, -C_{1-6} alkyl-heteroaryl, -C_{1-6} alkyl-heterocyclyl or -CO-C_{1-6} alkyl;

R^{11}, R^{12}, R^a, R^c, R^e and R^f independently represent hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl;

R^b and R^d independently represent hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl or -C_{1-6} alkyl-SO_2-C_{1-6} alkyl;

q represents 1 to 3;

wherein said alkyl groups may be optionally substituted by one or more (eg. 1, 2 or 3) halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenoxy, C_{3-6} cycloalkyl, amino, cyano or hydroxy groups;

and wherein said cycloalkyl, aryl, heteroaryl or heterocyclyl groups may be optionally substituted by one or more (eg. 1, 2 or 3) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, haloC_{1-6} alkyl, $-OCF_3$, oxo, C_{1-6} alkoxy, $-C_{1-6}$ alkoxy-CN, amino, cyano, nitro, $-NR^{22}COR^{23}$, $-CONR^{22}R^{23}$, $-COOR^{22}$, $-SO_2R^{22}$, $-C_{1-6}$ alkyl-NR^{22} R^{23} (wherein R^{22} and R^{23} independently represent hydrogen or C_{1-6} alkyl), $-C_{1-6}$ alkyl-C_{1-6} alkoxy, $-C_{1-6}$ alkanol or hydroxy groups;
or a pharmaceutically acceptable salt or solvate thereof.

2. A compound according to claim 1 which is a compound of formula E1-E744 or a pharmaceutically acceptable salt thereof.

3. A pharmaceutical composition comprising a compound of formula (I) as defined in claim 1 or claim 2 or a pharmaceutically acceptable salt or solvate thereof in admixture with one or more pharmaceutically acceptable diluents or carriers.

4. A compound of formula (I) as defined in claim 1 or claim 2 or a pharmaceutically acceptable salt or solvate thereof for use as a pharmaceutical.

5. Use of a compound of formula (I) as defined in claim 1 or claim 2 or a pharmaceutically acceptable salt or solvate thereof in the treatment of diseases characterised by elevated β-amyloid levels or β-amyloid deposits.

6. Use of a compound of formula (I) as defined in claim 1 or claim 2 or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for the treatment of diseases characterised by elevated β-amyloid levels or β-amyloid deposits.

7. A method of treatment or prophylaxis of diseases characterised by elevated β-amyloid levels or β-amyloid deposits which comprises administering to a patient an effective amount of a compound of formula (I) as defined in claim 1 or claim 2 or a pharmaceutically acceptable salt or solvate thereof.

8. A pharmaceutical composition comprising a compound of formula (I) as defined in claim 1 or claim 2 or a pharmaceutically acceptable salt or solvate thereof for use in the treatment of diseases characterised by elevated β-amyloid levels or β-amyloid deposits.

DERIVADOS DE HIDROXIETILAMINA PARA EL TRATAMIENTO DE LA ENFERMEDAD DE ALZHEIMER

MEMORIA DESCRIPTIVA

La presente invención se refiere a compuestos de hidroxietilamina novedosos que tienen actividad inhibidora de Asp2 (β-secretasa, BACE1 o Memapsina); procedimientos para su preparación; composiciones que los contienen; y su uso en el tratamiento de enfermedades caracterizadas por concentración elevada de β-amiloide o depósitos de β-amiloide, particularmente la enfermedad de Alzheimer.

La enfermedad de Alzheimer es un trastorno cerebral degenerativo en el cual la deposición extracelular de Aβ en forma de placas seniles representa una marca distintiva patológica de la enfermedad (Selkoe, D.J. (2001), *Physiological Reviews*, **81**: 741-766). La presencia de placas seniles va acompañada de una respuesta inflamatoria prominente y pérdida neuronal. El β-amiloide (Aβ) existe en formas fibrilares solubles e insolubles, y se ha identificado una forma fibrilar específica como la especie neurotóxica predominante (Vassar, R. y Citron, M. (2000), *Neuron* **27**: 419-422). Además, se ha reportado que la demencia se correlaciona más estrechamente con la concentración de amiloide soluble que con la carga de la placa (Naslund, J. y otros (2000), *J. Am. Med. Assoc.* **12**: 1571-1577; Younkin, S. (2001) *Nat. Med.* **1**: 8-19). Se sabe que el Aß es producido por la descomposición de la

proteína precursora de beta-amiloide (también conocida como APP) efectuada por una enzima aspartil proteasa conocida como Asp2 (también conocida como ß-secretasa, BACE1 o Memapsina) (De Strooper, B. y Konig, G. (1999), *Nature* **402**: 471-472).

Por lo tanto, se ha propuesto que la inhibición de la enzima Asp2 reduciría el procesamiento de APP y consecuentemente reduciría la concentración de los péptidos Aß encontrados en el cerebro. Por lo tanto, también se considera que la inhibición de la enzima Asp2 sería un blanco terapéutico efectivo en el tratamiento de la enfermedad de Alzheimer.

La APP es degradada por una variedad de enzimas proteolíticas (De Strooper, B. y Konig, G. (1999), *Nature* **402**: 471-472). Las enzimas clave de la ruta amiloidogénica son Asp2 (ß-secretasa) y γ-secretasa; ambas son proteinasas aspárticas y la descomposición de APP efectuada por estas enzimas genera Aß. Se ha mostrado que la ruta de α-secretasa, no amiloidogénica, que impide la formación de Aß, es catalizada por varias proteinasas, siendo el mejor candidato ADAM10, una desintegrina y metaloproteinasa. Se ha afirmado que Asp1 muestra actividad tanto α-secretasa como ß-secretasa *in vitro*. El patrón de expresión de Asp1 y Asp2 es muy diferente, siendo expresada altamente Asp2 en el páncreas y cerebro, mientras que la expresión Asp1 ocurre en muchos otros tejidos periféricos. El ratón Asp2 knockout indica que la falta de Asp2 suprime la producción de Aß y también muestra que en este modelo de animal la Asp1 endógena no puede sustituir la deficiencia de Asp2 (Luo, Y. y otros (2001), *Nat Neurosci* **4**: 231-

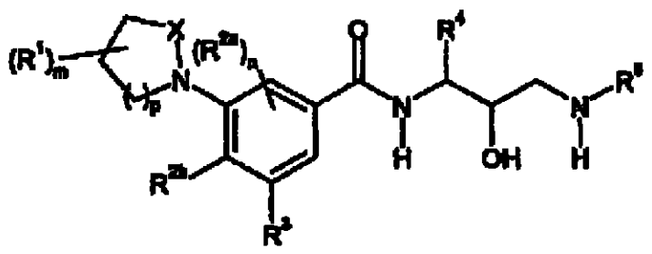
232; Cai, H. y otros (2001), *Nat Neurosci*, 4: 233-234; Roberds, S.L. y otros (2001), *Hum. Mol. Genet.* 10: 1317-1324).

Para que un agente sea terapéuticamente útil en el tratamiento de la enfermedad Alzheimer, es preferible que dicho agente sea un inhibidor potente de la enzima Asp2, pero idealmente también debe ser selectivo de Asp2 sobre otras enzimas de la familia de aspartil proteinasa, por ejemplo la catepsina D (Connor, G.E. (1998) "Cathepsin D" en "Handbook of Proteolytic Enzymes", Barrett, A. J., Rawlings, N. D., & Woesner, J. F. (Eds) Academic Press Londres, p. 828-836).

WO 01/70672, WO 20/02512, WO 02/02505, WO 02/02506 y WO 03/40096 (Elan Pharmaceuticals Inc.), describen una serie de compuestos de hidroxietilamina que tienen actividad ß-secretasa, lo que significa que son útiles en el tratamiento de la enfermedad de Alzheimer.

Los autores de la presente han encontrado una serie novedosa de compuestos que son inhibidores potentes de la enzima Asp2, indicando así el potencial de estos compuestos como efectivos en el tratamiento de la enfermedad de Alzheimer.

De esta manera, de acuerdo con un primer aspecto de la presente invención, se provee un compuesto de fórmula (I):



(I)

en donde:

R^1 representa alquilo de C_{1-6}, alquenilo de C_{2-6}, halógeno, alcoxi de C_{1-6}, amino, ciano, hidroxi, arilo, heteroarilo o heterociclilo;

R^{2a} representa hidrógeno, alquilo de C_{1-3}, alcoxi de C_{1-3} o halógeno;

m y n representan, independientemente, 0, 1 ó 2;

X representa CO, SO o SO_2;

p representa un entero de 1 a 3;

R^{2b} representa hidrógeno, alquilo de C_{1-6}, alquenilo de C_{2-6}, halógeno, alcoxi de C_{1-6}, amino, ciano, hidroxi, arilo, heteroarilo o heterociclilo;

R^3 representa halógeno, alquilo de C_{1-6}, alquenilo de C_{2-6}, arilo, heteroarilo, heterociclilo, -alquil(C_{1-6})-arilo, -alquil(C_{1-6})-heteroarilo, -alquil(C_{1-6})-heterociclilo, -alquenil(C_{2-6})-arilo, -alquenil(C_{2-6})-heteroarilo, -alquenil(C_{2-6})-heterociclilo, cicloalquilo de C_{3-8}, -alquil(C_{1-6})-cicloalquilo de C_{3-8}, ciano, azido, nitro, $-NR^7R^8$, $-NR^9COR^{10}$, $-NR^{11}SO_2R^{12}$, $-OR^{13}$, $-SO_2R^{14}$, $-SR^{15}$, $-C{=}CR^{16}$, -alquil(C_{1-6})-$(CF_2)_qCF_3$, $-CONR^{17}R^{18}$, $COOR^{19}$, -alquil(C_{1-6})-$NR^{20}R^{21}$ o –alquil(C_{1-6})-N_3, o R^3 y R^{2b} junto con el grupo fenilo al que están unidos, forman un anillo naftilo, o heterocíclico o heteroarilo benzofusionado, sustituido

opcionalmente con uno o dos grupos alquilo de C_{1-6};

R^4 representa –alquinilo de C_{2-6}, -alquil(C_{1-6})-arilo, -alquil(C_{1-6})-heteroarilo o –alquil(C_{1-6})-heterociclilo;

R^5 representa hidrógeno, alquilo de C_{1-10}, cicloalquilo de C_{3-10}, cicloalquenilo de C_{3-10}, arilo, heteroarilo, heterociclilo, -alquil(C_{1-6})-cicloalquilo de C_{3-10}, -cicloalquil(C_{3-10})-alquilo de C_{1-10}, -cicloalquil(C_{3-10})-alquil(C_{1-6})-arilo, -cicloalquil(C_{3-10})-arilo, -alquil(C_{1-6})-aril-heteroarilo, -C(R^aR^b)-CONH-alquilo de C_{1-6}, -C(R^cR^d)-CONH-cicloalquilo de C_{3-10}, -alquil(C_{1-6})-S-alquilo de C_{1-6}, -alquil(C_{1-6})-NR^eR^f, -alquil(C_{1-6})-arilo, -alquil(C_{1-6})-heteroarilo, -alquil(C_{1-6})-heterociclil-alquil(C_{1-6})-alcoxi(C_{1-6})-arilo, -alquil(C_{1-6})-alcoxi(C_{1-6})-heteroarilo o –alquil(C_{1-6})-alcoxi(C_{1-6})-heterociclilo;

R^7, R^8, R^9, R^{10}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20} y R^{21}, representan independientemente hidrógeno, alquilo de C_{1-6}, alquenilo de C_{2-6}, cicloalquilo de C_{3-6}, arilo, heteroarilo, heterociclilo, alquil(C_{1-6})-cicloalquilo de C_{3-6}, -alquil(C_{1-6})-arilo, -alquil(C_{1-6})-heteroarilo, -alquil(C_{1-6})-heterociclilo o –CO-alquilo de C_{1-6};

R^{11}, R^{12}, R^a, R^c, R^e y R^f representan independientemente hidrógeno, alquilo de C_{1-6} o cicloalquilo de C_{3-6};

R^b y R^d representan independientemente hidrógeno, alquilo de C_{1-6}, cicloalquilo de C_{3-6} o -alquil(C_{1-6})-SO_2-alquilo de C_{1-6};

q representa 1 a 3;

en donde dichos grupos alquilo pueden estar sustituidos opcionalmente con uno o más grupos (por ejemplo, 1, 2 ó 3) halógeno, alquilo

de C_{1-6}, alcoxi de C_{1-6}, alquenoxi de C_{2-6}, cicloalquilo de C_{3-8}, amino, ciano o hidroxi; y en donde dichos grupos cicloalquilo, arilo, heteroarilo o heterociclilo pueden estar sustituidos opcionalmente con uno o más grupos (por ejemplo 1, 2 ó 3) alquilo de C_{1-6}, alquenilo de C_{2-6}, alquinilo de C_{2-6}, halógeno, haloalquilo de C_{1-6}, $-OCF_3$, oxo, alcoxi de C_{1-6}, -alcoxi(C_{1-6})-CN, amino, ciano, nitro, $-NR^{22}COR^{23}$, $-CONR^{22}R^{23}$, $-COOR^{22}$, $-SO_2R^{22}$, -alquil(C_{1-6})-$NR^{22}R^{23}$ (en donde R^{22} y R^{23} representan independientemente hidrógeno o alquilo de C_{1-6}), -alquil(C_{1-6})-alcoxi de C_{1-6}, -alcanol de C_{1-6} o hidroxi;

o una sal o solvato farmacéuticamente aceptable del mismo.

En un aspecto particular de la presente invención, se provee un compuesto de fórmula (I) como se describe arriba, en donde:

X representa CO o SO_2; y

R^{2a} representa hidrógeno, alquilo de C_{1-3} o halógeno; y

R^3 y R^{2b}, junto con el grupo fenilo al que están unidos, forman un anillo heterocíclico o heteroarilo benzofusionado no sustituido; y

R^4 representa –alquil(C_{1-6})-arilo, -alquil(C_{1-6})-heteroarilo o –alquil(C_{1-6})-heterociclilo; y

R^5 representa hidrógeno, -alquilo de C_{1-10}, -cicloalquilo de C_{3-8}, -cicloalquenilo de C_{3-8}, arilo, heteroarilo, heterociclilo, -alquil(C_{1-6})-cicloalquilo de C_{3-8}, -alquil(C_{1-6})-aril-heteroarilo, -C(R^aR^b)-CONH-alquilo de C_{1-6}, -C(R^cR^d)-CONH-cicloalquilo de C_{3-8}, -alquil(C_{1-6})-S-alquilo de C_{1-6}, -alquil(C_{1-6})-NR^eR^f, -alquil(C_{1-6})-arilo, -alquil(C_{1-6})-heteroarilo, -alquil(C_{1-6})-heterociclilo, -alquil(C_{1-6})-alcoxi(C_{1-6})-arilo, -alquil(C_{1-6})-alcoxi(C_{1-6})-heteroarilo o –alquil(C_{1-6})-alcoxi(C_{1-6})-

heterociclilo; y

dichos grupos alquilo pueden estar sustituidos opcionalmente con uno o más grupos (por ejemplo, 1, 2 ó 3) halógeno, alcoxi de C_{1-6}, amino, ciano o hidroxi; y

en donde dichos grupos arilo, heteroarilo o heterociclilo pueden estar sustituidos opcionalmente con uno o más grupos (por ejemplo 1, 2 ó 3) alquilo de C_{1-6}, halógeno, $-OCF_3$, oxo, alcoxi de C_{1-6}, amino, ciano, nitro, $-NR^{22}COR^{23}$, $-alquil(C_{1-6})-NR^{22}R^{23}$ (en donde R^{22} y R^{23} representan independientemente hidrógeno o alquilo de C_{1-6}), $-alquil(C_{1-6})$-alcoxi de C_{1-6}, -alcanol de C_{1-6} o hidroxi.

Las referencias a alquilo incluyen referencias a isómeros alifáticos de cadena recta y ramificada del alquilo correspondiente. Se apreciará que se deben interpretar similarmente las referencias a alquenilo y alquenoxi. También se apreciará que cuando un grupo alquenilo o alquenoxi esté unido a un átomo de O, N o S, el doble enlace no está en la posición alfa con respecto a dicho átomo O, N o S.

Las referencias a cicloalquilo incluyen referencias a todos los isómeros alicíclicos (incluyendo los ramificados) del alquilo correspondiente. Cuando un grupo cicloalquilo está sustituido con dos o más grupos alquilo de C_{1-6}, dichos grupos cicloalquilo, junto con cualesquiera de dos grupos alquilo, pueden formar un grupo cicloalquilo de puente, que incluye biciclohéptilo, adamantilo, biciclooctilo y similares.

Las referencias a "arilo" incluyen referencias a anillos aromáticos

monocíclicos carbocíclicos (por ejemplo fenilo) y anillos aromáticos carbocíclicos bicíclicos (por ejemplo naftilo), o anillos carbocíclicos benzofusionados (por ejemplo cicloalquilo de C_{3-8} fusionado con un anillo de fenilo, tal como por ejemplo dihidroindenilo o tetrahidronaftalenilo).

Las referencias a "heteroarilo" incluyen referencias a anillos aromáticos heterocíclicos mono- y bicíclicos que contienen 1-4 heteroátomos seleccionados de nitrógeno, oxígeno y azufre. Los ejemplos de anillos aromáticos heterocíclicos monocíclicos incluyen, por ejemplo, tienilo, furilo, pirrolilo, triazolilo, imidazolilo, oxazolilo, tiazolilo, oxadiazolilo, isotiazolilo, isoxazolilo, tiadiazolilo, pirazolilo, pirimidilo, piridazinilo, pirazinilo, piridilo, tetrazolilo y similares. Los ejemplos de anillos aromáticos heterocíclicos bicíclicos incluyen, por ejemplo, quinolinilo, isoquinolinilo, quinazolinilo, quinoxalinilo, cinolinilo, naftiridinilo, indolilo, indazolilo, pirrolopiridinilo, benzofuranilo, benzotienilo, benzoimidazolilo, benzoxazolilo, benzoisoxazolilo, benzotiazolilo, benzoisotiazolilo, benzoxadiazolilo, benzotiadiazolilo y similares.

Las referencias a "heterociclilo" incluyen referencias a un anillo monocíclico no aromático de 5-7 miembros que contiene de 1 a 3 heteroátomos seleccionados de nitrógeno, azufre u oxígeno. Los ejemplos de anillos no aromáticos heterocíclicos incluyen por ejemplo, morfolinilo, piperidinilo, piperazinilo, tiomorfolinilo, oxatianilo, ditianilo, dioxanilo, pirrolidinilo, dioxolanilo, oxatiolanilo, imidazolidinilo, pirazolidinilo y similares.

Las referencias a "anillo heterocíclico o heteroarilo

benzofusionado" incluyen quinolinilo, isoquinolinilo, indolilo, indazolilo, dihidroindolilo, benzofuranilo, benzotienilo, benzoimidazolilo, benzoxazolilo, benzoisoxazolilo, benzotiazolilo, benzoisotiazolilo, benzoxadiazolilo, benzotiadiazolilo, dihidrocromeno, benzotriazolilo, tetrahidroquinoxalinilo y similares.

Preferiblemente, m es 0 ó 1, de preferencia 0. Cuando m representa 1, R^1 es preferiblemente arilo (por ejemplo fenilo).

Preferiblemente, n es 0 ó 1, de preferencia 1.

Cuando n representa 1, R^{2a} es preferiblemente alcoxi de C_{1-3} (por ejemplo metoxi) o halógeno (por ejemplo flúor), de preferencia halógeno (por ejemplo flúor).

Cuando n representa 1, R^{2a} está preferiblemente en la posición *orto* del anillo fenilo.

Cuando X representa SO_2, p es preferiblemente 2 ó 3, de preferencia 2, y cuando X representa CO, p es preferiblemente 1 ó 2, de preferencia 1.

Preferiblemente, R^{2b} es:

hidrógeno;

halógeno (por ejemplo cloro o flúor);

alquilo de C_{1-6} (por ejemplo metilo);

alcoxi de C_{1-6} (por ejemplo metoxi); o

heterociclilo (por ejemplo pirrolidinilo) sustituido opcionalmente con un grupo oxo (por ejemplo, 2-oxopirrolidin-1-ilo).

Muy preferiblemente, R^{2b} es hidrógeno o halógeno (por ejemplo flúor), de preferencia hidrógeno.

Preferiblemente, R^3 representa:

alquilo de C_{1-6} (por ejemplo, metilo, etilo, n-propilo, i-propilo, n-butilo, i-butilo, *sec*-butilo o *t*-butilo), sustituido opcionalmente con uno o más grupos (por ejemplo 1, 2 ó 3) hidroxi, halógeno (por ejemplo flúor) o alcoxi de C_{1-6} (por ejemplo metoxi o etoxi);

alquenilo de C_{2-6} (por ejemplo propenilo);

cicloalquilo de C_{3-8} (por ejemplo ciclopentilo o ciclohexilo);

ciano;

heterociclilo (por ejemplo, piperidinilo, pirrolidinilo o isotiazolidinilo) sustituido opcionalmente con uno o dos grupos oxo;

$-NR^7R^8$;

$-OR^{13}$;

$-SR^{15}$; o

$-CONR^{17}R^{18}$.

También preferiblemente, R^3 y R^{2b} junto con el grupo fenilo al que están unidos, representan indolilo, indazolilo, dihidroindolilo, benzofuranilo, dihidrocromenilo, benzotriazolilo, benzoimidazolilo o tetrahidroquinoxalinilo, sustituido opcionalmente con uno o dos grupos alquilo de C_{1-6} (por ejemplo metilo, etilo, n-propilo, i-propilo, n-butilo, i-butilo, *sec*-butilo, *t*-butilo o pentilo). Muy preferiblemente, R^3 y R^{2b} junto con el grupo fenilo al que están unidos, representan un grupo benzoimidazolilo o indolilo

sustituido con un grupo alquilo de C_{1-6} (por ejemplo etilo).

Muy preferiblemente, R^3 representa:

alquilo de C_{1-6} (por ejemplo n-propilo);

$-NR^7R^8$;

cicloalquilo de C_{3-8} (por ejemplo, ciclopentilo o ciclohexilo);

$-OR^{13}$; o

$-CONR^{17}R^{18}$.

Preferiblemente, R^7 y R^8 representan independientemente:

hidrógeno;

alquilo de C_{1-6} (por ejemplo, metilo, etilo, n-propilo, i-propilo, n-butilo, i-butilo, *sec*-butilo, *t*-butilo, pentilo, i-propilo, i-butilo, $-CH_2C(CH_3)_3$, $-CH(CH_2CH_3)CH_2CH_3$ o $-(CH_2)_2CH(CH_3)_2$);

cicloalquilo de C_{3-8} (por ejemplo ciclopentilo o ciclohexilo);

arilo (por ejemplo fenilo);

-alquil(C_{1-6})-cicloalquilo de C_{3-8} (por ejemplo $-CH_2$-ciclopropilo);

-alquil(C_{1-6})-arilo (por ejemplo $-CH_2$-fenilo o $-(CH_2)_2$-fenilo); o

-CO-alquilo de C_{1-6} (por ejemplo $-COCH_3$).

Muy preferiblemente, R^7 representa hidrógeno y R^8 representa alquilo de C_{1-6} (particularmente etilo o isopropilo, especialmente etilo).

Preferiblemente, R^{13} representa alquilo de C_{1-6} (por ejemplo metilo, etilo, n-propilo, i-propilo, n-butilo, i-butilo, *sec*-butilo o *t*-butilo o pentilo), sustituido opcionalmente con un grupo hidroxi o alcoxi de C_{1-6} (por ejemplo metoxi); de preferencia, R^{13} representa etilo o i-propilo.

Preferiblemente, R^{15} representa alquilo de C_{1-6} (por ejemplo metilo o etilo).

Preferiblemente, R^{17} y R^{18} representan alquilo de C_{1-6} (por ejemplo, ambos representan propilo, o uno representa propilo y el otro representa metilo).

Preferiblemente, R^4 representa –alquil(C_{1-6})-arilo (por ejemplo bencilo) o –alquil(C_{1-6})-heteroarilo (por ejemplo –CH_2-piridinilo, -CH_2-tiazolilo, -CH_2-furanilo, -CH_2-tienilo o –CH_2-pirazolilo), sustituido opcionalmente con uno o dos átomos de halógeno (por ejemplo cloro o flúor). Muy preferiblemente, R^4 representa –alquil(C_{1-6})-arilo (por ejemplo bencilo) sustituido opcionalmente con uno o dos átomos de halógeno (por ejemplo cloro o flúor); de preferencia, R^4 representa bencilo no sustituido.

Preferiblemente, R^5 representa:

-alquilo de C_{1-10} (por ejemplo metilo, etilo, n-propilo, n-butilo, n-pentilo o n-hexilo) sustituido opcionalmente con uno o más grupos alquilo de C_{1-6} (por ejemplo metilo), alcoxi de C_{1-6} (por ejemplo metoxi o –$OCH_2CH(CH_3)_2$) o alquenoxi de C_{2-6} (por ejemplo –$OCH_2C(CH_3)=CH_2$);

-cicloalquilo de C_{3-10} (por ejemplo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, bicicloheptilo, adamantilo o biciclooctilo), sustituido opcionalmente con uno o más grupos alquilo de C_{1-6} (por ejemplo, metilo, etilo o propilo) o halógeno (por ejemplo flúor);

-alquil(C_{1-6})-cicloalquilo de C_{3-10} (por ejemplo –CH_2-ciclohexilo o –CH_2-ciclopropilo);

-arilo (por ejemplo fenilo, dihidroindenilo o tetrahidronaftalenilo) sustituido opcionalmente con uno o más grupos hidroxi o alcoxi de C_{1-6} (por ejemplo metoxi);

-alquil(C_{1-6})-arilo (por ejemplo bencilo, -etil-fenilo, -etil-naftilo, -propil-fenilo, -C(H)(Me)-fenilo, -C(H)(Et)-fenilo, -C(Me)(Me)-bencilo o –C(Me)(Me)-fenilo), sustituido opcionalmente con uno o más grupos halógeno (por ejemplo cloro, bromo o flúor), hidroxi, -OCF_3, haloalquilo de C_{1-6} (por ejemplo –CH_2CF_3 o –CF_3), alquilo de C_{1-6} (por ejemplo, metilo, etilo, n-propilo, i-propilo, n-butilo, i-butilo, *sec*-butilo o *t*-butilo), alquenilo de C_{2-6} (por ejemplo etenilo), alquinilo de C_{2-6}, alcoxi de C_{1-6} (por ejemplo metoxi, etoxi, propoxi, isopropoxi o metiletoxi), ciano, nitro, -$COOR^{22}$ (por ejemplo COOH o COOMe), -SO_2R^{22} (por ejemplo –SO_2Me), -$NR^{22}COR^{23}$ (por ejemplo $NHCOCH_3$), -alquil(C_{1-6})-$NR^{22}R^{23}$ (por ejemplo –$CH_2N(CH_3)_2$), -alquil(C_{1-6})-alcoxi de C_{1-6} (por ejemplo –$CH_2OC(CH_3)_3$), -alcanol de C_{1-6} (por ejemplo –CH_2OH) o –alcoxi(C_{1-6})-CN (por ejemplo OCH_2CN);

-alquil(C_{1-6})-heteroarilo (por ejemplo, -CH_2-furanilo, -CH_2-quinolinilo, -CH_2-tiofenilo, -CH_2-indolilo, -CH_2-benzoimidazolilo, -CH_2-imidazolilo, -CH_2-benzofuranilo, -CH_2-tiazolilo, -CH_2-piridinilo, -CH_2-benzotiazolilo, -CH_2-pirazolilo, -CH_2-isoxazolilo, -CH_2-oxazolilo, -CH_2-pirrolilo, -CH_2-dihidrobenzofuranilo, -CH_2-dihidrobenzodioxinilo o –CH_2-dihidrocromenilo), sustituido opcionalmente con uno o más grupos alquilo de C_{1-6} (por ejemplo metilo, etilo, n-propilo, i-propilo, n-butilo, i-butilo, *sec*-butilo o *t*-butilo), alquenilo de C_{2-6} (por ejemplo, etenilo o propenilo), alquinilo de C_{2-6},

halógeno (por ejemplo, bromo o cloro), haloalquilo de C_{1-6} (por ejemplo, fluoroetilo o trifluorometilo), ciano, alcoxi de C_{1-6} (por ejemplo, metoxi), -$CONR^{22}R^{23}$ (por ejemplo –CONHMe) o –$COOR^{22}$ (por ejemplo, -COOMe);

-heterociclilo (por ejemplo, tetrahidropiranilo o tetrahidrotiopiranilo);

-alquil(C_{1-6})-heterociclilo (por ejemplo, -CH_2-tetrahidropiranilo);

-cicloalquil(C_{3-10})-alquilo de C_{1-10} (por ejemplo, -ciclobutil-isopropilo, -ciclobutil-etilo, -ciclobutil-propilo, -ciclopropil-etilo, -ciclopropil-propilo, -ciclopropil-isopropilo, -ciclopropil-t-butilo, -ciclopropil-$CH_2CH(CH_3)_2$, -ciclopropil-$(CH_2)_2CH(CH_3)_2$, -ciclopropil-$(CH_2)_2CH(CH_3)_2$ o-ciclopropil-$(CH_2)_3CH(CH_3)_2$);

-cicloalquil(C_{3-10})-alquil(C_{1-6})-arilo (por ejemplo –ciclopropil-CH_2-fenilo) sustituido opcionalmente con uno o más átomos de halógeno (por ejemplo cloro);

-cicloalquil(C_{3-10})-arilo (por ejemplo, -ciclopropil-fenilo) sustituido opcionalmente con uno o más grupos halógeno (por ejemplo cloro, bromo o flúor), hidroxi, -OCF_3, haloalquilo de C_{1-6} (por ejemplo, -CH_2CF_3 o-CF_3), alquilo de C_{1-6} (por ejemplo, metilo, etilo, n-propilo, i-propilo, n-butilo, i-butilo, *sec*-butilo o *t*-butilo), alquenilo de C_{2-6} (por ejemplo etenilo), alquinilo de C_{2-6}, alcoxi de C_{1-6} (por ejemplo, metoxi, etoxi, propoxi, isopropoxi o metiletoxi), ciano, nitro, -$COOR^{22}$ (por ejemplo, COOH o COOMe), -SO_2R^{22} (por ejemplo, -SO_2Me), -$NR^{22}COR^{23}$ (por ejemplo $NHCOCH_3$), -alquil(C_{1-6})-$NR^{22}R^{23}$ (por ejemplo –$CH_2N(CH_3)_2$), -alquil(C_{1-6})-alcoxi de C_{1-6} (por ejemplo –

$CH_2OC(CH_3)_3$), -alcanol de C_{1-6} (por ejemplo $-CH_2OH$) o -alcoxi(C_{1-6})-CN (por ejemplo OCH_2CN);

-$C(R^aR^b)$-CONH-alquilo de C_{1-6} (por ejemplo, -$C(R^aR^b)$-CONH-i-butilo);

-$C(R^cR^d)$-CONH-cicloalquilo de C_{3-10} (por ejemplo, $C(R^cR^d)$-CONH-ciclohexilo);

-alquil(C_{1-6})-S-alquilo de C_{1-6} (por ejemplo, -propil-S-metilo o –dimetiletil-S-isobutilo); o

-alquil(C_{1-6})-NR^eR^f (por ejemplo, -dimetilpropil-NR^eR^f).

Muy preferiblemente, R^5 representa:

-cicloalquilo de C_{3-10} (por ejemplo ciclohexilo);

-alquil(C_{1-6})-arilo (por ejemplo, bencilo) sustituido opcionalmente con uno o más grupos halógeno (por ejemplo, cloro, bromo o flúor), $-OCF_3$ o haloalquilo de C_{1-6} (por ejemplo $-CF_3$);

-alquil(C_{1-6})-heteroarilo (por ejemplo, $-CH_2$-tienilo, $-CH_2$-pirazolilo o $-CH_2$-isoxazolilo) sustituido opcionalmente con uno o más grupos alquilo de C_{1-6} (por ejemplo metilo, etilo, isopropilo, propilo o butilo) o haloalquilo de C_{1-6} (por ejemplo CH_2CF_3); o

-heterociclilo (por ejemplo, tetrahidropiranilo).

Preferiblemente, q representa 1 ó 2.

Preferiblemente, R^a representa hidrógeno o alquilo de C_{1-6} (metilo)

Preferiblemente, R^b y R^d representan independientemente alquilo

de C_{1-6} (por ejemplo, metilo, etilo, propilo o butilo) o –alquil(C_{1-6})-SO_2-alquilo de C_{1-6} (por ejemplo, -CH_2CH_2-SO_2CH_3) sustituido opcionalmente con uno o más grupos hidroxi.

Preferiblemente, R^c representa hidrógeno o alquilo de C_{1-6} (metilo).

Preferiblemente, R^e y R^f representan ambos alquilo de C_{1-6} (por ejemplo metilo).

Los compuestos preferidos de acuerdo con la invención incluyen los de los ejemplos E1-E744 mostrados más abajo, o una sal farmacéuticamente aceptable de los mismos.

Los compuestos muy preferidos de acuerdo con la invención incluyen:

ácido fórmico – 5-ciclopentil-3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-*N*-[(1S,2R)-3-{[(1-etil-1*H*-pirazol-4-il)metil]amino}-2-hidroxi-1-(fenilmetil)propil]-2-fluorobenzamida (1:1);

ácido fórmico – 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-2-fluoro-*N*-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-({[3-(trifluorometil)fenil]metil}-amino)propil]-5-[(1-metiletil)amino]benzamida (1:1);

ácido fórmico – 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-*N*-[(1*S*,2*R*)-3-{[(1-etil-1*H*-pirazol-4-il)metil]amino}-2-hidroxi-1-(fenilmetil)propil]-2-fluoro-5-[(1-metiletil)amino]benzamida (1:1);

ácido fórmico – 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-2-fluoro-*N*-{(1*S*,2*R*)-2-hidroxi-1-(fenilmetil)-3-[({3-[(trifluorometil)oxi]fenil}metil)-

amino]propil}-5-[(1-metiletil)amino]benzamida (1:1);

ácido fórmico – N-((1S,2R)-1-bencil-3-{[4-fluoro-3-(trifluorometil)-bencil]amino}-2-hidroxipropil)-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)-2-fluorobenzamida (1:1);

3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-2-fluoro-*N*-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-({[3-(trifluorometil)fenil]metil}amino)-propil]benzamida;

ácido fórmico – 3-(1,1-dioxidotetrahidro-2H-1,2-tiazin-2-il)-5-(etilamino)-N-[(1S,2R)-3-{[(5-etil-3-tienil)metil]amino}-2-hidroxi-1-(fenilmetil)-propil]benzamida (1:1); y

ácido fórmico – 3-(1,1-dioxidotetrahidro-2H-1,2-tiazin-2-il)-5-(etilamino)-2-fluoro-N-{(1S,2R)-2-hidroxi-1-(fenilmetil)-3-[({3-[(trifluorometil)oxi]-fenil}metil)amino]propil}benzamida (1:1);

o una sal farmacéuticamente aceptable de los mismos.

Los compuestos de fórmula (I) pueden formar sales de adición de ácido de los mismos. Se apreciará que para usar en medicina, las sales de los compuestos de fórmula (I) deben ser farmacéuticamente aceptables. Las sales farmacéuticamente aceptables adecuadas serán evidentes para el experto en la materia e incluyen las que se describen en *J. Pharm. Sci.*, 1977, **66**, 1-19, tales como las sales de adición de ácido formadas con ácidos inorgánicos u orgánicos, por ejemplo clorhidratos, bromhidratos, sulfatos, fosfatos, acetatos, benzoatos, citratos, nitratos, succinatos, lactatos, tartratos, fumaratos, maleatos, 1-hidroxi-2-naftoatos, palmoatos, metanosulfonatos, p-

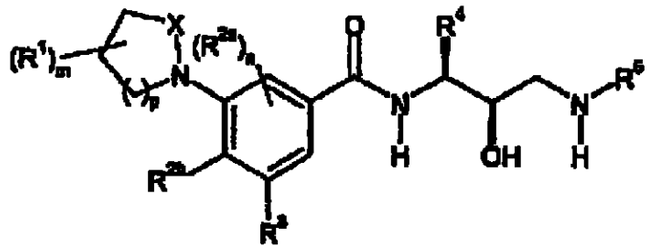
toluenosulfonatos, naftalenosulfonatos, formiatos o trifluoroacetatos. La presente invención incluye dentro de su alcance todas las formas estequiométricas y no estequiométricas posibles.

La presente invención también incluye dentro de su alcance profármacos de los compuestos de fórmula (I). Como se usa aquí, el término "profármaco" significa un compuesto que es convertido en el cuerpo, por ejemplo por hidrólisis en la sangre, en su forma activa que tiene los efectos medicinales. Profármacos farmacéuticamente aceptables se describen en T. Higuchi y V. Stella, "Prodrugs as Novel Delivery Systems", vol. 14, de la serie A.C.S. Symposium Series, Edward B. Roche, ed., "Bioreversible Carriers in Drug Design", American Pharmaceutical Association y Pergamon Press, 1987, y en D. Fleisher, S. Ramon y H. Barbra "Improved oral drug delivery: solubility limitations overcome by the use of prodrugs", *Advanced Drug Delivery Reviews* (1996) 19(2) 115-130, cada una de las cuales se incorpora aquí como referencia. Los ésteres pueden ser activos por sí solos o pueden ser hidrolizables bajo las condiciones *in vivo* en el cuerpo humano. Los grupos éster farmacéuticamente aceptables hidrolizables *in vivo*, que son adecuados incluyen los que se rompen fácilmente en el cuerpo humano para dejar el ácido original o sal.

Los compuestos de fórmula (I) se pueden preparar en forma cristalina o no cristalina y, si son cristalinos, pueden estar solvatados opcionalmente, por ejemplo como el hidrato. Esta invención incluye dentro de su alcance solvatos estequiométricos (por ejemplo hidratos), así como

compuestos que contienen cantidades variables de solventes (por ejemplo agua).

Algunos compuestos de fórmula (I) pueden existir en formas estereoisoméricas (por ejemplo diasterómeros y enantiómeros), y la invención se extiende a cada una de estas formas estereoisoméricas y sus mezclas, incluyendo racematos. Las diferentes formas estereoisoméricas se pueden separar una de otra mediante los métodos usuales, o cualquier isómero dado se puede obtener mediante síntesis estereoespecífica o asimétrica. La invención también se extiende a cualquier forma tautomérica y mezclas de las mismas. Preferiblemente, los compuestos de fórmula (I) están en forma de un solo enantiómero de fórmula (Ia):

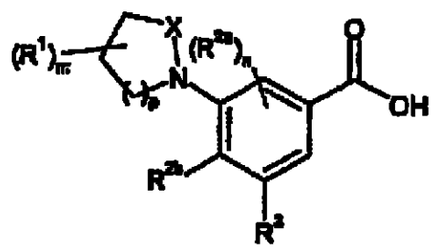


(Ia)

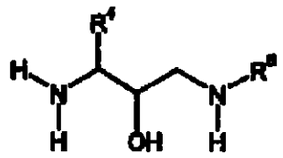
Los compuestos de fórmula (I) y las sales y solvatos de los mismos se pueden preparar con los métodos descritos más adelante, que constituyen un aspecto adicional de esta invención.

Un procedimiento de acuerdo con la invención para preparar un compuesto de fórmula (I), comprende:

(a) hacer reaccionar un compuesto de fórmula (II)



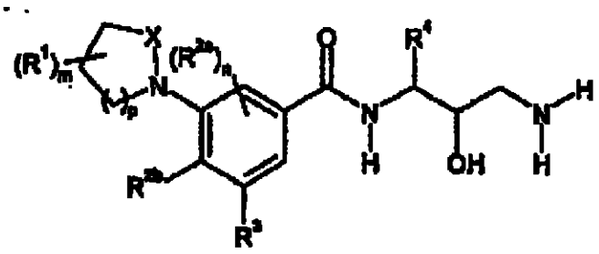
o un derivado activado y opcionalmente protegido del mismo, en donde R^1, m, X, p, R^{2a}, n, R^{2b} y R^3 son como se define arriba, con un compuesto de fórmula (III),



(III)

en donde R^4 y R^5 son como se define arriba; o

(b) preparación de un compuesto de fórmula (I) que comprende la aminación reductiva de un compuesto de fórmula (IV),



(IV)

en donde R^1, m, X, p, R^{2a}, n, R^{2b}, R^3 y R^4 son como se define arriba, con un aldehído o cetona apropiada; o

(c) desproteger un compuesto de fórmula (I), que está protegido;

y opcionalmente, después:

(d) interconversión de los compuestos de fórmula (I) con otros compuestos de fórmula (I).

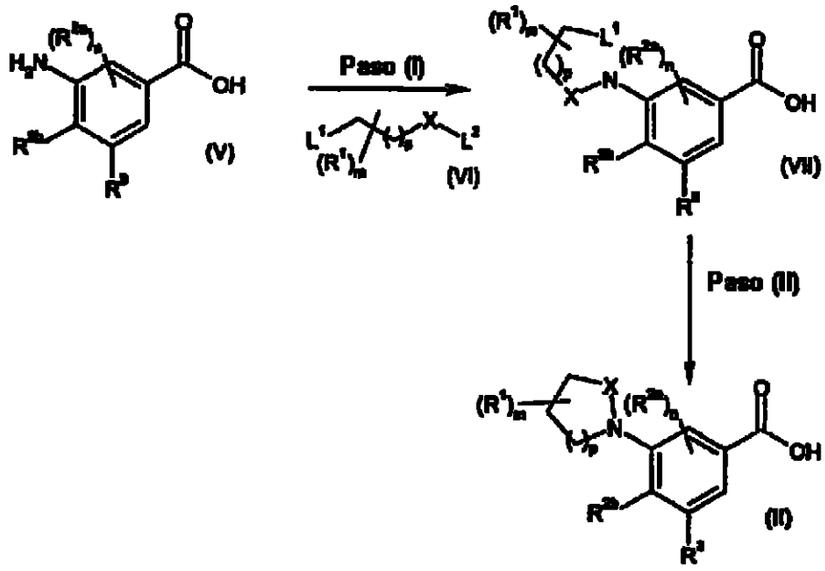
El procedimiento (a) comprende normalmente el uso de carbodiimida soluble en agua, HOBT y una base adecuada tal como alquilamina terciaria o piridina, en un solvente adecuado como DMF, a una temperatura adecuada, por ejemplo entre 0°C y la temperatura ambiente.

El procedimiento (b) comprende normalmente el uso de borohidrurotriacetato de sodio en presencia de un solvente adecuado tal como etanol y diclorometano, a una temperatura adecuada, por ejemplo entre 0°C y la temperatura ambiente.

En el procedimiento (c), los ejemplos de grupos protectores y los medios para su remoción se pueden encontrar en T.W. Greene y P.G.M. Wuts "Protective Groups in Organic Synthesis" (J. Wiley and Sons, 3ª ed. 1999). Los grupos protectores de amina adecuados incluyen arilsulfonilo (por ejemplo tosilo), acilo (por ejemplo acetilo), carbamoilo (por ejemplo benciloxicarbonilo o t-butoxicarbonilo) y arilalquilo (por ejemplo bencilo), que pueden ser removidos por hidrólisis o hidrogenólisis según sea apropiado. Otros grupos protectores de amina adecuados incluyen trifluoroacetilo (-$COCF_3$), que puede ser removido por hidrólisis catalizada con una base. Los grupos protectores de hidroxi adecuados serían los grupos basados en sililo tales como t-butildimetilsililo, que puede ser removido usando los métodos estándares, por ejemplo usando un ácido tal como ácido trifluoroacético o ácido clorhídrico, o una fuente de fluoruro tal como fluoruro de tetra-n-butilamonio.

El procedimiento (d) se puede realizar usando interconversiones convencionales tales como epimerización, oxidación, reducción, alquilación, sustitución aromática, hidrólisis de éster, formación o remoción de enlace amida y sulfonilación. Un ejemplo de dicha reacción de interconversión puede incluir la interconversión de un compuesto de fórmula (I) en donde R^3 representa un grupo que contiene alquenilo de C_{2-6}, a un compuesto correspondiente de fórmula (I) en donde R^3 representa un grupo que contiene alquilo de C_{1-6}, usando condiciones reductivas o hidrogenación estándar. Un ejemplo adicional de dicha reacción de interconversión puede incluir la interconversión de un compuesto de fórmula (I) en donde R^3 representa –alquil(C_{1-6})-N_3, a un compuesto correspondiente de fórmula (I) en donde R^3 representa –alquil(C_{1-6})-NH_2, usando hidrogenación estándar o condiciones reductivas. Un ejemplo más de dicha reacción de interconversión puede incluir la interconversión de un compuesto de fórmula (I) en donde R^3 representa un grupo nitro, a un compuesto correspondiente de fórmula (I) en donde R^3 representa NH_2, usando hidrogenación estándar o condiciones reductivas.

Los compuestos de fórmula (II), o sus derivados activados y opcionalmente protegidos, se pueden preparar de acuerdo con el siguiente procedimiento:

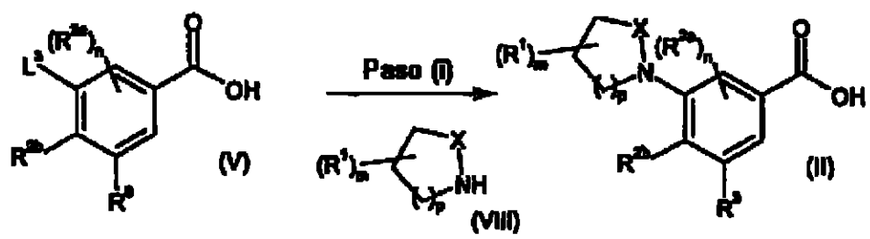


en donde R^{2a}, n, R^{2b}, R^3, p, X, R^1 y m son como se define arriba, y L^1 y L^2 representan independientemente un grupo saliente adecuado tal como un átomo de halógeno (por ejemplo yodo, cloro o bromo).

El paso (i) comprende normalmente el uso de un solvente adecuado, tal como diclorometano, y una base adecuada como trietilamina.

El paso (ii) comprende normalmente el uso de hidruro de sodio en presencia de un solvente adecuado como tetrahidrofurano, bajo nitrógeno.

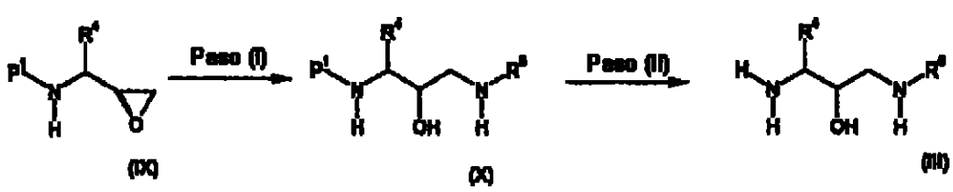
Los compuestos de fórmula (II), o los derivados activados y opcionalmente protegidos de los mismos, también se pueden preparar de acuerdo con el siguiente procedimiento:



en donde R^{2a}, n, R^{2b}, R^3, p, X, R^1 y m son como se define arriba, y L^3 representa un grupo saliente adecuado tal como un átomo de halógeno (por ejemplo yodo, cloro o bromo).

El paso (i) comprende normalmente el uso de carbonato de cesio, 4,5-bis(difenilfosfino)-9,9-dimetilxanteno y un catalizador adecuado, tal como tris(dibencilidenacetona)dipaladio (0), bajo condiciones adecuadas, tales como reflujo bajo argón en presencia de un solvente adecuado como dioxano.

Los compuestos de fórmula (III) se pueden preparar de acuerdo con el siguiente procedimiento:



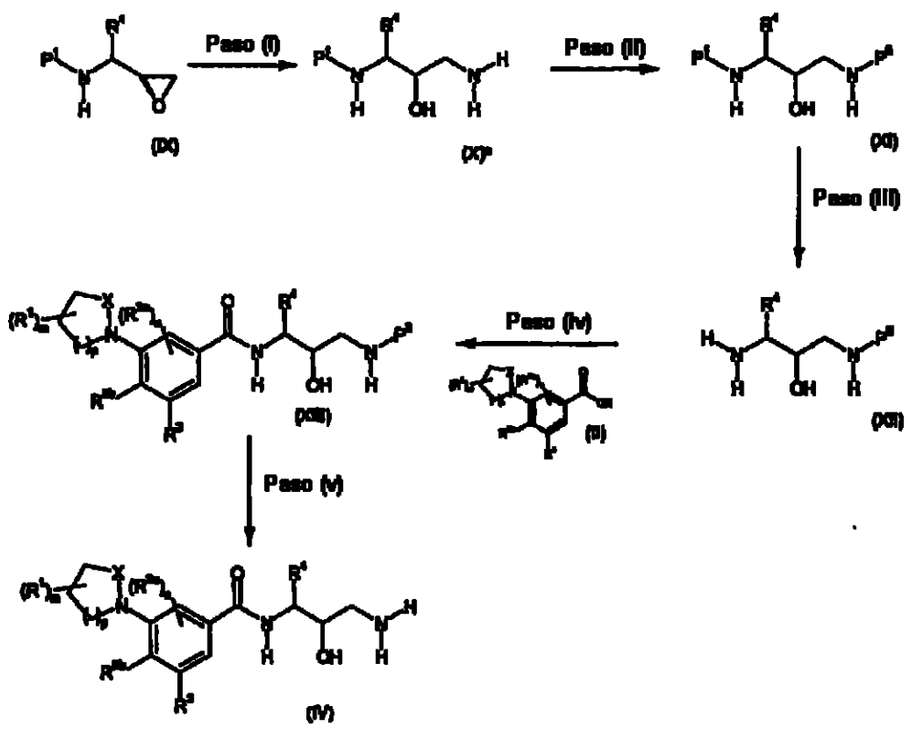
en donde R^4 y R^5 son como se define arriba y P^1 representa un grupo protector de amina adecuado, tal como t-butoxicarbonilo.

El paso (i) comprende normalmente la reacción de un compuesto de fórmula (IX) con un compuesto de fórmula NH_2R^5 en presencia de un solvente adecuado, por ejemplo etanol, a una temperatura adecuada, por

ejemplo a reflujo.

El paso (ii) comprende normalmente el uso de reacciones de desprotección adecuadas como se describe arriba para el procedimiento (c), por ejemplo cuando P^1 representa t-butoxicarbonilo, la desprotección comprende normalmente el uso de ácido trifluoroacético en presencia de un solvente adecuado como diclorometano, a una temperatura adecuada, por ejemplo entre 0°C y la temperatura ambiente.

Los compuestos de fórmula (IV) se pueden preparar de acuerdo con el siguiente procedimiento:



en donde R^1, m, X, p, R^{2a}, n, R^{2b}, R^3, R^4 y P^1 son como se define arriba, y P^2 representa un grupo protector de amina adecuado diferente de P^1,

tal como –$COOCH_2$-fenilo.

El paso (i) comprende normalmente la reacción de un compuesto de fórmula (IX) en amoniaco acuoso, en presencia de un solvente adecuado, por ejemplo etanol, a una temperatura adecuada, por ejemplo a reflujo.

Cuando P^2 representa –$COOCH_2$-fenilo, el paso (ii) comprende normalmente el uso de $ClCOOCH_2$-fenilo en presencia de una base adecuada, por ejemplo trietilamina, un solvente adecuado, por ejemplo dimetilformamida, a una temperatura adecuada, por ejemplo entre 0°C y la temperatura ambiente.

El paso (iii) comprende normalmente el uso de reacciones de desprotección adecuadas como se describe arriba para el procedimiento (c); por ejemplo, cuando P^1 representa t-butoxicarbonilo, la desprotección comprende normalmente el uso de ácido trifluoroacético en presencia de un solvente adecuado como diclorometano, a una temperatura adecuada, por ejemplo entre 0°C y la temperatura ambiente.

El paso (iv) comprende normalmente hacer reaccionar un compuesto de fórmula (XII) con un compuesto de fórmula (II) en presencia de carbodiimida soluble en agua y HOBT.

El paso (iv) comprende normalmente el uso de reacciones de desprotección adecuadas como se describe arriba para el procedimiento (c); por ejemplo, cuando P^2 representa –$COOCH_2$-fenilo, la desprotección comprende normalmente el uso de un catalizador adecuado, por ejemplo paladio, en presencia de un solvente adecuado, por ejemplo agua y etanol, y

en presencia de una fuente de hidrógeno adecuada, por ejemplo formiato de amonio, a una temperatura adecuada, por ejemplo 60°C.

Los compuestos de fórmula (V) están disponibles comercialmente, o se pueden preparar por interconversión de compuestos disponibles comercialmente de fórmula (V).

Los compuestos de fórmula (VI), (VIII) y (IX) son conocidos, o se pueden preparar de acuerdo con los procedimientos conocidos.

Como un aspecto adicional de la invención, se provee aquí un compuesto de fórmula (I), o una sal o solvato farmacéuticamente aceptable del mismo, para usar como un agente farmacéutico, particularmente en el tratamiento de pacientes con enfermedades caracterizadas por concentración elevada de ß-amiloide o depósitos de ß-amiloide.

De acuerdo con otro aspecto de la invención, se provee el uso de un compuesto de fórmula (I) o una sal o solvato fisiológicamente aceptable del mismo, para la fabricación de un medicamento para el tratamiento de pacientes con enfermedades caracterizadas por concentración elevada de ß-amiloide o depósitos de ß-amiloide.

En un aspecto adicional o alternativo, se provee un método de tratamiento de un sujeto humano o animal con una enfermedad caracterizada por concentración elevada de ß-amiloide o depósitos ß-amiloides, dicho método comprendiendo administrar a dicho sujeto humano o animal una cantidad efectiva de un compuesto de fórmula (I) o una sal o solvato fisiológicamente aceptable del mismo.

Como un aspecto adicional de la invención, se provee aquí una composición farmacéutica que comprende un compuesto de fórmula (I) o una sal o solvato farmacéuticamente aceptable del mismo, para usar en el tratamiento de enfermedades caracterizadas por concentración elevada de ß-amiloide o depósitos de ß-amiloide.

Será apreciado por el experto en la materia que al referirse aquí al tratamiento este se extiende a la profilaxis y también al tratamiento de enfermedades caracterizadas por concentración elevada de ß-amiloide o depósitos de ß-amiloide.

Los compuestos de acuerdo con la invención se pueden formular para su administración por cualquier vía conveniente y, por lo tanto, la invención también incluye dentro de su alcance composiciones farmacéuticas para usar en la terapia de enfermedades caracterizadas por concentración elevada de ß-amiloide o depósitos de ß-amiloide, que comprenden un compuesto de fórmula (I) o una sal o solvato fisiológicamente aceptable del mismo, si fuera conveniente junto con uno o más diluyentes o vehículos fisiológicamente aceptables.

Será apreciará que las enfermedades caracterizadas por concentración elevada de ß-amiloide o depósitos ß-amiloides incluyen la enfermedad de Alzheimer, deterioro cognitivo ligero, síndrome de Down, hemorragia cerebral hereditaria con ß-amiloidosis de tipo Dutch, angiopatía cerebral ß-amiloide y varios tipos de demencias degenerativas, tales como las asociadas con la enfermedad de Parkinson, parálisis supranuclear progresiva,

degeneración basal cortical y la enfermedad de Alzheimer de tipo de cuerpo difuso de Lewis.

Muy preferiblemente, la enfermedad caracterizada por concentración elevada de ß-amiloide o depósitos de ß-amiloide, es la enfermedad de Alzheimer.

También se provee un procedimiento para preparar dicha formulación farmacéutica que comprende mezclar los ingredientes.

Los compuestos de fórmula (I) se pueden usar en combinación con otros agentes terapéuticos. Ejemplos adecuados de estos otros agentes terapéuticos pueden ser los inhibidores de acetilcolina esterasa (tales como tetrahidroaminoacridina, clorhidrato de donepezilo y rivastigmina), inhibidores de gamma secretasa, agentes antiinflamatorios (tales como inhibidores de ciclooxigenasa II), antioxidantes (tales como vitamina E y ginkolidesor), estatinas o inhibidores de p-glicoproteína (P-gp) (tales como ciclosporina A, veraparnilo, tamoxifeno, quinidina, vitamina E-TGPS, ritonavir, acetato de megestrol, progesterona, rapamicina, 10,11-metanodibenzosuberano, fenotiazinas, derivados de acridina tales como GF120918, FK506, VX-710, LY335979, PSC-833, GF-102 y 918).

Cuando los compuestos se usan en combinación con otros agentes terapéuticos, los compuestos se pueden administrar ya sea de forma secuencial o simultánea por cualquier vía conveniente.

Los compuestos de acuerdo con la invención se pueden formular por ejemplo para administración oral, inhalación, intranasal, bucal, enteral,

parenteral, tópica, sublingual, intratecal o rectal, preferiblemente para administración oral.

Las tabletas y cápsulas para administración oral pueden contener excipientes convencionales tales como agentes aglutinantes, por ejemplo jarabe, acacia, gelatina, sorbitol, tragacanto, mucílago de almidón, celulosa o polivinilpirrolidona; rellenos, por ejemplo lactosa, celulosa microcristalina, azúcar, almidón de maíz, fosfato de calcio o sorbitol; lubricantes, por ejemplo estearato de magnesio, ácido esteárico, talco, polietilenglicol o sílice; desintegrantes, por ejemplo, almidón de papa, croscarmelosa de sodio o almidón glicolato de sodio; o agentes de mojado tales como laurilsulfato de sodio. Las tabletas se pueden recubrir de acuerdo con los métodos conocidos en la técnica. Las preparaciones orales líquidas pueden estar en la forma, por ejemplo, de suspensiones acuosas u oleosas, soluciones, emulsiones, jarabes o elíxires, o se pueden presentar como un producto seco para su reconstitución con agua u otro vehículo adecuado antes de usar. Dichas preparaciones líquidas pueden contener aditivos convencionales, tales como agentes de suspensión, por ejemplo, jarabe de sorbitol, metilcelulosa, jarabe de glucosa/azúcar, gelatina, hidroximetilcelulosa, carboximetilcelulosa, gel de estearato de aluminio o grasas comestibles hidrogenadas; agentes emulsionantes, por ejemplo lecitina, monooleato de sorbitán o acacia; vehículos no acuosos (que pueden incluir aceites comestibles), por ejemplo aceite de almendra, aceite de coco fraccionado, ésteres oleosos, propilenglicol o alcohol etílico; o conservadores, por ejemplo,

p-hidroxibenzoatos de metilo o propilo, o ácido sórbico. Las preparaciones también pueden contener sales amortiguadoras, saborizantes, agentes colorantes o edulcorantes (por ejemplo manitol), según sea apropiado. Para administración bucal, las composiciones pueden tomar la forma de tabletas o pastillas formuladas de la manera convencional.

Los compuestos también se pueden formular como supositorios, por ejemplo conteniendo bases de supositorio convencionales tales como manteca de cacao u otros glicéridos.

Los compuestos de acuerdo con la invención también se pueden formular para administración parenteral por inyección de bolo o infusión continua, y se pueden presentar en forma de dosis unitaria, por ejemplo como ampolletas, frascos, infusiones de volumen pequeño o jeringas preparadas, o en recipientes de dosis múltiples con un conservador. Las composiciones pueden tomar formas tales como soluciones, suspensiones o emulsiones, en vehículos acuosos o no acuosos, y pueden contener agentes de formulación tales como antioxidantes, amortiguadores, agentes antimicrobianos o agentes ajustadores de tonicidad. Alternativamente, el ingrediente activo puede estar en forma de polvo para su reconstitución antes de usar con un vehículo adecuado, por ejemplo agua estéril libre de pirógenos. La presentación sólida seca se puede preparar cargando asépticamente un polvo estéril en recipientes estériles individuales, o cargando asépticamente una solución estéril en cada recipiente y secando por congelación.

Cuando los compuestos de la invención se administran

tópicamente, se pueden presentar como una crema, ungüento o parche.

La composición puede contener de 0.1% a 99% en peso, de preferencia de 10% a 60% en peso, del material activo, dependiendo del método de administración.

La dosis del compuesto usado en el tratamiento de los trastornos anteriormente mencionados varía como es usual según la seriedad de los trastornos, el peso del paciente y otros factores similares. Sin embargo, como una guía general, las dosis unitarias adecuadas pueden ser de 0.05 a 3,000 mg, y dichas dosis unitarias se pueden administrar más de una vez al día, por ejemplo una vez, dos veces, tres veces o cuatro veces al día (de preferencia una o dos veces); y dicha terapia se puede prolongar varias semanas, meses o años.

Todas las publicaciones citadas en esta especificación, que incluyen sin limitación, patentes y solicitudes de patente, se incorporan aquí como referencia como si se indicara específica e individualmente que cada publicación individual es incorporada en la presente como referencia.

EJEMPLOS

Preparación de Intermediarios

Descripción 1

Ester metílico de ácido 3-amino-5-nitro-benzoico (D1)

A una solución de ácido 3-amino-5-nitro-benzoico (65 g, 357

mmol, 1 eq.) en MeOH (650 ml), a 0°C, se le agregó a gotas $SOCl_2$ (39 ml, 536 mmol, 1.5 eq.). La solución resultante se dejó calentar a temperatura ambiente y se agitó 16 h. Se agregó a gotas una porción más de $SOCl_2$ (10 ml, 137 mmol, 0.4 eq.) y la solución se agitó a temperatura ambiente durante 5 h, a 50°C durante 2 h, y después se enfrió a temperatura ambiente y se concentró al vacío. El residuo se disolvió en AcOEt y la fase orgánica se lavó con solución acuosa saturada de $NaHCO_3$, se secó sobre $MgSO_4$ y se concentró al vacío. El residuo sólido se trituró con AcOEt/iso-hexano, para dar el éster metílico de ácido 3-amino-5-nitro-benzoico (D1) (55 g, 78%) como un sólido amarillo claro.

Descripción 2

Ester metílico del ácido 3-(4-cloro-butanoilamino)-5-nitro-benzoico (D2)

A una solución del éster metílico del ácido 3-amino-5-nitro-benzoico (D1) (38 g, 194 mmol, 1 eq.) en CH_2Cl_2 (350 ml), se le agregó NEt_3 (32 ml, 230 mmol, 1.2 eq.), seguido por cloruro de 4-clorobutirilo (24.7 ml, 220 mmol, 1.13 eq.), gota a gota durante 20 min. La mezcla resultante se dejó calentar a temperatura ambiente y se agitó 30 min. La fase orgánica se lavó entonces con una solución acuosa de HCl 2N, se secó sobre $MgSO_4$ y se concentró al vacío. El residuo se trituró con iso-hexano y Et_2O, para dar el éster metílico del ácido 3-(4-cloro-butanoilamino)-5nitro-benzoico D2 (56 g, 96%), como un sólido pardo.

Descripción 3

Ester metílico del ácido 3-(5-cloro-pentanoilamino)-5-nitro-benzoico (D3)

Se agregó durante 2 min cloruro de 5-clorovalerilo (2.64 g, 17 mmol, 1.1 eq.) en CH_2Cl_2 (5 ml) a una solución agitada de éster metílico de ácido 3-amino-5-nitro-benzoico (D1) (3 g, 15.3 mmol, 1 eq.) y NEt_3 (2.6 ml, 18 mmol, 1.2 eq.) en CH_2Cl_2 (30 ml). La mezcla resultante se agitó 1 h a temperatura ambiente y después se lavó con una solución acuosa de HCl 2N, se secó sobre $MgSO_4$ y se concentró al vacío. El residuo se trituró con CH_2Cl_2 para dar el éster metílico del ácido 3-(5-cloro-pentanoilamino)-5-nitro-benzoico D3 (6 g, 112%), como un aceite pardo.

Descripción 4a

Ester metílico del ácido 3-amino-5-(2-oxo-pirrolidin-1-il)-benzoico (D4a)

Se cargó un matraz con éster metílico del ácido 3-nitro-5-(2-oxo-pirrolidin-1-il)-benzoico (B27) (5 g, 19 mmol, 1 eq.), paladio al 10% sobre carbón (50% en húmedo, 750 mg, 7.5% p/p), NH_4COOH (11.9 g, 190 mmol, 10 eq.) H_2O (30 ml) y MeOH (60 ml). La mezcla resultante se agitó a 50°C durante 1.5 h, se enfrió a temperatura ambiente y el catalizador se separó por filtración a través de una almohadilla de celite. La mayor parte del MeOH se removió al vacío y el residuo se diluyó con una solución acuosa saturada de $NaHCO_3$. La fase acuosa se extrajo dos veces con AcOEt. La fase orgánica

combinada se secó sobre $MgSO_4$ y se concentró al vacío, para dar un sólido blanquecino. Después, el catalizador se lavó tres veces con DMF y la fase orgánica combinada se concentró al vacío. El residuo se combinó con el material obtenido previamente y se trituró con Et_2O, para dar el éster metílico del ácido amino-5-(2-oxo-pirrolidin-1-il)-benzoico (D4a) (3.9 g, 88%) como un sólido blanco, que se usó en el siguiente paso sin mayor purificación.

Descripción 4a (Procedimiento alternativo)

Ester metílico del ácido 3-amino-5-(2-oxo-pirrolidin-1-il)-benzoico (D4a)

A una solución del ácido 3-amino-5-(2-oxo-pirrolidin-1-il)-benzoico (D6) (2.2 g, 10 mmol, 1 eq.) en MeOH/Et_2O (1:1, 20 ml), se le agregó clorhidrato de 1-(3-dimetilaminopropil)-3-etil-carbodiimida (2.3 g, 12 mmol, 1.2 eq.), DMAP (112 mg, 1 mmol, 0.1 eq.), y la mezcla resultante se agitó a temperatura ambiente durante 16 h; después se diluyó con AcOEt. La fase orgánica se lavó con una solución acuosa saturada de $NaHCO_3$, se secó sobre $MgSO_4$ y se concentró al vacío. El residuo se trituró con Et_2O, para dar el éster metílico del ácido 3-amino-5-(2-oxo-pirrolidin-1-il)-benzoico (D4a) (1.6 g, 68%) como un sólido blanco.

Descripción 4b

Ester metílico del ácido 3-amino-5-(2-oxo-piperidin-1-il)-benzoico (D4b)

El compuesto de la descripción 4b se preparó de manera análoga a la descripción 4a, a partir de éster metílico del ácido 3-nitro-5-(2-oxo-piperidin-1-il)-benzoico (B82).

Descripción 5

Acido 3-bromo-5-nitro-benzoico (D5)

A una solución de ácido 3-amino-5-nitro-benzoico (17.6 g, 96.6 mmol, 1 eq.) en solución acuosa de HBr al 48% (180 ml), a 0°C, se le agregó en porciones $NaNO_2$ (8.67 g, 126 mmol, 1.3 eq.) durante 20 min. La temperatura se mantuvo por debajo de 8°C durante esta adición. La mezcla resultante se agregó entonces a una suspensión de CuBr (9.7 g, 67.6 mmol, 0.7 eq.) en solución acuosa de HBr al 48% (50 ml), a 65°C durante 40 min. La temperatura se mantuvo por arriba de 60°C durante la adición. La mezcla resultante se agitó a 70°C durante 45 min, se enfrió a temperatura ambiente y se diluyó con 1L de agua. La fase acuosa se extrajo tres veces con Et_2O. La capa orgánica combinada se lavó dos veces con H_2O, se secó sobre $MgSO_4$ y se concentró al vacío, para dar el ácido 3-bromo-5-nitro-benzoico (D5) (21 g, 885) como un sólido pardo. $[M-H]^-$ = 245.7, t.r. = 2.82 min.

Descripción 6

Acido 3-amino-5-(2-oxo-pirrolidin-1-il)-benzoico (D6)

A una solución de ácido 3-nitro-5-(2-oxo-pirrolidin-1-il)-benzoico (A27) (4 g, 16 mmol, 1 eq.) en MeOH/H_2O (9:1, 40 ml), se le agregó paladio al 10% sobre carbón (50% en húmedo, 800 mg, 0.1 eq. p/p). La mezcla resultante se agitó 6 h a presión atmosférica bajo una atmósfera de hidrógeno. El catalizador se removió por filtración a través de una almohadilla de celite y el solvente se removió al vacío. El residuo se secó a 60°C al vacío durante 16 h, para dar el ácido 3-amino-5-(2-oxo-pirrolidin-1-il)-benzoico (D6) (3.34 g, 15.2 mmol, 95%) como un sólido pardo claro. $[M-H]^-$ = 218.8, t.r. = 1.86 min.

Descripción 7

Acido 3-bromo-5-yodo-benzoico (D7)

El compuesto de la descripción 7 está disponible comercialmente de Avocado Research Chemicals Ltd.

Descripción 8a

Ester metílico del ácido 3-bromo-5-yodo-benzoico (D8a)

A una solución de ácido 3-bromo-5-yodo-benzoico (D7) (14.6 g, 44.7 mmol, 1 eq.) en MeOH (150 ml), a 0 °C, se le agregó $SOCl_2$ (3.9 ml, 53.6 mmol, 1.2 eq.). La solución resultante se puso en reflujo durante 2 h, se enfrió a temperatura ambiente y se concentró al vacío. El residuo se diluyó con AcOEt y se lavó dos veces con una solución acuosa de NaOH 2N y después

con salmuera; se secó sobre $MgSO_4$ y se concentró al vacío, para dar el éster metílico del ácido 3-bromo-5-yodo-benzoico (D8a) (14.8 g, 97%), como un sólido pardo claro.

Descripción 8b

Ester *ter*-butílico del ácido 3-bromo-5-yodo-benzoico (D8b)

A una solución de ácido 3-bromo-5-yodo-benzoico (D7) (50 g, 153 mmol, 1 eq.) en CH_2Cl_2 (500 ml), se le agregó clorhidrato de 1-(3-dimetilaminopropil)-3-etil-carbodiimida (30.8 g, 160 mmol, 1.05 eq.), DMAP (14 g, 114 mmol, 0.75 eq.) y *ter*-butanol (90 ml, 917 mmol, 6 eq.). La mezcla resultante se agitó a temperatura ambiente durante 48 h. Entonces se agregó DMAP (4.67 g, 38 mmol, 0.25 eq.) y la solución se agitó durante otras 24 h; después se concentró al vacío. El residuo se disolvió en AcOEt y se lavó secuencialmente con una solución acuosa de HCl 2N, una solución acuosa de NaOH 1 N y salmuera; se secó sobre $MgSO_4$ y se concentró al vacío, para dar el éster *ter*-butílico del ácido 3-bromo-5-yodo-benzoico (D8b) (50.6 g, 86%), como un sólido pardo.

Descripción 8b (Procedimiento alternativo)

Ester *ter*-butílico del ácido 3-bromo-5-yodo-benzoico (D8b)

A una solución de ácido 3-bromo-5-yodo-benzoico (D7) (50 g, 153 mmol, 1 eq.) en CH_2Cl_2 (500 ml), se le agregó clorhidrato de 1-(3-dimetilaminopropil)-3-etil-carbodiimida (30.8 g, 160 mmol, 1.05 eq.), DMAP (14

g, 114 mmol, 0.75 eq.) y *ter*-butanol (90 ml, 917 mmol, 6 eq.). La mezcla resultante se agitó a temperatura ambiente durante 48 h y después se le agregó DMAP (4.67 g, 38 mmol, 0.25 eq.), y la solución se agitó durante otras 24 h; después se concentró al vacío. El residuo se diluyó con AcOEt y se lavó secuencialmente con una solución acuosa de HCl 2N, una solución acuosa 1N de NaOH y salmuera; se secó sobre $MgSO_4$ y se concentró al vacío, para dar el éster *ter*-butílico del ácido 3-bromo-5-yodo-benzoico (D8b) (50.6 g, 86%) como un sólido pardo.

Descripción 9a

Ester metílico del ácido 3-bromo-5-(2-oxo-pirrolidin-1-il)-benzoico (D9a)

Un matraz se cargó, bajo nitrógeno, con éster metílico del ácido 3-bromo-5-yodo-benzoico (D8a) (14.8 g, 43.4 mmol, 1 eq.), Cs_2CO_3 (21 g, 65 mmol, 1.5 eq.), tris(dibencilidenacetona)dipaladio (0) (794 mg, 0.87 mmol, 0.02 eq.), Xantphos (1.5 g, 2.6 mmol, 0.06 eq.) y dioxano (150 ml). Se le agregó pirrolidin-2-ona (5 ml, 5.54 mmol, 1.5 eq.) por medio de una jeringa y la mezcla resultante se agitó a 55 °C durante 5 días; después se enfrió a temperatura ambiente y se concentró al vacío. El residuo se dividió entre H_2O y AcOEt y la fase acuosa se volvió a extraer con AcOEt. La solución orgánica combinada se secó sobre $MgSO_4$ y se concentró al vacío, para dar un residuo sólido. La purificación del residuo por cromatografía de vaporización instantánea sobre gel de sílice (iso-hexano/AcOEt: 4/1 a 1/1), dio el éster

metílico del ácido 3-bromo-5-(2-oxo-pirrolidin-1-il)-benzoico (D9a) (6.4 g, 50%) como un sólido blanco. $[M+H]^+$ = 299.9, t.r. = 2.95 min.

Descripción 9a (Procedimiento alternativo)

Ester metílico del ácido 3-bromo-5-(2-oxo-pirrolidin-1-il)-benzoico (D9a)

A una solución de éster metílico del ácido 3-bromo-5-(4-cloro-butanoilamino)-benzoico (D13) (530 mg, 1.6 mmol, 1 eq.) en THF (5 ml), a temperatura ambiente, se le agregó NaH (60% en aceite mineral, 64 mg, 1.7 mmol, 1.1 eq.), y la mezcla resultante se agitó a temperatura ambiente durante 2 h. Después se le agregó H_2O y la mezcla resultante se diluyó con AcOEt. Las dos capas se separaron y la fase orgánica se secó sobre $MgSO_4$ y se concentró al vacío, para dar el éster metílico del ácido 3-bromo-5-(2-oxo-pirrolidin-1-il)-benzoico (D9a) (361 mg, 76%), como un sólido amarillo. $[M-H]^-$ = 296.3, t.r. = 2.49.

Descripción 9b

Ester *ter*-butílico del ácido 3-bromo-5-(2-oxo-pirrolidin-1-il)-benzoico (D9b)

Un matraz se cargó, bajo nitrógeno, con éster *ter*-butílico del ácido bromo-5-yodo-benzoico (D8b) (11.5 g, 30 mmol, 1 eq.), Cs_2CO_3 (13.7 g, 42 mmol, 1.5 eq.), tris(dibencilidenacetona)dipaladio (0) (549 mg, 0.6 mmol, 0.02 eq.), Xantphos (1.04 g, 1.8 mmol, 0.06 eq.) y dioxano (100 ml). Entonces

246
246

se le agregó pirrolidin-2-ona (2.5 ml, 33 mmol, 1.1 eq.) por medio de una jeringa y la mezcla resultante se agitó a 60 °C durante 60 h; después se enfrió a temperatura ambiente y se concentró al vacío. El residuo se dividió entre H_2O y AcOEt y la fase acuosa se volvió a extraer con AcOEt. La solución orgánica combinada se secó sobre $MgSO_4$ y se concentró al vacío, para dar un residuo sólido que se trituró con Et_2O para dar el éster *ter*-butílico del ácido 3-bromo-5-(2-oxo-pirrolidin-1-il)-benzoico (D9b) (6.63 g, 65%), como un sólido blanquecino. El filtrado se concentró al vacío. La purificación del residuo por cromatografía de vaporización instantánea sobre gel de sílice (iso-hexano/AcOEt: 4/1 a 1/1), dio 1.46 g (14%) más del éster *ter*-butílico del ácido 3-bromo-5-(2-oxo-pirrolidin-1-il)-benzoico (D9b), como un sólido blanco. $[M+H-tBu)]^+$ = 285.9, t.r. = 3.46 min.

Descripción 10

Ester *ter*-butílico del ácido 3-bromo-5-(2-oxo-piperidin-1-il)-benzoico (D10)

Un matraz se cargó, bajo nitrógeno, con éster *ter*-butílico del ácido 3-bromo-5-yodo-benzoico (D8b) (6.42 g, 16.7 mmol, 1 eq.), Cs_2CO_3 (7.6 g, 23.4 mmol, 1.4 eq.), tris(dibencilidenacetona)dipaladio (0) (307 mg, 0.33 mmol, 0.02 eq.), Xantphos (578 mg, 1 mmol, 0.06 eq.) y dioxano (120 ml). Entonces se le agregó δ-valerolactama (1.9 ml, 20 mmol, 1.2 eq.) por medio de una jeringa y la mezcla resultante se agitó a 60°C durante 40 h; después se enfrió a temperatura ambiente y se concentró al vacío. El residuo se

dividió entre H_2O y AcOEt y la fase acuosa se volvió a extraer con AcOEt. La solución orgánica combinada se secó sobre $MgSO_4$ y se concentró al vacío. La purificación por cromatografía de vaporización instantánea sobre gel de sílice (iso-hexano/AcOEt: 3/1 a 1/1) dio el éster *ter*-butílico del ácido 3-bromo-5-(2-oxo-piperidin-1-il)-benzoico (D10) (4 g, 68%) como un sólido blanco. t.r. = 2.88 min.

Descripción 11

Ester metílico del ácido 3-bromo-5-nitro-benzoico (D11)

A una solución de ácido 3-bromo-5-nitro-benzoico (D5) (22.3 g, 90.6 mmol, 1 eq.) en MeOH (300 ml), a 0°C, se le agregó $SOCl_2$ (7.9 ml, 108 mmol, 1.2 eq.), gota a gota. La solución resultante se agitó a reflujo durante 4 h y después se enfrió a temperatura ambiente y se concentró al vacío. El residuo se diluyó con AcOEt, se lavó dos veces con una solución acuosa de NaOH 2N y una vez con salmuera; se secó sobre $MgSO_4$ y se concentró al vacío, para dar el éster metílico del ácido 3-bromo-5-nitro-benzoico (D11) (22.1 g, 94%) como un sólido pardo claro; t.r. = 3.18 min.

Descripción 11 (Procedimiento alternativo)

Ester metílico del ácido 3-bromo-5-nitro-benzoico (D11)

A una solución enfriada con hielo de ácido 3-bromo-5-nitro-benzoico (D5) (2.5 g, 10 mmol, 1 eq.) en MeOH (25 ml), se le agregó $SOCl_2$ (1 ml, 15 mmol, 1.5 eq.), gota a gota. La solución resultante se dejó calentar a

temperatura ambiente y después se agitó a 60°C durante 3 h; se enfrió a temperatura ambiente y se concentró al vacío. El residuo se disolvió en AcOEt y la capa orgánica se lavó con una solución acuosa saturada de $NaHCO_3$, se secó sobre $MgSO_4$ y se concentró al vacío, para dar el éster metílico del ácido 3-bromo-5-nitro-benzoico (D11) (2.6 g, 100%) como un sólido amarillo; t.r. = 3.22 min.

Descripción 12

Ester metílico del ácido 3-amino-5-bromo-benzoico (D12)

A una solución de éster metílico del ácido 3-bromo-5-nitro-benzoico (D11) (12.1 g, 46.5 mmol, 1 eq.) en MeOH (200 ml), se le agregó $SnCl_2$ (44 g, 233 mmol, 5 eq.). La mezcla resultante se agitó a reflujo durante 4 h, se enfrió a temperatura ambiente y se concentró al vacío. El residuo se dividió entre AcOEt enfriado con hielo y H_2O. La fase acuosa se basificó con una solución acuosa de NaOH 2N, hasta que apareció un precipitado blanco; después lentamente con una solución acuosa 12.5N de NaOH, hasta que desapareció el precipitado. La temperatura se mantuvo a menos de 10 °C durante esta adición. Las dos capas se separaron y la fase acuosa se extrajo con AcOEt. La capa orgánica combinada se lavó con salmuera, se secó sobre $MgSO_4$ y se concentró al vacío, para dar el éster metílico del ácido 3-amino-5-bromo-benzoico (D12) (9.9 g, 93%) como un sólido pardo.

Descripción 13

Ester metílico del ácido 3-bromo-5-(4-cloro-butanoilamino)-benzoico (D13)

A una solución de éster metílico del ácido 3-amino-5-bromo-benzoico (D12) (460 mg, 2.0 mmol, 1 eq.) en CH_2Cl_2 (10 ml), a temperatura ambiente, se le agregó NEt_3 (306 µl, 2.2 mmol, 1.1 eq.) y después cloruro de 4-clorobutirilo (247, µl, 2.2 mmol, 1.1 eq.). La mezcla resultante se agitó a temperatura ambiente durante 16 h y entonces se diluyó con AcOEt. La fase orgánica se lavó con una solución acuosa de HCl 2N, se secó sobre $MgSO_4$ y se concentró al vacío, para dar el éster metílico del ácido 3-bromo-5-(4-cloro-butanoilamino)-benzoico (D13) (530 mg, 79 %) como un aceite amarillo claro; t.r. = 2.88 s.

Descripción 14

Ester metílico del ácido 3-(3-cloro-propano-1-sulfonilamino)-5-nitro-benzoico (D14)

A una solución de éster metílico del ácido 3-amino-5-nitro-benzoico (D1) (45 g, 229 mmol, 1 eq.) en CH_2Cl_2 (450 ml), se le agregó piridina (18.5 ml, 229 mmol, 1 eq.), DMAP (100 mg, 0.8 mmol, cantidad catalítica) y cloruro de 3-cloropropanosulfonilo (28 ml, 230 mmol, 1 eq.). La mezcla resultante se agitó durante 40 h, entonces se diluyó con AcOEt. La fase orgánica se diluyó con una solución acuosa de HCl 2N. El sólido resultante se filtró para dar éster metílico del ácido 3-(3-cloro-propano-1-

sulfonilamino)-5-nitro-benzoico (23 g, 32%). El filtrado se separó y la fase orgánica se lavó con una solución acuosa saturada de $NaHCO_3$, se secó sobre $MgSO_4$ y se concentró al vacío. El residuo se trituró con AcOEt e iso-hexano, para dar 50 g (65%) más de éster metílico del ácido 3-(3-cloro-propano-1-sulfonilamino)-5-nitro-benzoico (D14), como un sólido pardo claro. $[M-H]^-$ = 334.9, t.r. = 3.11 min.

Descripción 15

Ester metílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-nitro-benzoico (D15)

A una solución de éster metílico del ácido 3-(3-cloro-propano-1-sulfonilamino)-5-nitro-benzoico (D14) (73g, 217 mmol, 1 eq.) en EtOH (600 ml), se le agregó Et_3N (60 ml, 430 mmol, 2 eq.) y la mezcla resultante se puso en reflujo durante 3 h, se enfrió a temperatura ambiente y se concentró al vacío. El residuo se disolvió en AcOEt, se lavó con solución acuosa de HCl 2N, se secó sobre $MgSO_4$ y se concentró al vacío. El residuo se trituró con iso-hexano y AcOEt, para dar el éster metílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-nitro-benzoico (D15) (58 g, 88%) como un sólido pardo claro. $[M+H+NH_3]^+$ = 318.0, t.r. = 2.78 min.

Descripción 15 (Procedimiento alternativo)

Ester metílico del ácido 3-(1,1-Dioxo-1λ^6-isotiazolidin-2-il)-5-nitro-benzoico (D15)

Un matraz de 50 ml se cargó bajo nitrógeno con éster metílico del ácido 3-bromo-5-nitro-benzoico (D11) (1 g, 3.8 mmol, 1 eq.), Cs_2CO_3 (536 mg, 4.4 mmol, 1.2 eq.), tris(dibencilidenacetona)dipaladio (0) (5 mg, 0.0055 mmol, 0.0154 eq.), Xantphos (10 mg, 0.014 mmol, 0.04 eq.) y tolueno (15 ml). Después se le agregó 1,1-dióxido de isotiazolidina (D22a) (536 mg, 4.4 mmol, 1.1 eq.) y la mezcla resultante se agitó a 90 °C durante 16 h; después se enfrió a temperatura ambiente y se diluyó con H_2O y AcOEt. Las capas se separaron, la fase acuosa se diluyó con una solución acuosa saturada de $NaHCO_3$ y se extrajo con AcOEt. La fase orgánica combinada se secó sobre $MgSO_4$ y se concentró al vacío, para dar el éster metílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-nitro-benzoico (D15) (187 mg, 16%), como un sólido amarillo. $[M+H+NH_3]^+$ = 318.0, t.r. = 2. 81 min.

Descripción 16

Ester metílico del ácido 3-amino-5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-benzoico (D16)

Un matraz se cargó con éster metílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-nitro-benzoico (D15) (25 g, 83 mmol, 1 eq.), paladio (0) al 10% sobre carbón (50% en húmedo, 5 g, 10% p/p) y EtOH (500 ml). La suspensión resultante se agitó bajo una atmósfera de hidrógeno (presión

atmosférica) durante 4 h, y el catalizador se separó por filtración a través de una almohadilla de celite. El catalizador se lavó tres veces con DMF y la capa orgánica combinada se concentró al vacío. El residuo se disolvió en AcOEt y se volvió a filtrar a través de celite para remover el catalizador residual. La fase orgánica se concentró al vacío. El residuo se trituró con Et_2O para dar el éster metílico del ácido 3-amino-5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-benzoico (D16) (18 g, 80%), como un sólido pardo claro. $[M+H]^+$ = 271.0, t.r. = 2.16 min.

Descripción 17

Ester *ter*-butílico del ácido 3-bromo-5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-benzoico (D17)

Un matraz se cargó, bajo nitrógeno, con éster *ter*-butílico del ácido 3-bromo-5-yodo-benzoico D8b (1 g, 2.6 mmol, 1 eq.), Cs_2CO_3 (1.26 g, 3.9 mmol, 1.5 eq.), tris(dibencilidenacetona)dipaladio (0) (12 mg, 0.013 mmol, 0.005 eq.), Xantphos (22 mg, 0.038 mmol, 0.015 eq.) y tolueno (20 ml). Se agregó entonces 1,1-dióxido de isotiazolidina (D22a) (350 mg, 2.9 mmol, 1.1 eq.) y la mezcla resultante se agitó a 100°C durante 16 h; después se enfrió a temperatura ambiente y se diluyó con AcOEt. La fase orgánica se lavó con una solución acuosa saturada de $NaHCO_3$, se secó sobre $MgSO_4$ y se concentró al vacío. El residuo se trituró con Et_2O para dar el éster *ter*-butílico del ácido 3-bromo-5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-benzoico (D17) (350 mg 38%), como un sólido blanco.

Descripción 18

Ester *ter*-butílico del ácido 3-bromo-5-(1,1-dioxo-1λ^6-[1,2]tiazinan-2-il)-benzoico (D18)

El compuesto de la descripción 18 se preparó de manera análoga a la descripción 17b, a partir de éster *ter*-butílico del ácido 3-bromo-5-yodo-benzoico (D8b) (5.2 g, 13.6 mmol) y 1,1-dióxido de [1,2]tiazinano (D22b), produciendo el compuesto del título como un sólido amarillo claro (D18) (1.8 g, 34%). $[M+H\text{-}ter\text{-}Bu]^+$ = 335.9, t.r. = 3.26 min.

Descripción 19

Ester metílico del ácido 3-bromo-5-(3-cloro-propano-1-sulfonilamino)-benzoico (D19)

A una solución de éster metílico del ácido 3-amino-5-bromo-benzoico (D12) (2.3 g, 10 mmol, 1 eq.) en CH_2Cl_2 (30 ml), se le agregó piridina (1.6 ml, 20 mmol, 2 eq.), DMAP (320 mg, 2.5 mmol, 2.5 eq.) y cloruro de 3-clorosulfonilo (1.46 ml, 12 mmol, 1.2 eq.), a gotas. La mezcla resultante se agitó a temperatura ambiente durante 16 h y después se concentró al vacío. El residuo se disolvió en AcOEt y la fase orgánica se lavó secuencialmente con una solución acuosa de HCl 2N, una solución acuosa saturada de $NaHCO_3$ y salmuera; se secó sobre $MgSO_4$ y se concentró al vacío, para dar el éster metílico del ácido 3-bromo-5-(3-cloro-propano-1-sulfonilamino)-benzoico (D19) (3.36 g, 91%), como un sólido rojo. $[M-H]^-$ = 369.9, t.r. = 3.25 min.

Descripción 20

Cloruro de 4-cloro-1-butanosulfonilo (D20)

A una mezcla de 2,2-dióxido de [1,2]oxatiano (D23) (50 g, 367 mmol, 1 eq.) y $SOCl_2$ (29 ml, 401 mmol, 1.1 eq.), se le agregó DMF (4 ml, 51.6 mmol, 0.14 eq.). La mezcla resultante se agitó bajo nitrógeno a 70 °C durante 3 días. Se le agregó una segunda porción de $SOCl_2$ (10 ml, 137 mmol, 0. 37 eq.). La mezcla se agitó a 70 °C otros 3 días y después se enfrió a temperatura ambiente y se concentró al vacío. El residuo se diluyó con tolueno y después se concentró al vacío. Este procedimiento se repitió y el residuo se secó al vacío durante 16 h, para dar cloruro de 4-cloro-1-butanosulfonilo crudo (D20) (63 g, 90%).

Descripción 21a

3-Cloro-1-propanosulfonamida (D21a)

A una solución enfriada con hielo de cloruro de 3-cloro-1-propanosulfonilo (*Chem. Pharm. Bull*, 40 (1), 75-84, 1999) (30 ml, 250 mmol, 1 eq.) en CH_2Cl_2 (150 ml), se le agregó lentamente una solución acuosa de amoniaco (32%, 30 ml). La mezcla resultante se agitó a temperatura ambiente durante 16 h y se le agregó H_2O (20 ml). Las capas se separaron y la capa orgánica se secó sobre $MgSO_4$ y se concentró al vacío, para dar 3-cloro-1-propanosulfonamida cruda (D21a) (27 g, 69%), como un sólido blanco [*Chem. Pharm. Bull*, 40 (1), 75-84, 1999].

Descripción 21b

3-Cloro-1-butanosulfonamida (D21b)

A una solución enfriada con hielo de cloruro de 4-cloro-1-butanosulfonilo (D20) (43 g, 225 mmol, 1 eq.) en CH_2Cl_2 (350 ml), se le agregó lentamente una solución acuosa de amoniaco (25%, 140 ml). La mezcla resultante se agitó a temperatura ambiente durante 16 h y después se concentró al vacío. El residuo se diluyó con AcOEt y se lavó con salmuera. La fase orgánica se secó sobre $MgSO_4$ y se concentró al vacío, para dar 3-cloro-1-butanosulfonamida cruda (D21b) (31g, 88%).

Descripción 22a

1,1-Dióxido de isotiazolidina (D22a)

A una solución de 3-cloro-1-propanosulfonamida (D21a) (27 g, 170 mmol, 1 eq.) en EtOH (250 ml), a temperatura ambiente, se le agregó NaOEt (11.7 g, 170 mmol, 1 eq.). La mezcla resultante se puso en reflujo durante 5 h; después se enfrió a temperatura ambiente y se concentró al vacío. El sólido residual se extrajo exhaustivamente con CH_2Cl_2 y el extracto se concentró al vacío, para dar el 1,1-dióxido de isotiazolidina (D22a) (20 g, 100%).

Descripción 22b

1,1-Dióxido de [1,2]tiazinano (D22b)

A una solución de 3-cloro-1-butanosulfonamida (D21b) (31 g,

256
256

200 mmol, 1 eq.) en EtOH (500 ml), a temperatura ambiente, se le agregó NaOEt (14.9 g, 220 mmol, 1.1 eq.). La mezcla resultante se puso en reflujo durante 5 h; después se enfrió a temperatura ambiente y se concentró al vacío. El sólido residual se extrajo exhaustivamente con CH_2Cl_2 y el extracto se concentró al vacío. El sólido residual se trituró con Et_2O para dar el 1,1-dióxido de [1,2]tiazinano como un sólido pardo claro (D22b) (18.7 g, 69%).

Descripción 23

Acido 4-cloro-3,5-dinitrobenzoico (D23)

El compuesto de la descripción 23 está disponible comercialmente de Sigma-Aldrich Company.

Descripción 24

Acido 4-metoxi-3,5-dinitro-benzoico (D24)

A una solución de KOH (1.12 g, 20 mmol, 1 eq.) en MeOH (20 ml) a 0°C, se le agregó en porciones ácido 4-cloro-3,5-dinitrobenzoico (D23) (4.93 g, 20 mmol, 1 eq.). La mezcla resultante se puso en reflujo 1 h, y después se enfrió a temperatura ambiente. Se agregó una segunda porción de KOH (1.12 g, 20 mmol, 1 eq.), y la mezcla se puso en reflujo 90 minutos, se enfrió a temperatura ambiente y se diluyó con H_2O. La fase acuosa se acidificó a pH 1 y se extrajo con AcOEt. La fase orgánica se secó sobre $MgSO_4$ y se concentró al vacío, para dar ácido 4-metoxi-3,5-dinitro-benzoico crudo (D24) (4.49 g, 93%) como un sólido pardo claro.

25T
25T

Descripción 25

Ester metílico del ácido 4-metoxi-3,5-dinitro-benzoico (D25)

A una solución de ácido 4-metoxi-3,5-dinitro-benzoico crudo (D24) (4.43 g, 17.3 mmol, 1 eq.) en MeOH (60 ml), se le agregó H_2SO_4 concentrado (4 ml). La mezcla resultante se puso en reflujo 3 h, se enfrió a temperatura ambiente y se concentró al vacío. El residuo se dividió entre H_2O y AcOEt. Las dos capas se separaron y la fase orgánica se lavó con una solución acuosa saturada de $NaHCO_3$, se secó sobre $MgSO_4$ y se concentró al vacío. La purificación por cromatografía de vaporización instantánea sobre gel de sílice (iso-hexano/AcOEt: 85/15), dio el éster metílico del ácido 4-metoxi-3,5-dinitro-benzoico (D25) (2.84 g, 65%) como un sólido blanquecino.

Se prepararon los compuestos de las siguientes descripciones de forma análoga a la descripción 25, a partir de materias primas disponibles comercialmente:

Descripción	Materia prima
Ester metílico del ácido 4-cloro-3,5-dinitro-benzoico (D25a)	D24a
Ester metílico del ácido 3-amino-4-cloro-benzoico (D27c)	D26

Descripción 27a

Ester metílico del ácido 3,5-diamino-4-cloro-benzoico (D27a)

Una mezcla de éster metílico del ácido 4-cloro-3,5-dinitro-benzoico (D25a) (2.6 g, 10 mmol, 1 eq.) y $SnCl_2$ (18.95 g, 100 mmol, 10 eq.) en MeOH (80 ml) se puso en reflujo 1 h, se enfrió a temperatura ambiente y se

concentró al vacío. El residuo se dividió entre AcOEt y solución acuosa de NaOH 2N. La fase orgánica se secó sobre $MgSO_4$ y se concentró al vacío. El residuo se trituró con Et_2O/iso-hexano 1:1, para dar el éster metílico del ácido 3,5-diamino-4-cloro-benzoico (D27a) (1.56 g, 78%), como un sólido anaranjado claro.

Se prepararon los siguientes compuestos de forma análoga a la descripción 27a (usando 5 equivalentes de $SnCl_2$ para nitroarilos y 10 equivalentes para bis-nitroarilos), a partir de la materia prima indicada en el cuadro siguiente:

Descripción	Materia prima
Ester metílico del ácido 3,5-diamino-4-metoxi-benzoico (D27b)	D25b

Descripción 28c

Ester metílico del ácido 4-cloro-3-(4-cloro-butanoilamino)-benzoico (D28c)

Se agregó cloruro de 4-clorobutirilo (2.82 g, 20 mmol, 2.0 eq.) en CH_2Cl_2 (5 ml) durante 2 minutos, a una solución agitada de éster metílico del ácido 3-amino-4-cloro-benzoico (D27c) (1.66 g, 10 mmol, 1 eq.) y NEt_3 (2.22 g, 22 mmol, 2.2 eq.) en CH_2Cl_2 (40 ml). La mezcla resultante se agitó durante 1 hora a temperatura ambiente, se lavó después con solución acuosa de HCl 2N, se secó sobre $MgSO_4$ y se concentró al vacío. El residuo se trituró con CH_2Cl_2, para dar el éster metílico del ácido 4-cloro-3-(4-cloro-butanoilamino)-benzoico (D28c) (1.81 g, 48%) como un sólido rosa claro.

259
259

Se prepararon los siguientes compuestos de forma análoga al procedimiento descrito en D28c, a partir de la materia prima indicada en el cuadro siguiente:

Descripción	Precursor
Ester metílico del ácido 4-cloro-3,5-bis-(4-cloro-butanoilamino)-benzoico (D28a)	D27a
Ester metílico del ácido 3,5-bis-(4-cloro-butanoilamino)-4-metoxi-benzoico (D28b)	D27b

Descripción 30

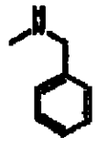
Ester *ter*-butílico del ácido (bencil-etil-amino)-(2-oxo-pirrolidin-1-il)-benzoico (D30)

Se cargó un matraz bajo nitrógeno con éster *ter*-butílico del ácido 3-bromo-5-(2-oxo-pirrolidin-1-il)-benzoico (D9b) (4.6 g, 13 mmol, 1 eq.), *ter*-butóxido de sodio (1.9 g, 19.5 mmol, 1.5 eq.), tris (dibencilidenoacetona)dipaladio (0) (395 mg, 0.65 mmol, 0.05 eq.), 2-(diciclohexilfosfino)bifenilo (341 mg, 0.97 mmol, 0.075 eq.) y tolueno (100 ml). Se agregó después mediante jeringa N-etilbencilamina (2.9 ml, 19.5 mmol, 1.5 eq.), y la mezcla resultante se agitó a 90°C durante 2 h, se enfrió después a temperatura ambiente y se diluyó con H_2O y AcOEt. Las capas se separaron, la fase acuosa se diluyó con una solución acuosa saturada de $NaHCO_3$ y se extrajo con AcOEt. La fase orgánica combinada se secó sobre $MgSO_4$ y se concentró al vacío. La purificación del residuo por cromatografía de vaporización instantánea sobre gel de sílice (iso-hexano/AcOEt: 1/2), dio el éster *ter*-butílico del ácido (bencil-etil-amino)-(2-oxo-pirrolidin-1-il)-benzoico

(D30) (3 g, 60%) como un sólido blanco. $[M+H]^+$ = 395.0, t.r. = 3.70 min.

Descripciones 31-35 (D31-D35)

Se prepararon los compuestos 31-35 de forma análoga a D30, a partir del bromuro de arilo adecuado y los materiales de partida de amina enlistados en el cuadro siguiente:

Descripción	Bromuro de arilo	Amina	$[M+H]^+$	t.r. (min)
Ester *ter*-butílico del ácido (bencil-metil-amino)-(2-oxo-pirrolidin-1-il)-benzoico (D31)	D9b		381.1	3.59
Ester *ter*-butílico del ácido (bencil-metil-amino)-(2-oxo-piperidin-1-il)-benzoico (D32)	D10		395.2	3.51
Ester *ter*-butílico del ácido (bencil-etil-amino)-(2-oxo-piperidin-1-il)-benzoico (D33)	D10			
Ester *ter*-butílico del ácido (bencil-metil-amino)-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-benzoico (D34)	D17		417.1	3.51
Ester *ter*-butílico del ácido (bencil-etil-amino)-(1,1-dioxo-1λ^6-[1,2]tiazinan-2-il)-benzoico (D35)	D18		445.2	3.82

Descripción 36

Acido 3-hidroxi-5-(2-oxo-pirrolidin-1-il)-benzoico (D36)

A una solución de ácido 3-amino-5-(2-oxo-pirrolidin-1-il)-benzoico (D6) (280 mg, 1.25 mmol, 1 eq.) en una mezcla de solución acuosa de HCl 2N (2.5 ml) y MeOH (5 ml), a 0°C, se le agregó en porciones durante 20 minutos NaN_3 (190 mg, 2.75 mmol, 2.2 eq.). Se le agregó H_2O (5 ml) y la mezcla resultante se calentó a 90°C durante 1 h, se enfrió después a temperatura ambiente y se diluyó con AcOEt. Las dos capas se separaron y la fase acuosa se extrajo dos veces con AcOEt (20 ml). La capa orgánica combinada se lavó con salmuera (20 ml), se secó sobre $MgSO_4$ y se concentró al vacío, para dar un producto crudo que se trituró con Et_2O/MeOH para dar ácido 3-hidroxi-5-(2-oxo-pirrolidin-1-il)-benzoico (D36) (110 mg, 40%), como un sólido canela claro.

Descripción 37

Ester *ter*-butílico del ácido 3-hidroxi-5-(2-oxo-pirrolidin-1-il)-benzoico (D37)

Se calentó a reflujo ácido 3-hidroxi-5-(2-oxo-pirrolidin-1-il)-benzoico (D36) (400 mg, 1.72 mmol, 1 eq.) en una mezcla de MeOH (20 ml) y H_2SO_4 concentrado (4 gotas) durante 7 h. La solución se enfrió después a temperatura ambiente y se concentró al vacío, para dar el éster metílico del ácido 3-hidroxi-5-(2-oxo-pirrolidin-1-il)-benzoico (D37) (300 mg, 74%) como un sólido pardo claro.

Descripción 37 (Procedimiento alternativo)

Ester *ter*-butílico del ácido 3-hidroxi-5-(2-oxo-pirrolidin-1-il)-benzoico (D37)

Se disolvió éster metílico del ácido 3-amino-5-(2-oxo-pirrolidin-1-il)-benzoico (D4a) (1.50 g, 6.4 mmol, 1 eq.) en una mezcla de solución acuosa de HCl 2N (25 ml) y MeOH (50 ml) a 0°C, y se trató en porciones con NaN_3 (950 mg, 13.8 mmol, 2.2 eq.) durante 20 minutos. Se le agregó H_2O (50 ml), y la mezcla resultante se calentó a 90°C durante 45 minutos; se enfrió después a temperatura ambiente y se diluyó con Et_2O (300 ml). Las dos capas se separaron y la fase orgánica se secó sobre $MgSO_4$ y se concentró al vacío, para dar el éster metílico del ácido 3-hidroxi-5-(2-oxo-pirrolidin-1-il)-benzoico (D37) (1.0 g, 67%) como un sólido canela.

Descripción 38

Ester metílico del ácido 3-(3-benciloxi-propoxi)-5-(2-oxo-pirrolidin-1-il)-benzoico (D38)

Una solución del éster metílico del ácido 3-hidroxi-5-(2-oxopirrolidin-1-il)-benzoico (D37) (300 mg, 1.28 mmol, 1 eq.), 3-benciloxipropan-1-ol (0.28 ml, 1.79 mmol, 1.4 eq.) y trifenilfosfina (470 mg, 1.79 mmol, 1.4 eq.) en THF (10 ml), a temperatura ambiente, se trató gota a gota con DEAD (0.282 ml, 1.79 mmol, 1.4 eq.). La mezcla se agitó durante 16 h a temperatura ambiente y se concentró después al vacío. La purificación por cromatografía de vaporización instantánea sobre gel de sílice (acetato de

etilo/iso-hexano: 1/4 a 1/1), dio éster metílico del ácido 3-(3-benciloxi-propoxi)-5-(2-oxo-pirrolidin-1-il)-benzoico (D38).

Descripción 39

Se preparó el compuesto de la descripción 39 de forma análoga a la descripción 38, a partir del compuesto de la descripción 37, usando el alcohol adecuado indicado en el cuadro siguiente:

Descripción	Alcohol
Ester metílico del ácido 3-(2-benciloxi-etoxi)-5-(2-pirrolidin-1-il)-benzoico (D39)	

Descripción 40

Acido 3-(2-benciloxi-etoxi)-5-(2-oxo-pirrolidin-1-il)-benzoico (D40)

Se preparó el compuesto de la descripción 40 por saponificación del compuesto de la descripción 39, de acuerdo con procedimientos conocidos.

Descripción 41

Ester metílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-hidroxi-benzoico (D41)

1-[3-Amino-5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-fenil]-propan-1-ona (D16) (1.0 g, 3.7 mmol, 1 eq.) disuelta en una mezcla de solución acuosa de HCl 2N (15 ml) y MeOH (30 ml), se agitó a 0°C y se trató en porciones con

nitrito de sodio (550 mg, 8.0 mmol, 2.2 eq.) durante 20 minutos. Se le agregó H_2O (50 ml) y la mezcla resultante se calentó a 90°C durante 45 minutos; se enfrió y se diluyó con Et_2O (300 ml). Las dos capas se separaron y la fase orgánica se secó sobre $MgSO_4$ y se concentró al vacío, para dar el éster metílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-hidroxi-benzoico crudo (D41) (800 mg, 80%) como un aceite pardo.

Descripción 41 (Procedimiento alternativo)

Ester metílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-hidroxi-benzoico (D41)

Una mezcla de éster metílico del ácido 3-benciloxi-5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-benzoico (D54) (4.5 g, 12.5 mmol, 1 eq.), NH_4COOH (7.7 g, 125 mmol, 10 eq.) y Pd al 10% sobre carbón (50% en húmedo, 1.0 g, 11% p/p) en MeOH (150 ml) y H_2O (10 ml), se calentó a 50°C durante 2 h. La mezcla de reacción fría se filtró a través de una almohadilla de celite y se concentró al vacío. Se le agregó H_2O (100 ml) al filtrado, que se extrajo después con AcOEt (150 ml). La solución orgánica se secó sobre $MgSO_4$ y se concentró al vacío. El residuo se cristalizó de Et_2O para dar el éster metílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-hidroxi-benzoico (D41) (2.6 g, 77%), como un sólido blanco.

Descripción 42

Ester dimetílico del ácido 5-hidroxi-isoftálico (D42)

El compuesto de la descripción 42 está disponible comercialmente de Sigma-Aldrich Company.

Descripción 43

Ester dimetílico del ácido 5-etoxi-isoftálico (D43)

Se agregaron K_2CO_3 (31.6 g, 223 mmol, 2.23 eq.) y yodoetano (17.8 ml, 230 mmol, 2.3 eq.) a una solución de éster dimetílico del ácido 5-hidroxi-isoftálico (D42) (21 g, 100 mmol, 1 eq.) en acetona (500 ml), a temperatura ambiente. La solución resultante se puso a reflujo 16 h, se enfrió después a temperatura ambiente y se concentró al vacío. El residuo se dividió entre H_2O y AcOEt. La fase acuosa se extrajo con AcOEt, y la capa orgánica combinada se lavó con solución acuosa de NaOH 2N y salmuera, se secó sobre $MgSO_4$ y se concentró al vacío, para dar el éster dimetílico del ácido 5-etoxi-isoftálico (D43) (23 g, 96%) como un sólido blanco. t.r. = 3.13 min.

Descripción 44

Ester dimetílico del ácido 5-benciloxi-isoftálico (D44)

Se agregaron K_2CO_3 (21 g, 153 mmol, 2 eq.) y bromuro de bencilo (11 ml, 92 mmol, 1.2 eq.) a una solución de éster dimetílico del ácido 5-hidroxi-isoftálico (D42) (16.1 g, 76.7 mmol, 1 eq.) en acetona (400 ml), a temperatura ambiente. La solución resultante se puso en reflujo 18 h, se

enfrió a temperatura ambiente y se concentró al vacío. El residuo se dividió entre H_2O y AcOEt. La fase acuosa se extrajo con AcOEt, y la capa orgánica combinada se lavó con una solución acuosa de NaOH 2N y salmuera, se secó sobre $MgSO_4$ y se concentró al vacío, para dar el éster dimetílico del ácido 5-benciloxi-isoftálico (D44) (24.2 g, 105%) como un sólido blanco. $[M+H]^+$ = 301.0, t.r. = 3.50 min.

Descripción 45

Ester monometílico del ácido 5-etoxi-isoftálico (D45)

A una solución del éster dimetílico del ácido 5-etoxi-isoftálico (D43) (22 g, 92.4 mmol, 1 eq.) en MeOH (440 ml), se le agregó solución acuosa de NaOH 1N (87.8 ml, 87.8 mmol, 0.95 eq.), y la solución resultante se agitó a temperatura ambiente durante 17 h. La mayor parte del MeOH se removió al vacío, y el residuo se dividió entre AcOEt y solución acuosa de NaOH 1N. La capa acuosa se extrajo con AcOEt, se acidificó a pH 1 y se volvió a extraer con AcOEt. El segundo extracto orgánico se secó sobre $MgSO_4$ y se concentró al vacío, para dar el éster monometílico del ácido 5-etoxi-isoftálico (D45) (17 g, 82%) como un sólido blanco. $[M+H+NH_3]^+$ 242.0, t.r. = 2.79 min.

Descripción 46

Ester monometílico del ácido 5-benciloxi-isoftálico (D46)

A una solución de éster dimetílico del ácido 5-benciloxi-isoftálico

(D44) (24 g, 80 mmol, 1 eq.) en MeOH (300 ml) se le agregó solución acuosa de NaOH 1N (76 ml, 76 mmol, 0.95 eq.), y la solución resultante se agitó a temperatura ambiente durante 17 h. Se agregó una segunda porción de solución acuosa de NaOH 1N (15 ml, 15 mmol, 0.2 eq.), y la solución se agitó durante otras 6 h. La mayor parte del MeOH se removió al vacío, y el residuo se dividió entre AcOEt y solución acuosa de NaOH 1N. La capa acuosa se extrajo con AcOEt, se acidificó a pH 1 y se volvió a extraer con AcOEt. El segundo extracto orgánico se secó sobre $MgSO_4$ y se concentró al vacío. El residuo se trituró con Et_2O, para dar el éster monometílico del ácido 5-benciloxi-isoftálico (D46) (15.5 g, 68%) como un sólido blanco. $[M+H]^+$ = 2.86.0, t.r. = 3.32 min.

Descripción 47

Ester metílico del ácido 3-benciloxicarbonilamino-5-etoxi-benzoico (D47)

Se agregaron NEt_3 (14.2 ml, 102 mmol, 1.3 eq.) y difenilfosforil azida (22 ml, 102 mmol, 1.3 eq.) a una suspensión de éster monometílico del ácido 5-etoxi-isoftálico (D45) (17.6 g, 78.6 mmol, 1 eq.) en tolueno (250 ml), y la mezcla se calentó a 80°C durante 3 h. Se agregó alcohol bencílico (12 ml, 118 mmol, 1.5 eq.), y la mezcla resultante se puso a reflujo 4 h, se enfrió a temperatura ambiente y se concentró al vacío. El residuo se disolvió en AcOEt (300 ml), y la solución resultante se lavó con solución acuosa de HCl 2N (100 ml), seguida de solución acuosa saturada de $NaHCO_3$ (100 ml), se

secó sobre $MgSO_4$ y se concentró al vacío. El residuo se trituró con Et_2O, para dar el éster metílico del ácido 3-benciloxicarbonilamino-5-etoxi-benzoico (D47) (15 g, 62%) como un sólido blanco. $[M-H]^-$ = 328.1, t.r. = 3.46 min.

Descripción 48

Ester metílico del ácido 3-benciloxi-5-(2-trimetilsilanil-etoxicarbonilamino)-benzoico (D48)

Se agregaron NEt_3 (8.2 g, 81 mmol, 1.5 eq.) y difenilfosforil azida (22.3 g, 81 mmol, 1.5 eq.) a una suspensión de éster monometílico del ácido 5-benciloxi-isoftálico (D46) (15.5 g, 54.2 mmol, 1 eq.) en tolueno (120 ml), y la mezcla resultante se calentó a 80°C durante 3 h. Se agregó 2-trimetilsililetanol (12.7 g, 108 mmol, 2 eq.), y la mezcla resultante se puso en reflujo 4 h, se enfrió a temperatura ambiente y se concentró al vacío. El residuo se disolvió en EtOAc (300 ml), y la solución resultante se lavó con solución acuosa de HCl 2N (100 ml), seguida de solución acuosa saturada de $NaHCO_3$ (100 ml); se secó sobre $MgSO_4$ y se concentró al vacío. El residuo se trituró con Et_2O e iso-hexano, para dar el éster metílico del ácido 3-benciloxi-5-(2-trimetilsilanil-etoxicarbonilamino)-benzoico (D48) (8.5 g, 40%) como un sólido blanco.

Descripción 49

Ester metílico del ácido 3-amino-5-etoxi-benzoico (D49)

Una mezcla de éster metílico del ácido 3-benciloxicarbonilamino-

5-etoxi-benzoico (D47) (15 g, 45.5 mmol, 1 eq.), paladio al 10% sobre carbón (50% en húmedo, 1.5 g, 5% p/p) y NH_4COOH (15 g, 455 mmol, 10 eq.), H_2O (50 ml) y MeOH (200 ml), se agitó a 50°C durante 2 h. La mezcla se enfrió a temperatura ambiente y el catalizador se filtró a través de una almohadilla de celite. La mayor parte del MeOH se removió al vacío, y el residuo se dividió entre solución acuosa saturada de $NaHCO_3$ y AcOEt. La fase acuosa se volvió a extraer con AcOEt. La fase orgánica combinada se secó sobre $MgSO_4$ y se concentró al vacío, para dar el éster metílico del ácido 3-amino-5-etoxi-benzoico (D49) (8.8 g, 99%) como un sólido verde claro, que se usó en el siguiente paso sin mayor purificación. $[M+H]^+$ = 196.1, t.r. = 2.49 min.

Descripción 50

Clorhidrato de éster metílico del ácido 3-amino-5-benciloxi-benzoico (D50)

Se trató éster metílico del ácido 3-benciloxi-5-(2-trimetilsilanil-etoxicarbonilamino)-benzoico (D48) (8.5 g, 21.2 mmol, 1 eq.) en THF (40 ml) con fluoruro de tetrabutilamonio 1M en THF (40 ml, 40 mmol, 1.9 eq.), y la solución resultante se agitó a temperatura ambiente durante 16 h y se concentró después al vacío. El residuo se disolvió en AcOEt (200 ml) y se lavó con H_2O (200 ml), se secó después sobre $MgSO_4$ y se concentró al vacío. El residuo se volvió a disolver en Et_2O/EtOAc y se trató con HCl 2N en Et_2O para dar, después de filtración, clorhidrato de éster metílico del ácido 3-amino-5-benciloxi-benzoico (D50) (5.0 g, 80%) como un sólido blanco.

Descripción 51

Ester metílico del ácido 3-(4-cloro-butanoilamino)-5-etoxi-benzoico (D51)

Se suspendió éster metílico del ácido 3-amino-5-etoxi-benzoico (D49) (4.0 g, 20.5 mmol, 1 eq.) en CH_2Cl_2 (40 ml), y se trató a temperatura ambiente con NEt_3 (2.32 g, 23 mmol, 1.1 eq.). La solución resultante se enfrió a 0°C, y se le agregó gota a gota cloruro de 4-clorobutirilo (3.1 g, 22 mmol, 1.1 eq.). La mezcla resultante se agitó a 0°C durante 3 h, y después se dejó calentando a temperatura ambiente. La solución se lavó con solución acuosa de HCl 2N, se secó sobre $MgSO_4$ y se concentró al vacío, para dar el éster metílico del ácido 3-(4-cloro-butanoilamino)-5-etoxi-benzoico (D51) (7.0 g, 115%) como un aceite pardo.

Descripción 52

Ester metílico del ácido 3-benciloxi-5-(3-cloro-propan-1-sulfonilamino)-benzoico (D52)

Una suspensión de clorhidrato de éster metílico del ácido 3-amino-5-benciloxi-benzoico (D50) (5.0 g, 17 mmol, 1 eq.) en CH_2Cl_2 (100 ml) se trató gota a gota con DMAP (400 mg, 3.2 mmol) y piridina (3.5 g, 44 mmol, 2.6 eq.), seguido de cloruro de 3-cloropropanosulfonilo (3.54 g, 20 mmol, 1.2 eq.) a temperatura ambiente. La mezcla resultante se agitó durante 16 h y se concentró después al vacío. El residuo se disolvió en AcOEt (200 ml), y la solución resultante se lavó con solución acuosa de HCl 2N (100 ml) seguido

de solución acuosa saturada de $NaHCO_3$ (100 ml), se secó sobre $MgSO_4$ y se concentró al vacío, para dar el éster metílico del ácido 3-benciloxi-5-(3-cloro-propano-1-sulfonilamino)-benzoico (D52) (6.0 g, 97%) como un sólido rosa claro. $[M+H]^+$ = 366.1, t.r. = 2.34 min.

Descripción 53

Ester metílico del ácido 3-(3-cloro-propano-1-sulfonilamino)-5-etoxi-benzoico (D53)

Una suspensión de éster metílico del ácido 3-amino-5-etoxi-benzoico (D49) (4.0 g, 20.5 mmol, 1 eq.) en CH_2Cl_2 (100 ml) se trató gota a gota con DMAP (400 mg, 3.2 mmol) y piridina (1.74 g, 22 mmol, 1.1 eq.) seguido de cloruro de 3-cloropropanosulfonilo (3.89 g, 22 mmol, 1.1 eq.). La mezcla resultante se agitó durante 16 h y se concentró después al vacío. El residuo se disolvió en AcOEt (200 ml), y la solución resultante se lavó con solución acuosa de HCl 2N (100 ml) seguido de solución acuosa saturada de $NaHCO_3$ (100 ml), se secó después sobre $MgSO_4$ y se concentró al vacío, para dar el éster metílico del ácido 3-(3-cloro-propano-1-sulfonilamino)-5-etoxi-benzoico (D53) (6.7 g, 98%) como un sólido anaranjado claro.

Descripción 54

Ester metílico del ácido 3-benciloxi-5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-benzoico (D54)

Una solución de éster metílico del ácido 3-benciloxi-5-(3-cloro-

propano-1-sulfonilamino)-benzoico (D52) (6.0 g, 17 mmol, 1 eq.) en EtOH (80 ml), se trató con NEt_3 (3.4 g, 34 mmol, 2 eq.). La mezcla resultante se puso a reflujo 8 h, se enfrió a temperatura ambiente y se concentró al vacío, para dar el éster metílico del ácido 3-benciloxi-5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-benzoico (D54) (4.5 g, 74%) como un sólido rosa claro.

Descripción 55

Ester dimetílico del ácido 5-dimetiltiocarbamoiloxi-isoftálico (D55)

A una solución de éster dimetílico del ácido 5-hidroxi-isoftálico (D42) (21 g, 100 mmol, 1 eq.) en DMF (300 ml) a temperatura ambiente, se le agregó DABCO (14.6 g, 130 mmol, 1.3 eq.) seguido de cloruro de dimetiltiocarbamoilo (14.8 g, 120 mmol, 1.2 eq.). La mezcla resultante se agitó a temperatura ambiente durante 16 h y a 60°C durante 2 h, se enfrió después a temperatura ambiente y se concentró al vacío. El residuo se dividió entre AcOEt y H_2O, y la fase acuosa se volvió a extraer con AcOEt. La solución orgánica combinada se lavó secuencialmente con solución de ácido cítrico acuoso al 5%, solución acuosa de NaOH 2N y salmuera, se secó después sobre $MgSO_4$ y se concentró al vacío, para dar el éster dimetílico del ácido 5-dimetiltiocarbamoiloxi-isoftálico (D55) (23.5 g, 79%) como un aceite amarillo claro. $[M+H]^+$ = 298.0, t.r. = 3.06 min.

Descripción 56

Ester dimetílico del ácido 5-dimetilcarbamoilsulfanil-isoftálico (D56)

Se agitó éster dimetílico del ácido 5-dimetiltiocarbamoiloxi-isoftálico (D55) (15.5 g, 52.2 mmol, 1 eq.) a 200°C durante 24 h bajo nitrógeno, y se enfrió después a temperatura ambiente. La purificación por cromatografía de vaporización instantánea sobre gel de sílice (iso-hexano/AcOEt: 4/1, después 3/1), dio éster dimetílico del ácido 5-dimetilcarbamoilsulfanil-isoftálico (D56) (7.0 g, 45%), y se recuperó éster dimetílico del ácido 5-dimetiltiocarbamoiloxi-isoftálico (D55) (2.77 g, 18%), ambos como sólidos blancos. $[M+H]^+$ = 298.0, t.r. = 2.92 min.

Descripción 57

Ester monometílico del ácido 5-dimetilcarbamoilsulfanil-isoftálico (D57)

A una solución de éster dimetílico del ácido 5-dimetilcarbamoilsulfanil-isoftálico (D56) (6 g, 20.2 mmol, 1 eq.) en THF (100 ml) a temperatura ambiente, se le agregó solución acuosa de NaOH 2N (9.6 ml, 19.2 mmol, 0.95 eq.). La mezcla resultante se agitó durante 11 h, y se dividió después entre AcOEt y H_2O. Las dos capas se separaron y la fase acuosa se extrajo con AcOEt. Después de acidificación a pH 1, la fase acuosa se extrajo dos veces con AcOEt. La solución orgánica se secó sobre $MgSO_4$, y se concentró después al vacío, para dar el éster monometílico del

ácido 5-dimetilcarbamoilsulfanil-isoftálico (D57) (4.54 g, 79%) como un sólido blanco.

Descripción 58

Ester metílico del ácido *ter*-butoxicarbonilamino-dimetilcarbamoil-sulfanil-benzoico (D58)

A una solución de éster monometílico del ácido 5-dimetilcarbamoilsulfanil-isoftálico crudo (D57) (4.56 g, 16.1 mmol, 1 eq.) en tolueno (100 ml), se le agregó trietilamina (6.7 ml, 48 mmol, 3 eq.) y difenilfosforilazida (5.2 ml, 24 mmol, 1.5 eq.). La mezcla resultante se agitó bajo nitrógeno a 80°C durante 3 h, y después se le agregó *ter*-butanol (4.6 ml, 48 mmol, 3 eq.). La solución se agitó a 80°C durante otras 16 h, y se enfrió después a temperatura ambiente y se concentró al vacío. El producto crudo se disolvió en AcOEt, y la solución resultante se lavó secuencialmente con solución acuosa de NaOH 2N, solución acuosa de HCl 2N y salmuera, se secó sobre $MgSO_4$ y se concentró al vacío. La purificación por cromatografía de vaporización instantánea sobre gel de sílice (iso-hexano/AcOEt: 3/1 a 6/4), dio éster metílico del ácido *ter*-butoxicarbonilamino-dimetilcarbamoilsulfanil-benzoico (D58) (2.24 g, 40%) como un sólido blanco.

Descripción 59

Acido 3-*ter*-butoxicarbonilamino-5-mercapto-benzoico (D59)

A una solución de éster metílico del ácido *ter*-

butoxicarbonilamino-dimetilcarbamoilsulfanil-benzoico (D58) (2.24 g, 6.3 mmol, 1 eq.) en MeOH (30 ml) y H_2O (23 ml), se le agregó solución acuosa de NaOH 2N (7 ml, 14 mmol, 2.2 eq.). La mezcla resultante se puso a reflujo 3 h, y se enfrió después a temperatura ambiente y se concentró al vacío. El residuo se dividió entre AcOEt y solución acuosa de NaOH 1N. La fase acuosa se acidificó a pH 1 y se extrajo dos veces con AcOEt. Las soluciones orgánicas combinadas se secó sobre $MgSO_4$ y se concentró después al vacío, para dar ácido 3-*ter*-butoxicarbonilamino-5-mercapto-benzoico (D59) (1.54 g, 90%) como un sólido blanco.

Descripción 60

Ester metílico del ácido 3-*ter*-butoxicarbonilamino-5-metilsulfanil-benzoico (D60)

A una solución de ácido 3-*ter*-butoxicarbonilamino-5-mercapto-benzoico (D59) (0.68 g, 2.52 mmol, 1 eq.) en acetona (15 ml), se le agregó K_2CO_3 (3.5 g, 25.3 mmol, 10 eq.) y yodometano (473 µl, 7.59 mmol, 3 eq.). La mezcla resultante se agitó a 50°C durante 2 h, se enfrió a temperatura ambiente y se concentró al vacío. El residuo se dividió entre AcOEt y H_2O. La capa orgánica se lavó con H_2O y salmuera, se seco sobre $MgSO_4$ y se concentró al vacío. La purificación por cromatografía de vaporización instantánea sobre gel de sílice (iso-hexano/AcOEt: 85/15), dio éster metílico del ácido 3-*ter*-butoxicarbonilamino-5-metilsulfanil-benzoico (D60) (0.47 g, 63%) como un sólido blanco. $[M-H]^-$ = 296.1, t.r. = 3.51 min.

Descripción 61

Ester etílico del ácido 3-*ter*-butoxicarbonilamino-5-etilsulfanil-benzoico (D61)

El compuesto de la descripción 61 se obtuvo a partir de 0.68 g (2.53 mmol) de éster metílico del ácido 3-*ter*-butoxicarbonilamino-5-metilsulfanil-benzoico (D59) y yodoetano, usando el procedimiento de la descripción 60, que dio el compuesto del título (D61) (0.58 g, 71%) como un sólido blanco. $[M-H]^-$ = 324.2, t.r.=3.79 min.

Descripción 62

Clorhidrato de éster metílico del ácido 3-amino-5-metilsulfanil-benzoico (D62)

Se disolvió éster metílico del ácido 3-*ter*-butoxicarbonilamino-5-metilsulfanil-benzoico (D60) (0.54 g, 1.82 mmol, 1 eq.) en dioxano (2 ml), y se le agregó HCl 4M en dioxano (16 mmol, 4 ml, 8.8 eq.). La solución se agitó a temperatura ambiente durante 2 h, dejando que la sal clorhidrato de la amina se precipitara. Este precipitado se filtró, se lavó con Et_2O y se secó, dando clorhidrato de éster metílico del ácido 3-amino-5-metilsulfanil-benzoico (D62) (0.224 g, 52%). $[M+H]^+$ = 198.1, t.r. = 2.68 min.

Descripción 63

Clorhidrato de éster etílico del ácido 3-amino-5-etilsulfanil-benzoico (D63)

El compuesto de la descripción 63 se preparó a partir de 0.57 g (1.75 mmol) de clorhidrato de éster etílico del ácido 3-*ter*-butoxicarbonilamino-5-etilsulfanil-benzoico (D61), de forma análoga a la descripción 62, que dio 0.335 g (73%) de clorhidrato de éster etílico del ácido 3-amino-5-etilsulfanil-benzoico (D63) como un sólido blanco. $[M+H]^+$ = 226.1, t.r. = 3.13 min.

Descripción 64

Ester metílico del ácido 3-(4-cloro-butanoilamino)-5-metilsulfanil-benzoico (D64)

A una solución de clorhidrato de éster metílico del ácido 3-amino-5-metilsulfanil-benzoico (D62) (0.13 g, 0.556 mmol, 1 eq.) en CH_2Cl_2 seco (2 ml) a 0°C, se le agregó NEt_3 (193 ml, 1.39 mmol, 2.5 eq.) y después cloruro de 4-clorobutirilo (69 ml, 0.612 mmol, 1.1 eq.), gota a gota, durante 2 minutos. La solución resultante se agitó a 0°C durante 15 minutos, y después a temperatura ambiente durante 30 minutos. La solución se diluyó después con AcOEt, se lavó secuencialmente con solución acuosa de HCl 2N, solución acuosa saturada de $NaHCO_3$ y salmuera, se secó sobre Na_2SO_4 y se concentró al vacío, para dar el éster metílico del ácido 3-(4-cloro-butanoilamino)-5-metilsulfanil-benzoico (D64) (173 mg, 103%) como cristales amarillos claros. $[M+H]^+$ = 302.0, t.r. = 3.20 min.

Descripción 65

Ester etílico del ácido 3-(4-cloro-butanoilamino)-5-etilsulfanil-benzoico (D65)

El compuesto de la descripción 65 se preparó a partir de 140 mg (0.535 mmol) de clorhidrato de éster etílico del ácido 3-amino-5-etilsulfanil-benzoico (D63), de forma análoga a la descripción 64, lo cual dio 182 mg (103%) de éster etílico del ácido 3-(4-cloro-butanoilamino)-5-etilsulfanil-benzoico (D65), como cristales amarillos claros. $[M+H]^+$ = 330.0, t.r. = 3.51 min.

Descripción 66

Ester metílico del ácido 3-(3-cloro-propano-1-sulfonilamino)-5-metilsulfanil-benzoico (D66)

A una solución de clorhidrato de éster metílico del ácido 3-amino-5-metilsulfanil-benzoico (D62) (130 mg, 0.556 mmol, 1 eq.) en CH_2Cl_2 (2 ml), se le agregó gota a gota piridina (142 ml, 1.75 mmol, 3 eq.), DMAP (6.8 mg, 0.056 mmol, 0.1 eq.) y después cloruro de 3-cloropropanosulfonilo (71 µl, 0.584 mmol, 1.05 eq.) durante 2 minutos. La mezcla resultante se agitó a temperatura ambiente durante 2 h, se diluyó con AcOEt, se lavó secuencialmente con solución acuosa de HCl 2N, solución acuosa saturada de $NaHCO_3$ y salmuera, se secó sobre Na_2SO_4 y se concentró al vacío, para dar clorhidrato de éster metílico del ácido 3-(3-cloro-propano-1-sulfonilamino)-5-metilsulfanil-benzoico (D66) (196 mg, 104%) como cristales pardos claros.

$[M-H]^-$ = 336.0, t.r. = 3.20 min.

Descripción 67

Ester etílico del ácido 3-(3-cloro-propano-1-sulfonilamino)-5-etilsulfanil-benzoico (D67)

El compuesto de la descripción 67 se preparó a partir de 140 mg (0.6 mmol) de clorhidrato de éster etílico del ácido 3-amino-5-etilsulfanil-benzoico (D63), de forma análoga a la descripción 66, lo cual dio 200 mg (102%) de éster etílico del ácido 3-(3-cloro-propano-1-sulfonilamino)-5-etilsulfanil-benzoico crudo (D67), como cristales pardos claros. $[M-H]^-$ = 364.0, t.r. = 3.49 min.

Descripción 68

Ester *ter*-butílico del ácido 3-(2-oxo-piperidin-1-il)-5-(E/Z)-propenil-benzoico (D68)

A una solución de éster *ter*-butílico del ácido 3-bromo-5-(2-oxo-piperidin-1-il)-benzoico (D10) (500 mg, 1.4 mmol, 1 eq.) en DME (14 ml) y H_2O (4 ml), se le agregó tetraquis(trifenilfosfina)-paladio (0) (81 mg, 0.07 mmol, 0.05 eq.), y la suspensión se agitó durante 10 minutos. Se agregaron complejo de 2,4,6-triprofenilciclotriboroxano-piridina (394 mg, 1.4 mmol, 1 eq.) y K_2CO_3 (193 mg, 1.4 mmol, 1 eq.), y la mezcla resultante se agitó a 90°C durante 1 h, se enfrió a temperatura ambiente y se diluyó con AcOEt. La fase orgánica se lavó con H_2O, se secó sobre $MgSO_4$ y se concentró al vacío. La

purificación por cromatografía de vaporización instantánea sobre gel de sílice (iso-hexano/AcOEt: 4/1), dio éster *ter*-butílico del ácido 3-(2-oxo-piperidin-1-il)-5-(E/Z)-propenil-benzoico (D68) (480 mg, 100%) de aducto como un aceite amarillo claro. $[M+H]^+$ = 316.2, t.r. = 3.41 min.

Descripciones 69-72

Los compuestos de las descripciones 69-72 se prepararon de forma análoga a la descripción 68, a partir del bromuro de arilo adecuado indicado en el cuadro siguiente, usando el complejo de 2,4,6-trialquenilciclotriboroxano-piridina adecuado, como es descrito por F. Kerins y D. F. O'Shea en *J. Org. Chem*, **2002**, 67, 4968-4971:

Descripción	Bromuro de arilo	$[M+H]^+$	t.r. (min)
Ester *ter*-butílico del ácido 3-(1,1-dioxo-1λ^6-[1,2]-tiazinan-2-il)-5-(E/Z)-propenil-benzoico (D69)	D18	(-*t*Bu) 296.1	3.61
Ester metílico del ácido 3-(2-oxo-pirrolidin-1-il)-5-vinil-benzoico (D70)	D9a		
Ester metílico del ácido 3-isopropenil-5-(2-oxo-pirrolidin-1-il)-benzoico (D71)	D9a	260.0	2.96
Ester metílico del ácido 3-(2-oxo-pirrolidin-1-il)-5-(E/Z)-propenil-benzoico (D72)	D9a	260.0	2.97

Descripción 73

Ester metílico del ácido 3-ciclopent-2-enil-5-(2-oxo-pirrolidin-1-il)-benzoico; éster metílico del ácido 3-ciclopent-3-enil-5-(2-oxo-pirrolidin-1-il)-benzoico; y éster metílico del ácido 3-ciclopent-1-enil-5-(2-oxo-pirrolidin-1-il)-benzoico (D73)

A una solución de éster metílico del ácido 3-bromo-5-(2-oxo-pirrolidin-1-il)-benzoico (D9a) (686 mg, 2.3 mmol, 1 eq.) en DMF (3 ml), se le agregó ciclopenteno (409 µl, 4.6 mmol, 2 eq.), acetato de paladio(II) (26 mg, 0.12 mmol, 0.05 eq.), tri(o-tolil)fosfina (71 mg, 0.23 mmol, 0.1 eq.) y trietilamina (969 µl, 7 mmol, 3 eq.). La mezcla resultante se agitó a 125°C durante 16 h, se enfrió después a temperatura ambiente y se dividió entre H_2O y Et_2O. Las dos capas se separaron y la fase orgánica se secó sobre Na_2SO_4 y se concentró al vacío, para dar una mezcla de éster metílico del ácido 3-ciclopent-2-enil-5-(2-oxo-pirrolidin-1-il)-benzoico, éster metílico del ácido 3-ciclopent-3-enil-5-(2-oxo-pirrolidin-1-il)-benzoico y éster metílico del ácido 3-ciclopent-1-enil-5-(2-oxo-pirrolidin-1-il)-benzoico (D73) (562 mg, 85%) como un aceite pardo.

Descripción 74

Ester metílico del ácido 3-ciclohex-2-enil-5-(2-oxo-pirrolidin-1-il)-benzoico; éster metílico del ácido 3-ciclohex-3-enil-5-(2-oxo-pirrolidin-1-il)-benzoico; y éster metílico del ácido 3-ciclohex-1-enil-5-(2-oxo-pirrolidin-1-il)-benzoico (D74)

Los compuestos de la descripción 74 se prepararon de forma análoga a la descripción 73, a partir de 686 mg (mmol) de éster metílico del ácido 3-bromo-5-(2-oxo-pirrolidin-1-il)-benzoico (D9a) y ciclohexeno, lo cual dio 207 mg (30%) de éster metílico del ácido 3-ciclohex-2-enil-5-(2-oxo-pirrolidin-1-il)-benzoico, éster metílico del ácido 3-ciclohex-3-enil-5-(2-oxo-

pirrolidin-1-il)-benzoico y éster metílico del ácido 3-ciclohex-1-enil-5-(2-oxo-pirrolidin-1-il)-benzoico (D74), después de purificación por cromatografía de vaporización instantánea sobre gel de sílice (iso-hexano/EtOAc: 5/1).

Descripción 75

Ester *ter*-butílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-(3-hidroxi-3-metil-but-1-inil)-benzoico (D75)

A una solución de éster *ter*-butílico del ácido 3-bromo-5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-benzoico (D17) (376 mg, 1 mmol, 1 eq.) en DME (5 ml) y H_2O (5 ml), se le agregó K_2CO_3 (345 mg, 2.5 mmol, 2.5 eq.), CuI (8 mg, 0.04 mmol, 0.04 eq.), trifenilfosfina (21 mg, 0.08 mmol, 0.08 eq.) y paladio al 10% sobre carbón (21 mg, 0.02 mmol, 0.02 eq.), y la solución se agitó a temperatura ambiente durante 15 minutos. Se agregó 2-metil-3-butin-2-ol (254 µl, 2.5 mmol, 2.5 eq.), y la mezcla resultante se agitó a 80°C durante 16 h y se enfrió después a temperatura ambiente. El catalizador se removió mediante filtración a través de una almohadilla de celite, y el filtrado se diluyó con AcOEt. La fase orgánica se lavó con solución acuosa de HCl 2N, solución acuosa saturada de $NaHCO_3$, se secó sobre $MgSO_4$ y se concentró al vacío. La purificación por cromatografía de vaporización instantánea sobre gel de sílice (iso-hexano/AcOEt: 4/1 a 2/1), dio éster *ter*-butílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-(3-hidroxi-3-metil-but-1-inil)-benzoico (D75) (142 mg, 37%) como un aceite incoloro, que se solidificó en reposo.

Descripción 76

Ester *ter*-butílico del ácido 3-(3-hidroxi-3-metil-but-1-inil)-5-(2-oxo-pirrolidin-1-il)-benzoico (D76)

Se preparó el compuesto de la descripción 76 usando un procedimiento análogo al descrito para la descripción 75, a partir de 390 mg de éster *ter*-butílico del ácido 3-bromo-5-(2-oxo-pirrolidin-1-il)-benzoico (D9b), lo cual dio 300 mg (76%) de éster *ter*-butílico del ácido 3-(3-hidroxi-3-metil-but-1-inil)-5-(2-oxo-pirrolidin-1-il)-benzoico (D76) como una espuma blanca.

Descripción 77

Ester monometílico del ácido 5-nitro-isoftálico (D77)

El compuesto de la descripción 77 está disponible comercialmente de Sigma-Aldrich Company.

Descripción 78

Ester 3-metílico - éster 1-*ter*-butílico del ácido 5-nitro-isoftálico (D78)

Una mezcla de éster monometílico del ácido 5-nitro-isoftálico (D77) (5.0 g, 22.2 mmol, 1 eq.), *ter*-BuOH (8.2 g, 111 mmol, 5 eq.), clorhidrato de EDAC (4.8 g, 25 mmol, 1.1 eq.) y DMAP (205 mg, 1.68 mmol, 0.07 eq.) disueltos en CH_2Cl_2 (50 ml), se agitó durante 1 hora a temperatura ambiente. La mezcla se diluyó después con CH_2Cl_2 (50 ml), se lavó con solución acuosa de HCl 2N (50 ml) y solución acuosa saturada de $NaHCO_3$ (50 ml), se secó

sobre $MgSO_4$ y se concentró al vacío, para dar el éster 3-metílico - éster 1-*ter*-butílico del ácido 5-nitro-isoftálico (D78) (5.3 g, 85%) como un aceite amarillo claro.

Descripción 79

Ester 3-metílico - éster 1-*ter*-butílico del ácido 5-amino-isoftálico (D79)

Una mezcla de éster 3-metílico - éster 1-*ter*-butílico del ácido 5-nitro-isoftálico (D78) (5.3 g, 19 mmol, 1 eq.), NH_4COOH (11.9 g, 190 mmol, 10 eq.) y paladio al 10% sobre carbón (50% en húmedo, 0.75 g, 7% p/p) en EtOH (50 ml) y H_2O (25 ml), se calentó a 50°C durante 30 minutos. Se le agregó MeOH (20 ml), y la solución resultante se calentó a 50°C durante otra hora, se enfrió después a temperatura ambiente, se filtró a través de una almohadilla de celite y se concentró al vacío. El residuo se diluyó con solución acuosa saturada de $NaHCO_3$ (100 ml), y la fase acuosa se extrajo con AcOEt (150 ml). La fase orgánica se secó sobre $MgSO_4$ y se concentró al vacío. El residuo se trituró con iso-hexano, para dar el éster 3-metílico - éster-1-*ter*-butílico del ácido 5-amino-isoftálico (D79) (3.4 g, 71%) como un sólido blanco.

Descripción 80

Ester 3-metílico - éster 1-*ter*-butílico del ácido 5-(4-cloro-butanoilamino)-isoftálico (D80)

Una suspensión de éster 3-metílico - éster 1-*ter*-butílico del ácido

5-amino-isoftálico (D79) (3.4 g, 13.5 mmol, 1 eq.) en CH_2Cl_2 (25 ml), se trató con NEt_3 (2.32 g, 23 mmol, 1.1 eq.) y se enfrió a 0°C. Se le agregó gota a gota cloruro de 4-clorobutirilo (1.6 g, 15.7 mmol, 1.1 eq.), y la solución resultante se agitó a 0°C durante 3 h y se dejó después calentando a temperatura ambiente y se lavó con solución acuosa de HCl 2N, se secó sobre $MgSO_4$ y se concentró al vacío. El residuo se trituró con iso-hexano y Et_2O, para dar el éster 3-metílico - éster 1-*ter*-butílico del ácido 5-(4-cloro-butanoilamino)-isoftálico (D80) (4.5 g, 94%) como un sólido blanco.

Descripción 81

Ester 3-metílico - éster 1-*ter*-butílico del ácido 5-(3-cloro-propano-1-sulfonilamino)-isoftálico (D81)

A una solución de éster 3-metílico - éster 1-*ter*-butílico del ácido 5-amino-isoftálico (D79) (5.0 g, 20 mmol, 1 eq.), DMAP (0.3 g, 2.46 mmol, 0.12 eq.) y piridina (1.64 g, 20 mmol, 1 eq.) en CH_2Cl_2 (80 ml), se le agregó gota a gota cloruro de 3-cloropropanosulfonilo (2.4 ml, 20 mmol, 1 eq.). La mezcla resultante se agitó durante 16 h y se diluyó después con AcOEt (150 ml). La fase orgánica se lavó con solución acuosa de HCl 2N y solución acuosa saturada de $NaHCO_3$, se secó sobre $MgSO_4$ y se concentró al vacío, para dar el éster 3-metílico - éster 1-*ter*-butílico del ácido 5-(3-cloro-propan-1-sulfonilamino)-isoftálico (D81) (7.8 g, 99%) como un sólido anaranjado claro.

Descripción 82

Ester 3-metílico - éster 1-*ter*-butílico del ácido 5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-isoftálico (D82)

Una mezcla de éster 3-metílico - éster 1-*ter*-butílico del ácido 5-(3-cloro-propan-1-sulfonilamino)-isoftálico (D81) (7.8 g, 20 mmol, 1 eq.) y NEt_3 (4.0 g, 40 mmol, 2 eq.) en EtOH (100 ml) se puso a reflujo 3 h, se enfrió a temperatura ambiente y se concentró al vacío. El residuo se diluyó con AcOEt, y la fase orgánica se lavó con solución acuosa de HCl 2N y solución acuosa saturada de $NaHCO_3$, se secó sobre $MgSO_4$ y se concentró al vacío, para dar el éster 3-metílico - éster 1-*ter*-butílico del ácido 5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-isoftálico (D82) (4.4 g, 62%) como un sólido blanco.

Descripción 83

Ester monometílico del ácido 5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-isoftálico (D83)

Una suspensión de éster 3-metílico - éster 1-*ter*-butílico del ácido 5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-isoftálico (D82) (4.4 g, 12.4 mmol, 1 eq.) en CH_2Cl_2 (10 ml) se trató con TFA (10 ml), y la mezcla resultante se agitó durante 2 h a temperatura ambiente. Se le agregó tolueno (10 ml), y la mezcla resultante se concentró al vacío. El residuo se trituró con Et_2O, para dar el éster monometílico del ácido 5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-isoftálico (D83) (3.6 g, 97%) como un sólido blanco.

Descripción 84

Ester metílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-hidroximetil-benzoico (D84)

Una solución de éster monometílico del ácido 5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-isoftálico (D83) (500 mg, 1.67 mmol, 1 eq.) en THF (30 ml) se trató con BH_3-Me_2S (solución 2M en THF, 1.0 ml, 2 mmol, 1.2 eq.), y la mezcla se puso a reflujo 30 minutos y se enfrió después a temperatura ambiente. Se le agregó gota a gota MeOH (5 ml), y la mezcla resultante se concentró al vacío. El residuo se diluyó con AcOEt (100 ml), y la solución resultante se lavó con solución acuosa de HCl 2N (100 ml) y solución acuosa saturada de $NaHCO_3$, se secó sobre $MgSO_4$ y se concentró al vacío, para dar el éster metílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-hidroximetil-benzoico (D84) (450 mg, 95%) como un aceite incoloro claro.

Descripción 85

Ester metílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-metanosulfoniloximetil-benzoico (D85)

Una solución de ácido 3-(1,1-dioxo-1λ^6isotiazolindin-2-il)-5-etoximetil-benzoico (D84) (400 mg, 1.4 mmol, 1 eq.) en CH_2Cl_2 (20 ml) se trató con NEt_3 (303 mg, 3.0 mmol, 2.1 eq.) y anhídrido metanosulfónico (261 mg, 1.5 mmol, 1.1 eq.), y se agitó durante 30 minutos a temperatura ambiente. La solución se lavó después con solución acuosa de HCl 2N (30 ml) y solución acuosa saturada de $NaHCO_3$ (30 ml), se secó sobre $MgSO_4$ y se concentró al

vacío. El residuo se trituró en Et_2O, para dar el éster metílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-metanosulfoniloximetil-benzoico (D85) (390 mg, 77%) como un sólido blanco.

Descripción 86

Ester metílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-formil-benzoico (D86)

Una solución de éster metílico del ácido 3-(1,1-dioxo-lλ^6-isotiazolidin-2-il)-5-hidroximetil-benzoico (D84) (500 mg, 1.8 mmol, 1 eq.) en CH_2Cl_2 (20 ml) se trató con MnO_2 (763 mg, 8.8 mmol, 4.9 eq.), y la mezcla resultante se agitó durante 3 h a temperatura ambiente. Se le agregó una segunda porción de MnO_2 (500 mg, 5.8 mmol, 3.2 eq.), y la mezcla se agitó durante 3 h cuando se agregó una tercera porción de MnO_2 (300 mg, 3.5 mmol, 1.9 eq.). La mezcla se agitó durante 2 h y se filtró después a través de una almohadilla de celite. El filtrado se concentró al vacío, para dar el éster metílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-formil-benzoico (D86) (450 mg, 88%) como un sólido ceroso amarillo.

Descripción 87

Ester metílico del ácido 5-nitro-N,N-dipropil-isoftalámico (D87)

Una suspensión de éster monometílico del ácido 5-nitro-isoftálico (D77) (1.0 g, 4.44 mmol, 1 eq.) en CH_2Cl_2 (40 ml) se trató con $(COCl)_2$ (655 mg, 5.2 mmol, 1.2 eq.), seguido de unas cuantas gotas de DMS. La mezcla

resultante se agitó durante 1 hora a temperatura ambiente y después se le agregó dipropilamina (1.65 g, 15 mmol, 3.4 eq.), y la solución resultante se agitó durante otros 30 minutos. La solución se lavó después con solución acuosa de HCl 2N (50 ml), solución acuosa saturada de $NaHCO_3$ (50 ml), se secó sobre $MgSO_4$ y se concentró al vacío, para dar el éster metílico del ácido 5-nitro-N,N-dipropil-isoftalámico (D87) (1.5 g, 110%) como un aceite amarillo claro.

Descripción 88

Ester metílico del ácido 5-amino-N,N-dipropil-isoftalámico (D88)

Una mezcla de éster metílico del ácido 5-nitro-N,N-dipropil-isoftalámico (D87) (1.5 g, 4.9 mmol, 1 eq.), NH_4COOH (3.0 g, 49 mmol, 10 eq.), Pd al 10% sobre carbón (50% en húmedo, 250 mg, 0.082 equivalentes p/p), EtOH (20 ml) y H_2O (10 ml), se calentó a 50°C durante 90 minutos. La mezcla se enfrió a temperatura ambiente, se filtró a través de una almohadilla de celite y se concentró al vacío. El residuo se disolvió en AcOEt (200 ml), y la solución resultante se lavó con solución de $NaHCO_3$ saturado (100 ml), se secó sobre $MgSO_4$ y se concentró al vacío, para dar el éster metílico del ácido 5-amino-N,N-dipropil-isoftalámico (D88) (1.2 g, 88%) como un sólido ceroso blanco.

Descripción 89

Ester metílico del ácido 5-(4-cloro-butanoilamino)-N,N-dipropil-isoftalámico (D89)

Una solución de éster metílico del ácido 5-amino-N,N-dipropil-isoftalámico (D88) (1.2 g, 4.3 mmol, 1 eq.) en CH_2Cl_2 (10 ml), se trató con NEt_3 (525 mg, 5.2 mmol, 1.2 eq.). La solución se enfrió a 0°C, y se le agregó gota a gota cloruro de 4-clorobutirilo (733 mg, 5.0 mmol, 1.2 eq.). La mezcla de reacción se dejó después calentando a temperatura ambiente y se agitó durante 1 hora. La solución se lavó con solución acuosa de HCl 2N (20 ml), se secó sobre $MgSO_4$ y se concentró al vacío, para dar el éster metílico del ácido 5-(4-cloro-butanoilamino)-N,N-dipropil-isoftalámico (D89) (1.7 g, 104%) como un aceite incoloro.

Descripción 90

Ester metílico del ácido 5-(5-cloro-pentanoilamino)-N,N-dipropil-isoftalámico (D90)

El compuesto de la descripción 90 se preparó de forma análoga a la descripción 89, a partir de éster metílico del ácido 5-amino-N,N-dipropil-isoftalámico (D88) y cloruro de 5-clorovalerilo.

Descripción 91

Ester metílico del ácido 5-(3-cloro-propano-1-sulfonilamino)-N,N-dipropil-isoftalámico (D91)

Una solución de éster metílico del ácido 5-amino-N,N-dipropil-isoftalámico (D88) (1.4 g, 5.0 mmol, 1 eq.), DMAP (100 mg) y piridina (392 mg, 5.0 mmol, 1.1 eq.) en CH_2Cl_2 (20 ml), se trató gota a gota con cloruro de 3-cloropropan-1-sulfonilo (946 mg, 5.3 mmol, 1.1 eq.). La mezcla resultante se agitó durante 16 h a temperatura ambiente, y se diluyó después con AcOEt (100 ml). La solución resultante se lavó con solución acuosa de HCl 2N (50 ml) seguido de solución acuosa saturada de $NaHCO_3$ (50 ml), se secó sobre $MgSO_4$ y se concentró al vacío. El residuo se trituró con Et_2O, para dar el éster metílico del ácido 5-(3-cloro-propano-1-sulfonilamino)-N,N-dipropil-isoftalámico (D91) (1.8 g, 86%) como un sólido rosa.

Descripción 92

Ester metílico del ácido 5-(4-cloro-butano-1-sulfonilamino)-N,N-dipropil-isoftalámico (D92)

El compuesto de la descripción 92 se preparó de forma análoga a la descripción 91, a partir de éster metílico del ácido 5-amino-N,N-dipropil-isoftalámico (D88) y cloruro de 4-cloro-butano-1-sulfonilo.

Descripción 93

Ester metílico del ácido (2S,3R)-3-hidroxi-2-((S)-2-hidroxi-1-fenil-etilamino)-hexanoico (D93)

El compuesto de la descripción 93 se obtuvo de acuerdo con Alker, D.; Hamblett, G.; Harwood, L. M.; Robertson, S. M.; David, J.; Williams, C. E. *Tetrahedron*, **54** (22), 1998,6089-6098.

Descripción 94

Ester metílico del ácido (2S,3R)-2-*ter*-butoxicarbonilamino-3-hidroxi-hexanoico (D94)

Ester metílico del ácido (2S,3R)-3-hidroxi-2-((S)-2-hidroxi-1-fenil-etilamino)-hexanoico (D93) (2.88 g, 10.25 mmol, 1 eq.), paladio al 10% sobre carbón (50% en húmedo, 2 g, 35% p/p), HCOOH (5 ml, en exceso) en MeOH (50 ml), se agitaron a 60°C durante 1 hora. La mezcla se enfrió después a temperatura ambiente, se filtró a través de una almohadilla de celite y se concentró después al vacío. El residuo se disolvió en dioxano/agua (1/1, 50 ml), y después se agregaron $NaHCO_3$ (10 g, en exceso) y dicarbonato de di-*ter*-butilo (3.37 g, 15 mmol, 1.5 eq.). La mezcla resultante se agitó a temperatura ambiente durante 2 h y se concentró después al vacío. El residuo se disolvió en AcOEt, y la fase orgánica se lavó sucesivamente con solución acuosa de HCl 2N y solución acuosa saturada de $NaHCO_3$, se secó sobre $MgSO_4$ y se concentró al vacío. La purificación por cromatografía de vaporización instantánea sobre gel de sílice (CH_2Cl_2/MeOH: 99/1), dio éster

metílico del ácido (2S,3R)-2-*ter*-butoxicarbonilamino-3-hidroxi-hexanoico (D94) (1.88 g, 70%) como una goma incolora.

Descripción 95

Acido (S)-2-*ter*-butoxicarbonilamino-4-metilsulfanil-butírico (D95)

El compuesto de la descripción 95 está disponible comercialmente de Sigma-Aldrich Company.

Descripción 96

Ester *ter*-butílico del ácido ((S)-1-isobutilcarbamoil-3-metilsulfanil-propil)-carbámico (D96)

Acido (S)-2-*ter*-butoxicarbonilamino-4-metilsulfanil-butírico (D95) (2.0 g, 8.0 mmol, 1 eq.), clorhidrato de EDAC (1.84 g, 9.6 mmol, 1.2 eq.), HOBT (1.47 g, 9.6 mmol, 1.2 eq.), 4-etilmorfolina (1.76 g, 16 mmol, 2 eq.) e iso-butilamina (952 ml, 9.6 mmol, 1.2 eq.) en CH_2Cl_2 (10 ml), se agitaron a temperatura ambiente durante 16 h. La solución se concentró al vacío, y el residuo se disolvió en AcOEt. La fase orgánica se lavó con solución acuosa de HCl 2N, solución acuosa saturada de $NaHCO_3$ y salmuera, se secó sobre $MgSO_4$ y se concentró al vacío, para dar el éster *ter*-butílico del ácido ((S)-1-isobutilcarbamoil-3-metilsulfanil-propil)-carbámico (D96) (2.38 g, 98%) como un aceite incoloro.

Descripción 97

Ester etílico del ácido (3-metoxi-fenil)-acético (D97)

El compuesto de la descripción 97 está disponible comercialmente de Sigma-Aldrich Company.

Descripción 98

Ester etílico del ácido 2-(3-metoxi-fenil)-2-metil-propiónico (D98)

A una solución de éster etílico del ácido (3-metoxi-fenil)-acético (D97) (19.72 g, 0.101 m, 1 eq.) en THF (200 ml), se le agregó NaH (8.8 g, 0.222 moles, 2.2 eq.) y después yodometano (26 ml, 0.4 moles, 4 eq.). La mezcla resultante se agitó a temperatura ambiente durante 16 h, y se dividió después entre AcOEt y una solución acuosa de $NaHCO_3$ saturado. Las dos capas se separaron y la capa orgánica se lavó con salmuera, se secó sobre $MgSO_4$ y se concentró al vacío, para dar el éster etílico del ácido 2-(3-metoxi-fenil)-2-metil-propiónico (D98) (20.85 g, 98%) como un aceite anaranjado.

Descripción 99

Acido 2-(3-metoxi-fenil)-2-metil-propiónico (D99)

A una solución de éster etílico del ácido 2-(3-metoxi-fenil)-2-metil-propiónico (D98) (20.95 g, 94 mmol, 1 eq.) en EtOH (200 ml), se le agregó solución acuosa de NaOH 2N (90 ml, 180 mmol, 1.9 eq.), y la mezcla resultante se agitó a 70°C durante 16 h, y se enfrió después a temperatura ambiente. La mayor parte del EtOH se removió al vacío, y el residuo se

extrajo con AcOEt y se acidificó después a pH 1. La fase acuosa se extrajo después con AcOEt, y la fase orgánica se secó sobre $MgSO_4$ y se concentró al vacío, para dar ácido 2-(3-metoxi-fenil)-2-metil-propiónico (D99) (15 g, 82%) como un aceite amarillo.

Descripción 100

Ester bencílico de ácido [1-(3-metoxi-fenil)-1-metil-etil]-carbámico (D100)

A una solución de ácido 2-(3-metoxi-fenil)-2-metil-propiónico (D99) (1 g, 5.15 mmol, 1 eq.) en tolueno (20 ml) a temperatura ambiente, se le agregó NEt_3 (1.07 ml, 7.72 mmol, 1.5 eq.) y después difenilfosforilazida (2.2 ml, 10.3 mmol, 2 eq.). La mezcla resultante se calentó después a 80°C durante 2 h, se le agregó después alcohol bencílico (1.61 ml, 15.45 mmol, 3 eq.) y la solución se calentó durante otras 2 h, se enfrió a temperatura ambiente y se dividió entre EtOAc y una solución acuosa de $NaHCO_3$ saturado. Las dos capas se separaron, la fase acuosa se secó sobre $MgSO_4$ y se concentró al vacío. La purificación del residuo por cromatografía de vaporización instantánea sobre gel de sílice (iso-hexano/AcOEt: 9/1), dio éster bencílico de ácido [1-(3-metoxi-fenil)-1-metil-etil]-carbámico (D100) (1 g, 65%) como una goma amarilla.

Descripción 101

Ester *ter*-butílico del ácido ((S)-(S)-1-oxiranil-2-fenil-etil)-carbámico (D101)

El compuesto de la descripción 101 está disponible comercialmente de Chirex (ref. 1819W94, lote #9924382).

Descripción 102

Ester *ter*-butílico del ácido ((1S,2R)-3-amino-1-bencil-2-hidroxi-propil)-carbámico (D102)

A una solución de éster *ter*-butílico del ácido ((S)-(S)-1-oxiranil-2-fenil-etil)-carbámico (D101) (25 g, 95.1 mmol, 1 eq.)) en MeOH (350 ml), se le agregó amoníaco acuoso (32% p/p, 180 ml, 3.2 moles, 3.3 eq.). La mezcla resultante se agitó a temperatura ambiente durante 16 h y se concentró después al vacío, para dar el éster *ter*-butílico del ácido ((1S,2R)-3-amino-1-bencil-2-hidroxi-propil)-carbámico (D102) (25.2 g, 95%) como un sólido blanco.

Descripción 103

Ester bencílico de ácido ((2R,3S)-3-*ter*-butoxicarbonilamino-2-hidroxi-4-fenil-butil)-carbámico (D103)

Una solución de éster *ter*-butílico del ácido ((1S,2R)-3-amino-1-bencil-2-hidroxi-propil)-carbámico (D102) (25.6 g, 91.4 mmol, 1 eq.) en DMF (250 ml) a 0°C se trató con NEt_3 (15 ml, 108 mmol, 1.2 eq.), y después se le

agregó gota a gota cloroformiato de bencilo (14 ml, 98 mmol, 1.1 eq.) en DMF (50 ml). La solución resultante se agitó a 0°C durante 1 hora y a temperatura ambiente durante 16 h, y se concentró después al vacío. El residuo se dividió entre AcOEt y solución acuosa saturada de $NaHCO_3$. El precipitado resultante se diluyó con H_2O y se filtró, para dar el éster bencílico de ácido ((2R,3S)-3-*ter*-butoxicarbonilamino-2-hidroxi-4-fenil-butil)-carbámico (D103) (31.5 g, 83%) como un sólido blanco.

Descripción 104

Ester bencílico de ácido ((2R,3S)-3-amino-2-hidroxi-4-fenil-butil)-carbámico (D104)

Una solución de éster bencílico de ácido ((2R,3S)-3-*ter*-butoxicarbonilamino-2-hidroxi-4-fenil-butil)-carbámico (D103) (31.5 g, 76.1 mmol, 1 eq.) en THF (300 ml), se trató con solución de HCl 4N en dioxano (40 ml, 160 mmol, 2.1 eq.). La solución resultante se agitó a temperatura ambiente durante 2 h y se concentró después al vacío. El residuo se trituró con Et_2O/iso-hexano, para dar clorhidrato de éster bencílico de ácido ((2R,3S)-3-amino-2-hidroxi-4-fenil-butil)-carbámico (D104) (22.1 g, 83%) como un sólido blanco.

Descripción 105

Ester bencílico de ácido [(2R,3S)-2-hidroxi-3-(1-[3-(2-oxo-pirrolidin-1-il)-5-pentiloxi-fenil]-metanoil)-amino)-4-fenil-butil]-carbámico (D105)

A una suspensión de ácido 3-(2-oxo-pirrolidin-1-il)-5-pentiloxi-benzoico (A13) (530 mg, 1.82 mmol, 1 eq.) en CH_2Cl_2 (20 ml), se le agregó HOBT (300 mg, 2.2 mmol, 1.2 eq.) y clorhidrato de EDAC (420 mg, 2.2 mmol, 1.2 eq.). Después de agitación durante 5 minutos, se le agregó clorhidrato de ácido 3-(2-oxo-pirrolidin-1-il)-5-pentiloxi-benzoico (D104) (570 mg, 1.82 mmol, 1 eq.), y la mezcla resultante se agitó a temperatura ambiente durante 16 h. La mezcla de reacción se diluyó después con CH_2Cl_2 (20 ml), se lavó con solución acuosa saturada de $NaHCO_3$, se secó sobre $MgSO_4$ y se concentró al vacío, para dar el éster bencílico de ácido [(2R,3S)-2-hidroxi-3-({1-[3-(2-oxo-pirrolidin-1-il)-5-pentiloxi-fenil]-metanoil}-amino)-4-fenil-butil]-carbámico (D105) (510 mg, 48%) como un sólido blanco.

Descripción 106

Ester bencílico de ácido [(2R,3S)-3-({1-[3-etilamino-5-(2-oxo-pirrolidin-1-il)-fenil]-metanoil}-amino)-2-hidroxi-4-fenil-butil]-carbámico (D106)

El compuesto de la descripción 106 se preparó de forma análoga a la descripción 105, a partir de clorhidrato de ácido 3-(2-oxo-pirrolidin-1-il)-5-pentiloxi-benzoico (D104) y ácido 3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzoico (A31).

Descripción 107

Ester bencílico de ácido [(2R,3S)-3-({1-[3-isopropilamino-5-(2-oxo-pirrolidin-1-il)-fenil]-metanoil}-amino)-2-hidroxi-4-fenil-butil]-carbámico (D107)

El compuesto de la descripción 107 se preparó de forma análoga a la descripción 105, a partir de clorhidrato de ácido 3-(2-oxo-pirrolidin-1-il)-5-isopropilamino-benzoico (A44) y éster bencílico de ácido ((2R,3S)-3-amino-2-hidroxi-4-fenil-butil)-carbámico (D104).

Descripciones 108-119

Se prepararon los siguientes compuestos (D108-D119) a partir del compuesto de la descripción 104, de forma análoga al procedimiento de la descripción 105, usando el ácido adecuado.

Descripción	Acido
[(2R,3S)-3-({[3-(1,1-Dioxidotetrahidro-2H-1,2-tiazin-2-il)-5-(etilamino)fenil]carbonil}amino)-2-hidroxi-4-fenilbutilcarbamato de fenilmetilo (D108)	A73
[(2R,3S)-3-({[3-(1,1-Dioxidotetrahidro-2H-1,2-tiazin-2-il)-5-(etilamino)-2-fluorofenil]carbonil}amino)-2-hidroxi-4-fenilbutil]carbamato de fenilmetilo (D109)	A119
[(2R,3S)-3-({[3-Ciclopentil-5-(2-oxo-1-pirrolidinil)fenil]carbonil}amino)-2-hidroxi-4-fenilbutil]carbamato de fenilmetilo (D110)	A107
[(2R,3S)-2-Hidroxi-3-({[3-[(1-metiletil)oxi]-5-(2-oxo-1-pirrolidinil)fenil]carbonil}amino)-4-fenilbutil]carbamato de fenilmetilo (D111)	A12
{(2R,3S)-3-[({3-(1,1-Dioxidotetrahidro-2H-1,2-tiazin-2-il)-5-[(1-metiletil)oxi]fenil}carbonil)amino]-2-hidroxi-4-fenilbutil}carbamato de fenilmetilo (D112)	A168
[(2R,3S)-3-({[3-Ciclopentil-5-(1,1-dioxidotetrahidro-2H-1,2-tiazin-2-il)fenil]carbonil}amino)-2-hidroxi-4-fenilbutilcarbamato de fenilmetilo (D113)	A126

Descripción	Acido
[(2R,3S)-3-({[3-(Etiloxi)-5-(2-oxo-1-pirrolidinil)fenil]carbonil}amino)-2-hidroxi-4-fenilbutilcarbamato de fenilmetilo (D114)	A11
[(2R,3S)-3-({[3-(1,1-Dioxido-2-isotiazolindinil)-5-(etiloxi)fenil]carbonil}amino)-2-hidroxi-4-fenilbutil]carbamato de fenilmetilo (D115)	A18
{(2R,3S)-3-[({3-(1,1-Dioxido-2-isotiazolidinil)-5-[(1-metiletil)oxi]fenil}carbonil)amino]-2-hidroxi-4-fenilbutil}carbamato de fenilmetilo (D116)	A19
[(2R,3S)-3-({[3-Ciclopentil-5-(1,1-dioxido-2-isotiazolidinil)fenil]carbonil}amino)-2-hidroxi-4-fenilbutil]carbamato de fenilmetilo (D117)	A169
[(2R,3S)-3-({[3-(1,1-Dioxido-2-isotiazolidinil)-5-etilamino)fenil]carbonil}amino)-2-hidroxi-4-fenilbutil]carbamato de fenilmetilo (D118)	A70
[(2R,3S)-3-({[3-(1,1-Dioxidotetrahidro-2H-1,2-tiazin-2-il)-5-(etiloxi)fenil]carbonil}amino)-2-hidroxi-4-fenilbutil]carbamato de fenilmetilo (D119)	A170

Descripciones 120-131

Se prepararon los siguientes compuestos (D120-D131), de forma análoga al procedimiento descrito para el ejemplo 182, usando el precursor adecuado:

Descripción	Precursor
N-[(1S,2R)-3-Amino-2-hidroxi-1-(fenilmetil)propil]-3-(1,1-dioxidotetrahidro-2H-1,2-tiazin-2-il)-5-(etilamino)benzamida (D120)	D108
N-[(1S,2R)-3-Amino-2-hidroxi-1-(fenilmetil)propil]-3-(1,1-dioxidotetrahidro-2H-1,2-tiazin-2-il)-5-(etilamino)-2-fluorobenzamida (D121)	D109
N-[(1S,2R)-3-Amino-2-hidroxi-1-(fenilmetil)propil]-3-ciclopentil-5-(2-oxo-1-pirrolidinil)benzamida (D122)	D110
N-[(1S,2R)-3-Amino-2-hidroxi-1-(fenilmetil)propil]-3-[(1-metiletil)oxi]-5-(2-oxo-1-pirrolidinil benzamida (D123)	D111
N-[(1S,2R)-3-Amino-2-hidroxi-1-(fenilmetil)propil]-3-(1,1-dioxidotetrahidro-2H-1,2-tiazin-2-il)-5-[(1-metiletil)oxi]benzamida (D124)	D112

Descripción	Precursor
N-[(1S,2R)-3-Amino-2-hidroxi-1-(fenilmetil)propil]-3-ciclopentil-5-(1,1-dioxidotetrahidro-2H-1,2-tiazin-2-il)benzamida (D125)	D113
N-[(1S,2R)-3-Amino-2-hidroxi-1-(fenilmetil)propil]-3-(etiloxi)-5-(2-oxo-1-pirrolidinil)benzamida (D126)	D114
N-[(1S,2R)-3-Amino-2-hidroxi-1-(fenilmetil)propil]-3-(1,1-dioxido-2-isotiazolidinil)-5-(etiloxi)benzamida (D127)	D115
N-[(1S,2R)-3-Amino-2-hidroxi-1-(fenilmetil)propil]-3-(1,1-dioxido-2-isotiazolidinil)-5-[(1-metiletil)oxi]benzamida (D128)	D116
N-[(1S,2R)-3-Amino-2-hidroxi-1-(fenilmetil)propil]-3-ciclopentil-5-(1,1-dioxido-2-isotiazolidinil)benzamida (D129)	D117
N-[(1S,2R)-3-Amino-2-hidroxi-1-(fenilmetil)propil]-3-(1,1-dioxido-2-isotiazolidinil)-5-(etilamino)benzamida (D130)	D118
N-[(1S,2R)-3-Amino-2-hidroxi-1-(fenilmetil)propil]-3-(1,1-dioxidotetrahidro-2H-1,2-tiazin-2-il)-5-(etiloxi)benzamida (D131)	D119

Descripción 132

3-Nitro-5-[(1*E/Z*)-1-propen-1-il]benzoato de metilo (D132)

Se preparó 3-nitro-5-[(1*E/Z*)-1-propen-1-il]benzoato de metilo (D132) a partir de 3-bromo-5-nitrobenzoato de metilo (D11), de forma análoga a la descripción 68 (D68). Sin ion molecular. t.r. = 3.42 min.

Descripción 133

3-Amino-5-propilbenzoato de metilo (D133)

Se preparó 3-amino-5-propilbenzoato de metilo (D133) a partir de 3-nitro-5-[(1E/Z)-1-propen-1-il]benzoato de metilo (D132), de forma análoga a la que se describe para el éster 116 (B116).

302

Descripción 134

3-[(3-Buten-1-ilsulfonil)amino]-5-propilbenzoato de metilo (D134)

A una solución de 3-amino-5-propilbenzoato de metilo (D133) (2.49 g, 12.9 mmol, 1 eq.) en CH_2Cl_2 (25 ml), se agregaron piridina (1.13 ml, 14 mmol, 1.1 eq.), cloruro de 2-propen-1-sulfonilo (2 g, 12.9 mmol, 1 eq.) y DMAP (350 mg, 2.9 mmol, 0.2 eq.), y la mezcla resultante se agitó a temperatura ambiente durante 4 días. La solución se diluyó con AcOEt, y la fase orgánica se lavó con H_2O, se secó sobre $MgSO_4$ y se concentró al vacío. La purificación del residuo por cromatografía de vaporización instantánea sobre gel de sílice (iso-hexano/AcOEt: 4:1), dio 3-[(3-buten-1-ilsulfonil)amino]-5-propilbenzoato de metilo (D134) (1.3 g, 32%) como un aceite incoloro. [M-H]$^-$ = 310.0, t.r. = 3.39 min.

Descripción 135

3-[(3-Buten-1-ilsulfonil)(2-propen-1-il)amino]-5-propilbenzoato de metilo (D135)

A una solución de 3-[(3-buten-1-ilsulfonil)amino]-5-propilbenzoato de metilo (D134) (1.3 g, 4.2 mmol, 1 eq.), 2-propen-1-ol (280 µl, 4.2 mmol, 1 eq.) y trifenilfosfina (1.28 g, 4.9 mmol, 1.15 eq.) en tolueno (20 ml), a temperatura ambiente, se le agregó lentamente azodicarboxilato de diisopropilo (964 ml, 4.9 mmol, 1.15 eq.). La solución resultante se agitó a esta temperatura durante 30 minutos, y se concentró después al vacío. La purificación del residuo por cromatografía de vaporización instantánea sobre

303

gel de sílice (iso-hexano/AcOEt: 4:1), dio 3-[(3-buten-1-ilsulfonil)(2-propen-1-il)amino]-5-propilbenzoato de metilo (D135) (1.1 g, 75%) como un aceite amarillo. $[M+H]^+$ = 352.1, t.r. = 3.63 min.

Descripción 136

Acido 2-fluoro-3,5-dinitrobenzoico (D136)

Una solución acuosa de HNO_3 al 70% (80 ml) se agregó gota a gota a H_2SO_4 (160 ml). La temperatura se mantuvo abajo de 10°C usando un baño de hielo. Se le agregó en porciones ácido 2-fluorobenzoico (14 g, 0.1 moles, 1 eq.) durante 5 minutos, y después la suspensión incolora se calentó lentamente a 90°C y se agitó a esta temperatura durante 1 hora, y después a 100°C durante 3 h. La solución se enfrió entonces a temperatura ambiente y se vació cuidadosamente en hielo (1 l) diluido con H_2O (1.5 l). La fase acuosa se extrajo tres veces con AcOEt, y la capa orgánica combinada se secó sobre $MgSO_4$ y se concentró al vacío. El residuo se trituró con Et_2O para dar ácido 2-fluoro-3,5-dinitrobenzoico (D136) (13.6 g, 59%), como un sólido amarillo claro, que se usó en el siguiente paso sin mayor purificación. Sin ion molecular, t.r. = 2.06 min.

Descripción 137

2-Fluoro-3,5-dinitrobenzoato de metilo (D137)

Se preparó 2-fluoro-3,5-dinitrobenzoato de metilo (D137) de forma análoga a la descripción 25 (D25), a partir de ácido 2-fluoro-3,5-

dinitrobenzoico (D136).

Descripción 138

3-Amino-2-fluoro-5-nitrobenzoato de metilo (D138)

A una solución de 2-fluoro-3,5-dinitrobenzoato de metilo (D137) (24.4 g, 0.1 moles, 1 eq.) en AcOH (1 l), se le agregó hierro (27.5 g, 0.5 moles, 5 eq.), y la suspensión resultante se agitó vigorosamente durante 1 hora. La temperatura se mantuvo abajo de 35°C con un poco de enfriamiento usando un baño de hielo durante ese período. Se agregó tolueno (200 ml), y la suspensión se filtró a través de una almohadilla de celite. La solución restante se concentró al vacío, y el residuo se dividió entre AcOEt y una solución acuosa saturada de $NaHCO_3$. Las dos capas se separaron, y la fase acuosa se extrajo dos veces con AcOEt. La fase orgánica combinada se secó sobre $MgSO_4$ y se concentró al vacío, para dar 3-amino-2-fluoro-5-nitrobenzoato de metilo (D138) (17 g, 79%), como un sólido amarillo que se usó en el siguiente paso sin mayor purificación. $[M-H]^-$ = 212.9, t.r. = 2.68 min.

Descripción 139

3-[(4-Clorobutanoil)amino]-2-fluoro-5-nitrobenzoato de metilo (D139)

A una solución de 3-amino-2-fluoro-5-nitrobenzoato de metilo (D138) (12 g, 56 mmol, 1 eq.) en CH_2Cl_2 (150 ml) a temperatura ambiente, se le agregó NEt_3 (11.7 ml, 84 mmol, 1.5 eq.) y cloruro de 4-clorobutanoilo (6.9

ml, 61.6 mmol, 1.1 eq.), y la mezcla resultante se agitó durante 2 h, se lavó después con una solución acuosa de HCl 2N y una solución acuosa saturada de $NaHCO_3$, se secó sobre $MgSO_4$ y se concentró al vacío. La purificación del residuo por cromatografía de vaporización instantánea sobre gel de sílice (iso-hexano/AcOEt:4/1), dio 3-[(4-clorobutanoil)amino]-2-fluoro-5-nitrobenzoato de metilo (D139) (16.2 g, 91%), como un sólido amarillo. $[M+H]^+$ = 319.1, t.r. = 3.12 min.

Descripción 140

2-Fluoro-5-nitro-3-(2-oxo-1-pirrolidinil)benzoato de metilo (D140)

A una solución de 3-[(4-clorobutanoil)amino]-2-fluoro-5-nitrobenzoato de metilo (D139) (8.5 g, 26.7 mmol, 1 eq.) en THF (100 ml), se le agregó NaH (dispersión al 60% en aceite mineral, 1.17 g, 29.4 mmol, 1.1 eq.), y la mezcla resultante se agitó a temperatura ambiente durante 1.5 h y se diluyó después con AcOEt. La fase orgánica se lavó con H_2O, se secó sobre $MgSO_4$ y se concentró al vacío. La purificación del residuo por cromatografía de vaporización instantánea sobre gel de sílice (iso-hexano/AcOEt:2/1), dio 2-fluoro-5-nitro-3-(2-oxo-1-pirrolidinil) benzoato de metilo (D140) (3.3 g, 43%) como un sólido amarillo. $[M+H]^+$ = 283.1, t.r. = 2.53 min.

Descripción 141

3-{Bis[(3-cloropropil)sulfonil]amino}-2-fluoro-5-nitrobenzoato de metilo (D141)

A una solución de 3-amino-2-fluoro-5-nitrobenzoato de metilo (D138) (500 mg, 2.34 mmol, 1 eq.) en CH_2Cl_2 (50 ml), se le agregó NEt_3 (840 µl, 6.0 mmol, 2.6 eq.), después cloruro de 3-cloro-1-propanosulfonilo (624 µl, 5.0 mmol, 2.1 eq.), y la mezcla resultante se agitó durante 1 hora. La fase orgánica se lavó después con una solución acuosa de HCl 2N, se secó sobre $MgSO_4$ y se concentró al vacío, para dar 3-{bis[(3-cloropropil)sulfonil]amino}-2-fluoro-5-nitrobenzoato de metilo (D141) (900 mg, 78%) como una espuma parda que se usó en el siguiente paso sin mayor purificación. Sin ion molecular, t.r. = 3.51 min.

Descripción 142

3-{Bis[(4-clorobutil)sulfonil]amino}-2-fluoro-5-nitrobenzoato de metilo (D142)

El 3-{bis[(4-clorobutil)sulfonil]amino}-2-fluoro-5-nitrobenzoato de metilo (D142) se obtuvo a partir de 3-amino-2-fluoro-5-nitrobenzoato de metilo (D138), de forma análoga a la descrita para 3-{bis[(3-cloropropil)sulfonil]amino}-2-fluoro-5-nitrobenzoato de metilo (D141), usando cloruro de 4-cloro-1-butanosulfonilo (D20) en lugar de cloruro de 3-cloro-1-propanosulfonilo. $[M+H+NH_3]^+$ = 540.1, t.r. = 3.62 min.

Descripción 143

Acido 3-{[(3-cloropropil)sulfonil]amino}-2-fluoro-5-nitrobenzoico (D143)

A una solución de 3-{bis[(3-cloropropil)sulfonil]amino}-2-fluoro-5-nitrobenzoato de metilo crudo (D141) (900 mg, 1.81 mmol, 1 eq.) en MeOH (25 ml), se le agregó una solución de MeOH acuoso 2N (15 ml, 30 mmol, en exceso), y la mezcla resultante se agitó durante 1 hora. La mayor parte del MeOH se removió al vacío, y el residuo se dividió entre AcOEt y una solución acuosa de HCl 2N. Las dos capas se separaron y la fase acuosa se secó sobre $MgSO_4$ y se concentró al vacío. El residuo se trituró con Et_2O/iso-hexano, para dar ácido 3-{[(3-cloropropil)sulfonil]amino}-2-fluoro-5-nitrobenzoico (D143) (600 mg, 97%) como un sólido canela claro, que se usó en el siguiente paso sin mayor purificación. Sin ion molecular, t.r. = 3.05 min.

Descripción 144

Acido 3-{[(4-clorobutil)sulfonil]amino}-2-fluoro-5-nitrobenzoico (D144)

El ácido 3-{[(4-clorobutil)sulfonil]amino}-2-fluoro-5-nitrobenzoico (D144) se obtuvo a partir de 3-{bis[(4-clorobutil)sulfonil]amino}-2-fluoro-5-nitrobenzoato de metilo (D142) de forma análoga al procedimiento descrito para ácido 3-{[(3-cloropropil)sulfonil]amino}-2-fluoro-5-nitrobenzoico (D143).

Descripción 145

3-{[(3-Cloropropil)sulfonil]amino}-2-fluoro-5-nitrobenzoato de metilo (D145)

El 3-{[(3-cloropropil)sulfonil]amino}-2-fluoro-5-nitrobenzoato de metilo (D145) se preparó de forma análoga a la descripción 25, a partir de ácido 3-{[(3-cloropropil)sulfonil]amino}-2-fluoro-5-nitrobenzoico (D143). $[M-H]^-$ = 353.0, t.r. = 3.05 min.

Descripción 146

3-{[(4-clorobutil)sulfonil]amino}-2-fluoro-5-nitrobenzoato de metilo (D146)

El 3-{[(4-clorobutil)sulfonil]amino}-2-fluoro-5-nitrobenzoato de metilo (D146) se preparó de forma análoga a la descripción 25, a partir de ácido 3-{[(4-clorobutil)sulfonil]amino}-2-fluoro-5-nitrobenzoico (D144). $[M+H+NH_3]^+$ = 386.1, t.r. = 3.13 min.

Descripción 147

3-(1,1-Dioxido-2-isotiazolidinil)-2-fluoro-5-nitrobenzoato de metilo (D147)

A una solución de 3-{[(3-cloropropil)sulfonil]amino}-2-fluoro-5-nitrobenzoato de metilo (D145) (300 mg, 0.85 mmol, 1 eq.) en EtOH (30 ml), se le agregó NEt_3 (280 µl, 2 mmol, 2.3 eq.), y la solución resultante se puso a reflujo 1.5 h, se enfrió después a temperatura ambiente y se concentró al

vacío. El residuo se disolvió en AcOEt, y la fase orgánica se lavó con solución acuosa de HCl 2N, se secó sobre $MgSO_4$ y se concentró al vacío. El residuo se trituró con AcOEt/Et_2O, para dar 3-(1,1-dioxido-2-isotiazolidinil)-2-fluoro-5-nitrobenzoato de metilo (D147) (150 mg, 55%) como un sólido canela claro que se usó en el siguiente paso sin mayor purificación. $[M+H+NH_3]^+$ = 336.3, t.r. = 2.50 min.

Descripción 148

3-(1,1-Dioxidotetrahidro-2H-1,2-tiazin-2-il)-2-fluoro-5-nitro-benzoato de metilo (D148)

El 3-(1,1-dioxidotetrahidro-2H-1,2-tiazin-2-il)-2-fluoro-5-nitrobenzoato de metilo (D148) se preparó de forma análoga al procedimiento para 3-(1,1-dioxido-2-isotiazolidinil)-2-fluoro-5-nitrobenzoato de metilo (D147), a partir de 3-{[(4-clorobutil)sulfonil]amino}-2-fluoro-5-nitrobenzoato de metilo (D146). $[M+H+NH_3]^+$ = 350.1, t.r. = 2.79 min.

Descripción 149

3-(1,1-Dioxidotetrahidro-2H-1,2-tiazin-2-il)-2-(metiloxi)-5-nitro-benzoato de metilo (D149)

A una solución de 3-{[(4-clorobutil)sulfonil]amino}-2-fluoro-5-nitrobenzoato de metilo (D146) (1.5 g, 4.1 mmol, 1 eq.) en MeOH (30 ml) se le agregó NEt_3 (1.2 ml, 8.6 mmol, 2.1 eq.), y la solución resultante se puso a reflujo 1.5 h, se enfrió después a temperatura ambiente y se concentró al

vacío. El residuo se disolvió en AcOEt, y la fase orgánica se lavó con una solución acuosa de HCl 2N, se secó sobre $MgSO_4$ y se concentró al vacío. El residuo se trituró con AcOEt/Et_2O, para dar 3-(1,1-dioxidotetrahidro-2H-1,2-tiazin-2-il)-2-(metiloxi)-5-nitrobenzoato de metilo (D149) (1.2 g, 55%), como un sólido pardo claro que se usó en el siguiente paso sin mayor purificación. $[M+H]^+$ = 345.1, t.r. = 2.80 min.

Descripción 150

5-Amino-2-fluoro-3-(2-oxo-1-pirrolidinil)benzoato de metilo (D150)

A una solución de 2-fluoro-5-nitro-3-(2-oxo-1-pirrolidinil) benzoato de metilo (D140) (3.3 g, 11.7 mmol, 1 eq.) en EtOH (100 ml) y H_2O (10 ml), se le agregó NH_4COOH (7.4 g, 117 mmol, 10 eq.) y paladio al 10% sobre carbón (50% en húmedo, 660 mg, 10% p/p), y la mezcla resultante se puso a reflujo 2 h y después se enfrió a temperatura ambiente. El catalizador se removió por filtración a través de una almohadilla de celite, y la mayor parte del solvente se removió al vacío. El residuo se dividió entre AcOEt y H_2O, y las dos capas se separaron. La fase orgánica se secó sobre $MgSO_4$ y se concentró al vacío, para dar 5-amino-2-fluoro-3-(2-oxo-1-pirrolidinil)benzoato de metilo (D150) (1.85 g, 63%), como un sólido amarillo claro que se usó en el siguiente paso sin mayor purificación. $[M+H]^+$ = 253.0, t.r. = 2.12 min.

Descripciones 151-153 (D151-153)

Los siguientes compuestos se obtuvieron del precursor adecuado, de forma análoga al procedimiento descrito para 5-amino-2-fluoro-3-(2-oxo-1-pirrolidinil)benzoato de metilo (D150).

Descripción	Precursor	$[M+H]^+$	t.r. (min)
5-Amino-3-(1,1-dioxido-2-isotiazolidinil)-2-fluorobenzoato de metilo (D151)	D147	289.1	2.12
5-Amino-3-(1,1-dioxidotetrahidro-2H-1,2-tiazin-2-il)-2-fluorobenzoato de metilo (D152)	D148	303.1	2.33
5-Amino-3-(1,1-dioxidotetrahidro-2H-1,2-tiazin-2-il)-2-(metiloxi)benzoato de metilo (D153)	D149	315.1	2.18

Descripción 154

2-Fluoro-5-({[4-(metiloxi)fenil]metil}amino)-3-(2-oxo-1-pirrolidinil)-benzoato de metilo (D154)

El 2-fluoro-5-({[4-(metiloxi)fenil]metil}amino)-3-(2-oxo-1-pirrolidinil)benzoato de metilo (D154) se preparó a partir de 5-amino-2-fluoro-3-(2-oxo-1-pirrolidinil)benzoato de metilo (D150), de forma análoga al procedimiento descrito para el éster 35 (B35), usando 4-(metiloxi)benzaldehído en lugar de propionaldehído. $[M+H]^+$ = 373.4, t.r. = 2.85 min.

311
312

Descripción 155

5-(Etil{[4-(metiloxi)fenil]metil}amino)-2-fluoro-3-(2-oxo-1-pirrolidinil)-benzoato de metilo (D155)

El 5-(etil{[4-(metiloxi)fenil]metil}amino)-2-fluoro-3-(2-oxo-1-pirrolidinil)benzoato de metilo (D155) se preparó a partir de 2-fluoro-5-({[4-(metiloxi)fenil]metil}amino)-3-(2-oxo-1-pirrolidinil) benzoato de metilo (D154), de forma análoga al procedimiento descrito para el éster 35 (B35), usando acetaldehído en lugar de propionaldehído. $[M+H]^+$ = 401.4, t.r. = 3.11 min.

Descripción 156

5-Bromo-2-fluoro-3-(2-oxo-1-pirrolidinil)benzoato de metilo (D156)

A una solución de 5-amino-2-fluoro-3-(2-oxo-1-pirrolidinil)-benzoato de metilo (D150) (650 mg, 2.6 mmol, 1 eq.) en una solución acuosa de HBr al 48% a 0°C se le agregó en porciones $NaNO_2$, y la mezcla resultante se agitó a 0°C durante 30 minutos. Se le agregó CuBr (260 mg, 1.82 mmol, 0.7 eq.) en una solución acuosa de HBr al 48% (1 ml) y la mezcla resultante se agitó a 90°C durante 1 h; después se enfrió a temperatura ambiente y se dividió entre H_2O y AcOEt. Las dos capas se separaron y la fase orgánica se secó sobre $MgSO_4$ y se concentró al vacío. La purificación del residuo por cromatografía de vaporización instantánea sobre gel de sílice (iso-hexano/AcOEt: 2/1), dio 5-bromo-2-fluoro-3-(2-oxo-1-pirrolidinil)benzoato de metilo (D156) (145 mg, 18%), como un sólido blanco. $[M+H]^+$ = 318.1, t.r. =

2.51 min.

Descripciones 157-158 (D157-158)

Los siguientes compuestos se prepararon de manera análoga al procedimiento descrito en la descripción 156 (D156), a partir de la anilina apropiada:

Descripción	Precursor	t.r. (min)
5-Bromo-3-(1,1-dioxido-2-isotiazolidinil)-2-fluorobenzoato de metilo	D151	2.55
5-Bromo-3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-2-fluorobenzoato de metilo	D152	

Descripciones 159-161 (D159-161)

Los siguientes compuestos se prepararon de manera análoga al procedimiento descrito en la descripción 68 (D68), a partir del bromuro de arilo apropiado indicado en el cuadro siguiente:

Descripción	Precursor	$[M+H]^+$	t.r. (min)
2-Fluoro-3-(2-oxo-1-pirrolidinil)-5-[(1*E/Z*)-1-propen-1-il]benzoato de metilo (D159)	D156	278.4	2.60
3-(1,1-Dioxido-2-isotiazolidinil)-2-fluoro-5-[(1*E/Z*)-1-propen-1-il]benzoato de metilo (D160)	D157	314.2	2.67
3-(1,1-Dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-2-fluoro-5-[(1*E/Z*)-1-propen-1-il]benzoato de metilo (D161)	D158		

Descripción 162

4-Metil-3,5-dinitrobenzoato de metilo (D162)

El 4-metil-3,5-dinitrobenzoato de metilo (D162) se preparó de

manera análoga a la descripción 25, a partir de ácido 4-metil-3,5-dinitrobenzoico disponible comercialmente. $[M+H]^+$ = 240.2, t.r. = 3.07 min.

Descripción 163

3-Amino-4-(metiloxi)-5-nitrobenzoato de metilo (D163)

A una solución de 4-(metiloxi)-3,5-dinitrobenzoato de metilo (D25) (5.0 g, 19.5 mmol, 1 eq.) en AcOH (150 ml), a temperatura ambiente, se le agregó en porciones polvo de fierro (9.0 g, 161 mmol, 8.2 eq.), y la mezcla resultante se agitó durante 3 h. Se le agregó tolueno (500 ml) y la fase orgánica se filtró a través de una almohadilla de celite y después se concentró al vacío. El residuo se disolvió en AcOEt y la fase orgánica se lavó con una solución acuosa saturada de $NaHCO_3$, se secó sobre $MgSO_4$ y se concentró al vacío. La trituración del residuo con Et_2O/iso-hexano dio 3-amino-4-(metiloxi)-5-nitrobenzoato de metilo (D163) (3.65 g, 83%) como un sólido amarillo, que se usó en el siguiente paso sin mayor purificación. $[M+H]^+$ = 226.9, t.r. = 2.76 min.

Descripción 164

3-Amino-4-metil-5-nitrobenzoato de metilo (D164)

El 3-amino-4-metil-5-nitrobenzoato de metilo (D164) se obtuvo de 4-metil-3,5-dinitrobenzoato de metilo (D162) de manera análoga al procedimiento descrito para 3-amino-4-(metiloxi)-5-nitrobenzoato de metilo (D163). $[M+H]^+$ = 211.0, t.r. = 2.81 min.

314
315

Descripción 165

3-Yodo-4-(metiloxi)-5-nitrobenzoato de metilo (D165)

A una solución de 3-amino-4-(metiloxi)-5-nitrobenzoato de metilo (D163) (370 mg, 1.64 mmol, 1 eq.) en tolueno (20 ml), a 0°C, se le agregó yodo (218 mg, 0.86 mmol, 0.5 eq.) y después nitrito de 1,1-dimetiletilo (200 mg, 1.75 mmol, 1.1 eq.); la mezcla resultante se agitó a temperatura ambiente durante 15 h; después se dividió entre AcOEt y salmuera. Las dos capas se separaron y la fase orgánica se secó sobre $MgSO_4$ y se concentró al vacío. La purificación del residuo por cromatografía de vaporización instantánea sobre gel de sílice dio 3-yodo-4-(metiloxi)-5-nitrobenzoato de metilo (D165) (280 mg, 51%), como un sólido pardo claro. Sin ion molecular. t.r. = 3.33 min.

Descripción 166

4-(Metiloxi)-3-nitro-5-[(1*E/Z*)-1-propen-1-il]benzoato de metilo (D166)

El 4-(metiloxi)-3-nitro-5-[(1*E/Z*)-1-propen-1-il]benzoato de metilo (D166) se preparó de 3-yodo-4-(metiloxi)-5-nitrobenzoato de metilo (D165) de manera análoga al procedimiento de la descripción 68 (D68). Sin ion molecular. t.r. = 3.46 min.

Descripción 167

3-Amino-4-(metiloxi)-5-[(1*E/Z*)-1-propen-1-il]benzoato de metilo (D167)

A una solución de 4-(metiloxi)-3-nitro-5-[(1*E/Z*)-1-propen-1-il]benzoato de metilo (D166) (1.0 g, 4.0 mmol, 1 eq.) en AcOH (150 ml), a temperatura ambiente, se le agregó en porciones polvo de fierro (1.4 g, 25 mmol, 6.25 eq.) y la mezcla resultante se agitó durante 3 h a temperatura ambiente. Se le agregó polvo de fierro (1 g, 17.9 mmol, 4.2 eq.) y la mezcla se agitó otra hora. Entonces se agregó nuevamente polvo de fierro (1 g, 17.9 mmol, 4.2 eq.) y la mezcla se agitó a 45°C durante 3 h; después se enfrió a temperatura ambiente y se agitó a esta temperatura durante 14 h. Se le agregó tolueno (200 ml) y la fase orgánica se filtró a través de una almohadilla de celite; después se concentró al vacío. El residuo se disolvió en AcOEt y la fase orgánica se lavó con una solución acuosa saturada de $NaHCO_3$, se secó sobre $MgSO_4$ y se concentró al vacío para dar 3-amino-4-(metiloxi)-5-[(1*E/Z*)-1-propen-1-il]benzoato de metilo (D167) (800 mg, 90%), como un aceite pardo que se usó en el siguiente paso sin mayor purificación. $[M+H]^+$ = 222.1, t.r. = 2.99 min.

Descripción 168

3-[bis[(4-Clorobutil)sulfonil]amino]-4-(metiloxi)-5-[(1*E/Z*)-1-propen-1-il]benzoato de metilo (D168)

A una solución de 3-amino-4-(metiloxi)-5-[(1*E/Z*)-1-propen-1-

il]benzoato de metilo (D167) (800 mg, 3.6 mmol, 1 eq.) en CH_2Cl_2 (50 ml), se le agregó NEt_3 (1.5 ml, 10.8 mmol, 3.0 eq.) y después cloruro de 4-cloro-1-butanosulfonilo (D20) (2 g, 10.8 mmol, 3.0 eq.); la mezcla resultante se agitó durante 1 h. La fase orgánica se lavó entonces con una solución acuosa de HCl 2N y una solución acuosa saturada de $NaHCO_3$; se secó sobre $MgSO_4$ y se concentró al vacío. La purificación del residuo por cromatografía de vaporización instantánea sobre gel de sílice (iso-hexano/AcOEt: 9/1 a 3/1), dio 3-{bis[(4-clorobutil)sulfonil]amino}-4-(metiloxi)-5-[(1*E/Z*)-1-propen-1-il]benzoato de metilo (D168) (1.0 g, 52%) como un aceite amarillo claro.

Descripción 169

Acido 3-{[(4-clorobutil)sulfonil]amino}-4-(metiloxi)-5-[(1*E/Z*)-1-propen-1-il]benzoico (D169)

A una solución de 3-{bis[(4-clorobutil)sulfonil]amino}-4-(metiloxi)-5-[(1*E/Z*)-1-propen-1-il]benzoato de metilo (D168) (1.0 g, 1.88 mmol, 1 eq.) en MeOH (20 ml), se le agregó una solución acuosa de NaOH 2N (10 ml, 20 mmol, exceso) y la mezcla resultante se agitó durante 1 h. La mayor parte del MeOH se removió al vacío y el residuo se dividió entre AcOEt y una solución acuosa de HCl 2N. Las dos capas se separaron y la fase acuosa se secó sobre $MgSO_4$ y se concentró al vacío. El residuo se trituró con Et_2O/iso-hexano, para dar ácido 3-{[(4-clorobutil)sulfonil]amino}-4-(metiloxi)-5-[(1*E/Z*)-1-propen-1-il]benzoico (D169) (470 mg, 69%), como un sólido cremoso claro, que se usó en el siguiente paso sin mayor purificación. $[M-H]^-$ = 360.0, t.r. =

317
318

3.19 min.

Descripción 170

3-[[(4-Clorobutil)sulfonil]amino]-4-(metiloxi)-5-[(1*E*)-1-propen-1-il]benzoato de metilo (D170)

El 3-[[(4-clorobutil)sulfonil]amino]-4-(metiloxi)-5-[(1*E/Z*)-1-propen-1-il]benzoato de metilo (D170) se preparó de ácido 3-[[(4-clorobutil)sulfonil]amino]-4-(metiloxi)-5-[(1*E/Z*)-1-propen-1-il]benzoico (D169), de manera análoga a la descripción 25 (D25).

Descripciones 171-172 (D171-172)

Los siguientes compuestos se obtuvieron de sus precursores correspondientes de manera análoga al procedimiento de la descripción 2 (D2):

Descripción	Precursor	$[M+H]^+$	t.r. (min)
3-[(4-Clorobutanoil)amino]-4-(metiloxi)-5-nitrobenzoato de metilo (D171)	D163	331.0	3.13
3-[(4-Clorobutanoil)amino]-4-metil-5-nitrobenzoato de metilo (D172)	D164	315.1	3.02

Descripciones 173-174 (D173-174)

Los siguientes compuestos se obtuvieron de sus precursores correspondientes de manera análoga al procedimiento de la descripción 14 (D14):

Descripción	Precursor	$[M+H]^+$	t.r. (min)
3-{[(3-Cloropropil)sulfonil]amino}-4-(metiloxi)-5-nitrobenzoato de metilo (D173)	D163	364.9	3.10
3-{[(3-Cloropropil)sulfonil]amino}-4-metil-5-nitrobenzoato de metilo (D174)	D164	349.0	3.12

Descripciones 175-176 (D175-176)

Los siguientes compuestos se obtuvieron de sus precursores correspondientes de manera análoga al procedimiento de la descripción 14 (D14), usando cloruro de 4-cloro-1-butanosulfonilo (D20) en lugar de cloruro de 3-cloro-1-propanosulfonilo:

Descripción	Precursor	$[M+H]^+$	t.r. (min)
3-{[(4-Clorobutil)sulfonil]amino}-4-(metiloxi)-5-nitrobenzoato de metilo (D175)	D163		
3-{[(4-Clorobutil)sulfonil]amino}-4-metil-5-nitrobenzoato de metilo (D176)	D164	362.8	3.21

Descripciones 177-178 (D177-178)

Los siguientes compuestos se obtuvieron de sus precursores correspondientes de manera análoga al procedimiento descrito para el éster 27 (B27):

Descripción	Precursor	$[M+H]^+$	t.r. (min)
4-(Metiloxi)-3-nitro-5-(2-oxo-1-pirrolidinil)benzoato de metilo (D177)	D171	295.1	2.61
4-Metil-3-nitro-5-(2-oxo-1-pirrolidinil)benzoato de metilo (D178)	D172	279.0	2.60

Descripciones 179-182 (D179-182)

Los siguientes compuestos se obtuvieron de sus precursores correspondientes de manera análoga al procedimiento de la descripción 15 (D15):

Descripción	Precursor	$[M+H]^+$	t.r. (min)
3-(1,1-Dioxido-2-isotiazolidinil)-4-(metiloxi)-5-nitrobenzoato de metilo (D179)	D173	331.0	2.78
3-(1,1-Dioxido-2-isotiazolidinil)-4-metil-5-nitrobenzoato de metilo (D180)	D174		
3-(1,1-Dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-4-(metiloxi)-5-nitrobenzoato de metilo (D181)	D175	345.0	2.90
3-(1,1-Dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-4-metil-5-nitrobenzoato de metilo (D182)	D176	329.0	2.93

Descripciones 183-188 (D183-188)

Los siguientes compuestos se obtuvieron de sus precursores correspondientes de manera análoga al procedimiento de síntesis de la descripción 16 (D16), usando el precursor apropiado indicado en el cuadro siguiente:

Descripción	Precursor	$[M+H]^+$	t.r. (min)
3-Amino-4-(metiloxi)-5-(2-oxo-1-pirrolidinil)benzoato de metilo (D183)	D177	265.1	2.18
3-Amino-4-metil-5-(2-oxo-1-pirrolidinil)benzoato de metilo (D184)	D178	249.1	2.16
3-Amino-5-(1,1-dioxido-2-isotiazolidinil)-4-(metiloxi)benzoato de metilo (D185)	D179	301.0	2.25
3-Amino-5-(1,1-dioxido-2-isotiazolidinil)-4-metilbenzoato de metilo (D186)	D180	285.0	2.22
3-Amino-5-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-4-(metiloxi)benzoato de metilo (D187)	D181	315.1	2.40
3-Amino-5-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-4-metilbenzoato de metilo (D188)	D182	299.0	2.42

Descripción 189

Ester etílico del ácido 4-((*Z/E*)-but-2-enilamino)-3,5-diyodo-benzoico (D189)

A una solución de éster etílico del ácido 4-amino-3,5-diyodo-benzoico (disponible comercialmente de Maybridge) (72.6 g, 0.17 mmol, 1 eq.), en DMF (450 ml), a 0°C y bajo nitrógeno, se le agregó en porciones NaH (60% en aceite mineral, 7.3 g, 0.18 mmol, 1.05 eq.) durante 2 min. Después de 10 min se le agregó durante 5 min bromuro de crotilo (21.5 ml, 0.21 mmol, 1.2 eq.) en DMF (50 ml), por medio de una cánula; la mezcla resultante se dejó calentar a temperatura ambiente durante 30 min. Se le agregaron 5 ml de EtOH y la mezcla se concentró al vacío. El residuo se disolvió en AcOEt y la fase orgánica se lavó con H_2O. La fase acuosa se extrajo con AcOEt y la fase orgánica combinada se lavó con salmuera, se secó sobre $MgSO_4$ y se concentró al vacío, para dar el éster etílico del ácido 4-((*Z/E*)-but-2-enilamino)-3,5-diyodo-benzoico (D189) (82 g, 100%) como un sólido rosa, que se usó en el siguiente paso sin mayor purificación. $[M+H]^+$ = 472.0, t.r. = 4.93 min.

Descripción 190

Ester etílico del ácido 3-etil-7-yodo-1*H*-indol-5-carboxílico (D190)

A una solución de éster etílico del ácido 4-((*Z/E*)-but-2-enilamino)-3,5-diyodo-benzoico (D189) (15 g, 31.8 mmol, 1 eq.) en DMF (150 ml), a temperatura ambiente y bajo nitrógeno, se le agregó $Pd(OAc)_2$ (357 mg, 1.6 mmol, 0.05 eq.), NaCOOH (6.5 g, 95.6 mmol, 3 eq.), Na_2CO_3 (8.4 g, 79.6

mmol, 2.5 eq.) y NBu_4Cl (8.0 g, 35.0 mmol, 1.1 eq.). La suspensión resultante se agitó bajo nitrógeno a 80°C durante 30 min; después se enfrió a temperatura ambiente y se concentró al vacío. El residuo se dividió entre AcOEt y H_2O y las dos fases se separaron. La fase orgánica se secó sobre $MgSO_4$ y se concentró al vacío. La purificación del residuo por cromatografía de vaporización instantánea sobre gel de sílice (iso-hexano/AcOEt: 9/1), dio el éster etílico del ácido 3-etil-7-yodo-1*H*-indol-5-carboxílico (D190) (6.3 g, 58%) como un sólido blanco. $[M+H]^+$ = 344.0, t.r. = 3.86 min.

Descripción 191

3-Bromo-5-(2-oxo-5-fenil-1-piperidinil)benzoato de 1,1-dimetiletilo (D191)

Un matraz bajo nitrógeno se cargó con éster metílico del ácido 3-bromo-5-yodo-benzoico (D8b) (840 mg, 2.2 mmol, 1.1 eq.), Cs_2CO_3 (900 mg, 2.8 mmol, 1.4 eq.), tris(dibencilidenacetona)dipaladio (0) (92 mg, 0.1 mmol, 0.05 eq.), Xantphos (120 mg, 0.2 mmol, 0.1 eq.) y tolueno (40 ml). Se agregó entonces 5-fenil-2-piperidinona (Koelsch, *J. Am. Chem. Soc.* 1943, (65), 2093; 350 mg, 2 mmol, 1eq.) y la mezcla resultante se agitó a 100 °C durante 2.5 h; después se enfrió a temperatura ambiente y se concentró al vacío. El residuo se dividió entre AcOEt y una solución acuosa saturada de $NaHCO_3$. Las capas se separaron y la fase orgánica se secó sobre $MgSO_4$ y se concentró al vacío para dar un residuo sólido. La purificación del residuo por cromatografía de vaporización instantánea sobre gel de sílice (iso-hexano/AcOEt: 4/1 a 1/1),

dio 3-bromo-5-(2-oxo-5-fenil-1-piperidinil)benzoato de 1,1-dimetiletilo (D191) (480 mg, 51%) como un sólido blanco. $[M+H]^+$ = 432.2, t.r. = 3.82 min.

Descripción 192

3-(2-Oxo-5-fenil-1-piperidinil)-5-[(1*E/Z*)-1-propen-1-il]benzoato de 1,1-dimetiletilo (D192)

El 3-(2-oxo-5-fenil-1-piperidinil)-5-[(1*E/Z*)-1-propen-1-il]benzoato de 1,1-dimetiletilo (D192) se preparó de manera análoga al procedimiento de la descripción 68 (D68), a partir de 3-bromo-5-(2-oxo-5-fenil-1-piperidinil)benzoato de 1,1-dimetiletilo (D191). $[M+H]^+$ = 392.3, t.r. = 3.83 min.

Descripción 193

3-(1,1-Dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-nitrobenzoato de metilo (Dl93)

El 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-nitrobenzoato de metilo (D193) se obtuvo de 3-bromo-5-nitrobenzoato de metilo (D11), de manera análoga al procedimiento de la descripción 15 (D15) (procedimiento alternativo), usando 1,1-dióxido de tetrahidro-2*H*-1,2-tiazina (D22b) en lugar de 1,1-dióxido de isotiazolidina (D22a). $[M+H+NH_3]^+$ = 332.2, t.r. = 2.75 min.

Descripción 194

3-Amino-5-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)benzoato de metilo (D194)

El 3-amino-5-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)benzoato de metilo (D194) se obtuvo de 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-nitrobenzoato de metilo (D193), de manera análoga al procedimiento de la descripción 2 (D2). $[M+H]^+$ = 285.1, t.r. = 2.12 min.

Descripción 195

3-[(4-Clorobutanoil)amino]-5-(1,1-dioxido-2-isotiazolidinil)-benzoato de metilo (D195)

El 3-[(4-clorobutanoil)amino]-5-(1,1-dioxido-2-isotiazolidinil)-benzoato de metilo (D195) se obtuvo de 3-amino-5-(1,1-dioxido-2-isotiazolidinil)benzoato de metilo (D16), de manera análoga al procedimiento de la descripción 13 (D13).

Descripción 196

3-Amino-4-metil-5-nitrobenzoato de metilo (D196)

A una solución de 4-metil-3,5-dinitrobenzoato de metilo (D162) (30 g, 0.125 mmol, 1 eq.) en MeOH (150 ml) y ciclohexeno (300 ml), se le agregó paladio al 10% sobre carbón (50% en húmedo, 3 g, 5% p/p), y la suspensión resultante se puso en reflujo 7 h; después se enfrió a temperatura ambiente. El catalizador se separó por filtración a través de una almohadilla

de celite y la mayor parte del solvente se removió al vacío. El precipitado formado se separó por filtración para dar 3-amino-4-metil-5-nitrobenzoato de metilo (D196) (22 g, 84%), como un sólido amarillo, que se usó en el siguiente paso sin mayor purificación. $[M+H]^+$ = 211.0, t.r. = 2.81 min.

Descripción 197

4-Nitro-1*H*-indazol-6-carboxilato de metilo (D197)

A una suspensión de 3-amino-4-metil-5-nitrobenzoato de metilo (D196) (3.5 g, 16.7 mmol, 1 eq.) en H_2O (100 ml), a 0°C, se le agregó una solución acuosa de HCl al 36% (15 ml), y la suspensión resultante se trató con $NaNO_2$ (1.35 g, 19.6 mmol, 1.2 eq.); después se calentó a temperatura ambiente y se agitó por 1.5 h. El material insoluble se removió por filtración y se le agregaron pequeñas cantidades de urea a los licores madre. La solución resultante se diluyó con H_2O (500 ml) y se trató con H_2SO_4 (17.5 ml); después se calentó a 50°C durante 15 min, se enfrió a temperatura ambiente y se extrajo con AcOEt. La fase orgánica se secó sobre $MgSO_4$ y después se concentró al vacío. El residuo se trituró con MeOH para dar 4-nitro-1*H*-indazol-6-carboxilato de metilo (D197) (0.8 g, 22%), como un sólido cremoso que se usó en el siguiente paso sin mayor purificación. $[M+H]^+$ = 222.1, t.r. = 2.84 min.

Descripción 198

1-Etil-4-nitro-1*H*-indazol-6-carboxilato de metilo (D198)

A una solución de 4-nitro-1*H*-indazol-6-carboxilato de metilo (D197) (500 mg, 2.3 mmol, 1 eq.) en DMF (10 ml), a temperatura ambiente, se le agregó K_2CO_3 (346 mg, 2.5 mmol, 1.1 eq.) y después yoduro de etilo (200 µl, 2.5 mmol, 1.1 eq.). La suspensión resultante se agitó a temperatura ambiente durante 15 min y después a 40°C durante 30 min; se enfrió a temperatura ambiente y se dividió entre AcOEt y una solución acuosa de HCl 2N. Las dos capas se separaron y la fase orgánica se secó sobre $MgSO_4$ y se concentró al vacío. La purificación del residuo por cromatografía de vaporización instantánea sobre gel de sílice (iso-hexano/AcOEt: 2/1), dio 1-etil-4-nitro-1*H*-indazol-6-carboxilato de metilo (D198) (200 mg, 35%) como un sólido amarillo claro. $[M+H]^+$ = 250.1, t.r. = 3.11 min.

Descripción 199

4-Amino-1-etil-1*H*-indazol-6-carboxilato de metilo (D199)

A una solución de 1-etil-4-nitro-1*H*-indazol-6-carboxilato de metilo (D198) (2.2 g, 8.8 mmol, 1 eq.) en MeOH (100 ml) y H_2O (10 ml), se le agregó paladio al 10% sobre carbón (50% en húmedo, 700 mg, 16% p/p), y la mezcla resultante se agitó a 60°C durante 30 min; después se enfrió a temperatura ambiente. El catalizador se removió por filtración a través de una almohadilla de celite y la mayor parte del solvente se removió al vacío. El residuo se dividió entre AcOEt y una solución acuosa saturada de $NaHCO_3$, y

las dos capas se separaron. La fase orgánica se secó sobre $MgSO_4$ y se concentró al vacío. El residuo se trituró con iso-hexano para dar 4-amino-1-etil-1*H*-indazol-6-carboxilato de metilo (D199) (1.55 g, 80%), que se usó en el siguiente paso sin mayor purificación. $[M+H]^+$ = 220.1, t.r. = 3.31 min.

Descripción 200

4-[(*E*)-2-(Dimetilamino)etenil]-3,5-dinitrobenzoato de metilo (D200)

A una solución de 4-metil-3,5-dinitrobenzoato de metilo (D162) (20 g, 83.3 mmol, 1 eq.) en DMF (30 ml), se le agregó dimetilacetal de *N,N*-dimetilformamida (35 ml, exceso), y la solución resultante se agitó a 45°C durante 30 min; después se enfrió a temperatura ambiente y se concentró al vacío. La trituración del residuo con Et_2O/iso-hexano dio 4-[(*E*)-2-(dimetilamino)etenil]-3,5-dinitrobenzoato de metilo (D200) (20 g, 81%) como un sólido rojo oscuro, que se usó en el siguiente paso sin mayor purificación.

Descripción 201

4-Amino-1*H*-indol-6-carboxilato de metilo (D201)

A una solución de 4-[(*E*)-2-(dimetilamino)etenil]-3,5-dinitrobenzoato de metilo (D200) (10 g, 34 mmol, 1 eq.) en MeOH (250 ml), se le agregó paladio al 10% sobre carbón (50% en húmedo, 1.0 g, 5% p/p), y la mezcla resultante se agitó bajo una atmósfera de hidrógeno durante 7 h. El catalizador se removió por filtración a través de una almohadilla de celite y la

solución se concentró al vacío. El residuo se trituró con AcOEt/iso-hexano para dar 4-amino-1*H*-indol-6-carboxilato de metilo (D201) (5 g, 77%) como un sólido rosa oscuro. $[M+H]^+$ = 191.0, t.r. = 1.20 min.

Descripción 202

4-Amino-1-etil-1*H*-indol-6-carboxilato de metilo (D202)

A una solución de 4-amino-1*H*-indol-6-carboxilato de metilo (D201) (900 mg, 4.74 mmol, 1 eq.) en DMF (25 ml), a temperatura ambiente, se le agregó NaH (dispersión en aceite mineral al 60%, 200 mg, 5 mmol, 1.05 eq.), y después de 15 min se le agregó yoduro de etilo (400 µl, 5 mmol, 1.05 eq.). La mezcla resultante se agitó durante 30 min y después la mayor parte del solvente se removió al vacío. El residuo se diluyó con AcOEt y la fase orgánica se lavó con una solución acuosa de HCl 2N, se secó sobre $MgSO_4$ y se concentró al vacío. La purificación del residuo por cromatografía de vaporización instantánea sobre gel de sílice (iso-hexano/AcOEt: 1/1), dio un aceite que se diluyó con Et_2O y se trató con una solución de HCl 4N en Et_2O. El precipitado obtenido se separó por filtración para dar 4-amino-1-etil-1*H*-indol-6-carboxilato de metilo, sal clorhidrato (D202) (800 mg, 66%), como un sólido blanco. $[M+H]^+$ = 219.0, t.r. = 2.50 min.

Descripción 203

4-Amino-3,5-dinitrobenzoato de metilo (D203)

El 4-amino-3,5-dinitrobenzoato de metilo (D203) se preparó de

manera análoga a la descripción 25 a partir de ácido 4-amino-3,5-dinitrobenzoico, disponible comercialmente. $[M-H]^-$ = 240.1, t.r. = 2.42 min.

Descripción 204

3,4-Diamino-5-nitrobenzoato de metilo (D204)

A una solución de 4-amino-3,5-dinitrobenzoato de metilo (D203) (3.0 g, 12.4 mmol, 1 eq.) en MeOH (40 ml) y ciclohexano (80 ml), se le agregó paladio al 10% sobre carbón (50% en húmedo, 2.0 g, 33% p/p), y la mezcla resultante se puso en reflujo 30 min; después se enfrió a temperatura ambiente. El catalizador se separó por filtración a través de una almohadilla de celite y se lavó con DMF. La fase orgánica combinada se concentró al vacío y el residuo se trituró con Et_2O/iso-hexano, para dar 3,4-diamino-5-nitrobenzoato de metilo (D204) (2.1 g, 80%), como un sólido rojo que se usó en el siguiente paso sin mayor purificación. $[M+H]^+$ = 212.2, t.r. = 2.46 min.

Descripción 205

4-Amino-3-(etilamino)-5-nitrobenzoato de metilo (D205)

A una solución de 3,4-diamino-5-nitrobenzoato de metilo (D204) (1.5 g, 7.1 mmol, 1 eq.) en DMF (30 ml), a temperatura ambiente, se le agregó K_2CO_3 (2.2 g, 16.0 mmol, 2.25 eq.) y después yoduro de etilo (1.28 ml, 16.0 mmol, 2.25 eq.). La suspensión resultante se agitó a 60°C durante 2 h y después se le agregó yoduro de etilo (1 ml, 12.5 mmol, 1.8 eq.); la mezcla resultante se agitó otras 6 h; después se enfrió a temperatura ambiente y se

dividió entre AcOEt y una solución acuosa saturada de $NaHCO_3$. Las dos capas se separaron y la fase orgánica se lavó con H_2O, se secó sobre $MgSO_4$ y se concentró al vacío. El residuo se trituró con Et_2O para dar 4-amino-3-(etilamino)-5-nitrobenzoato de metilo (D205) (0.85 g, 50%), como un sólido rojo que se usó en el siguiente paso sin mayor purificación. $[M+H]^+$ = 240.2, t.r. = 2.95 min.

Descripción 206

1-Etil-4-nitro-1*H*-benzoimidazol-6-carboxilato de metilo (D206)

Se disolvió 4-amino-3-(etilamino)-5-nitrobenzoato de metilo (D205) (850 mg, 3.55 mmol, 1 eq.) en ácido fórmico (20 ml), y la solución resultante se agitó a 100°C durante 45 min; después se enfrió a temperatura ambiente y se diluyó con AcOEt (200 ml). La fase orgánica se lavó con una solución acuosa de NaOH 2N, se secó sobre $MgSO_4$ y se concentró al vacío, para dar 1-etil-4-nitro-1*H*-benzoimidazol-6-carboxilato de metilo (D206) (700 mg, 79%) como un sólido pardo, que se usó en el siguiente paso sin mayor purificación. $[M+H]^+$ = 250.1, t.r. = 2.41 min.

Descripción 207

4-Amino-1-etil-1*H*-benzoimidazol-6-carboxilato de metilo (D207)

A una solución de 1-etil-4-nitro-1*H*-benzoimidazol-6-carboxilato de metilo (D206) (700 mg, 2.81 mmol, 1 eq.) en MeOH (50 ml) y H_2O (5 ml), se le agregó paladio al 10% sobre carbón (50% en húmedo, 400 mg, 28% p/p)

y NH_4COOH (1.77 g, 28.1 mmol, 10 eq.); la mezcla resultante se agitó a 70°C durante 30 min y después se enfrió a temperatura ambiente. El catalizador se separó por filtración a través de una almohadilla de celite y la mayor parte del MeOH se removió al vacío. El residuo se diluyó con AcOEt y la capa orgánica se lavó con una solución acuosa saturada de $NaHCO_3$, se secó sobre $MgSO_4$ y se concentró al vacío para dar 4-amino-1-etil-1*H*-benzoimidazol-6-carboxilato de metilo (D207) (500 mg, 81%), como un sólido blanco que se usó en el siguiente paso sin mayor purificación. $[M+H]^+$ = 220.2, t.r. = 2.17 min.

Descripción 208

4-[(2-Cloroetil)amino]-3,5-dinitrobenzoato de metilo (D208)

A una solución de 4-cloro-3,5-dinitrobenzoato de metilo (D25a) (5.0 g, 19.2 mmol, 1 eq.) en MeOH (300 ml), se le agregó clorhidrato de 2-cloroetilamina (4.64 mg, 40 mmol, 2.1 eq.) y NEt_3 (5.5 ml, 40 mmol, 2.1 eq.) y la mezcla resultante se puso en reflujo durante 5 min; después se enfrió a temperatura ambiente. La mayor parte del solvente se evaporó al vacío y el residuo se filtró para dar 4-[(2-cloroetil)amino]-3,5-dinitrobenzoato de metilo (D208) (9 g, 156%) como un sólido amarillo, que se usó en el siguiente paso sin mayor purificación. $[M+H]^+$ = 304.1, t.r. = 3.06 min.

330

332

Descripción 209

8-Nitro-1,2,3,4-tetrahidro-6-quinoxalincarboxilato de metilo (D209)

A una solución de 4-[(2-cloroetil)amino]-3,5-dinitrobenzoato de metilo crudo (D208) (9 g, 19.2 mmol, 1 eq.) en MeOH (75 ml) y ciclohexeno (150 ml), se le agregó paladio al 10% sobre carbón (50% en húmedo, 4.5 g, 25% p/p), y la mezcla resultante se puso en reflujo durante 3 h; después se enfrió a temperatura ambiente. El catalizador se separó por filtración a través de una almohadilla de celite y la mayor parte del solvente se removió al vacío. El residuo se dividió entre AcOEt y una solución acuosa de HCl 2N, y las dos capas se separaron. La fase acuosa se extrajo dos veces con AcOEt y la capa orgánica combinada se lavó con una solución acuosa saturada de $NaHCO_3$, se secó sobre $MgSO_4$ y se concentró al vacío. La purificación del residuo por cromatografía de vaporización instantánea sobre gel de sílice (iso-hexano/AcOEt: 1/1) dio 8-nitro-1,2,3,4-tetrahidro-6-quinoxalincarboxilato de metilo (D209) (1.5 g, 34%), como un sólido rojo. $[M-H]^-$ = 236.2, t.r. = 2.65 min.

Descripción 210

4-Etil-8-nitro-1,2,3,4-tetrahidro-6-quinoxalincarboxilato de metilo (D210)

Se preparó 4-etil-8-nitro-1,2,3,4-tetrahidro-6-quinoxalin-carboxilato de metilo (D210) a partir de 8-nitro-1,2,3,4-tetrahidro-6-quinoxalincarboxilato de metilo (D209), de manera análoga al procedimiento

descrito para el éster 35 (B35), usando acetaldehído en lugar de propionaldehído. $[M+H]^+$ = 266.3, t.r. = 3.07 min.

Descripción 211

8-Amino-4-etil-1,2,3,4-tetrahidro-6-quinoxalincarboxilato de metilo (D211)

El 8-amino-4-etil-1,2,3,4-tetrahidro-6-quinoxalincarboxilato de metilo (D211) se preparó a partir de 4-etil-8-nitro-1,2,3,4-tetrahidro-6-quinoxalincarboxilato de metilo (D210), de manera análoga al procedimiento de la descripción 207 (D207). $[M+H]^+$ = 236.2, t.r. = 2.23 min.

Descripción 212

4-Amino-3-nitrobenzoato (D212) de etilo

El 4-amino-3-nitrobenzoato de etilo (D212) se preparó de manera análoga a la descripción 25 a partir de ácido 4-amino-3-nitrobenzoico disponible comercialmente, usando EtOH como solvente en lugar de MeOH.

Descripción 213

4-Amino-3-bromo-5-nitrobenzoato de etilo (D213)

A una solución de 4-amino-3-nitrobenzoato de etilo (D212) (21.0 g, 100 mmol, 1 eq.) en CH_2Cl_2 (500 ml), a temperatura ambiente, se le agregó bromo (6.7 ml, 130 mmol, 1.3 eq.), y la mezcla resultante se puso en reflujo durante 4 h; después se le agregó bromo (2 ml, 40 mmol, 0.4 eq.) y la mezcla

resultante se puso en reflujo otras 3 h; después se enfrió a temperatura ambiente. La fase orgánica se lavó dos veces con una solución acuosa de $Na_2S_2O_3$ al 10% y dos veces con H_2O; se secó sobre $MgSO_4$ y se concentró al vacío, para dar 4-amino-3-bromo-5-nitrobenzoato de etilo (D213) (27.1 g, 94%) como un sólido amarillo que se usó en el siguiente paso sin mayor purificación.

Descripción 214

3-Bromo-5-nitro-4-[(trifluoroacetil)amino]benzoato de etilo (D214)

A una solución de 4-amino-3-bromo-5-nitrobenzoato de etilo (D213) (27.1 g, 93.1 mmol, 1 eq.) en CH_2Cl_2 (500 ml), a temperatura ambiente, se le agregó *N,N*-diisopropiletilamina (22 ml, 130 mmol, 1.4 eq.) y anhídrido de ácido trifluoroacético (15.8 ml, 111.7 mmol, 1.2 eq.), y la mezcla resultante se agitó durante 2 h. Se le agregó *N,N*-diisopropiletilamina (22 ml, 130 mmol, 1.4 eq.) y anhídrido de ácido trifluoroacético (15.8 ml, 111.7 mmol, 1.2 eq.), y la mezcla resultante se agitó durante otras 2 h. Se le agregó H_2O y las dos capas se separaron. La fase orgánica se lavó dos veces con una solución acuosa de HCl 2N, H_2O, se secó sobre $MgSO_4$ y se concentró al vacío. La purificación del residuo por cromatografía de vaporización instantánea sobre gel de sílice (iso-hexano/AcOEt: 9/1 a 3/1), dio 3-bromo-5-nitro-4-[(trifluoroacetil)amino]benzoato de etilo (D214) (29.4 g, 82%) como un sólido amarillo.

335

Descripción 215

3-Bromo-4-[(3-metil-2-buten-1-il)(trifluoroacetil)amino]-5-nitrobenzoato de etilo (D215)

A una solución de 3-bromo-5-nitro-4-[(trifluoroacetil)amino]-benzoato de etilo (D214) (12.0 g, 31.3 mmol, 1 eq.) en CH_3CN (100 ml), se le agregó K_2CO_3 (5.6 g, 40 mmol, 1.3 eq.) y 1-bromo-3-metil-2-buteno (5.1 ml, 43.8 mmol, 1.4 eq.), y la mezcla resultante se puso en reflujo durante 1 h; después se enfrió a temperatura ambiente. El precipitado formado se separó por filtración a través de una almohadilla de celite y se lavó con CH_3CN. La capa orgánica combinada se concentró al vacío y el residuo se diluyó con AcOEt. La capa orgánica se lavó con salmuera, se secó sobre $MgSO_4$ y se concentró al vacío. La purificación del residuo por cromatografía de vaporización instantánea sobre gel de sílice (iso-hexano/AcOEt: 9/1 a 4/1), dio 3-bromo-4-[(3-metil-2-buten-1-il)(trifluoroacetil)amino]-5-nitrobenzoato de etilo (D215) (12.9 g, 91%) como un aceite naranja.

Descripciones 216-217 (D216-217)

Los siguientes compuestos se obtuvieron de 3-bromo-5-nitro-4-[(trifluoroacetil)amino]benzoato de etilo (D214) de manera análoga, usando el bromuro de alilo apropiado:

334
336

Descripción	Bromuro de alilo
3-Bromo-4-[(2*E/Z*)-2-buten-1-il(trifluoroacetil)amino]-5-nitrobenzoato de etilo(D216)	
3-Bromo-5-nitro-4-[2-propen-1-il(trifluoroacetil)amino]benzoato de etilo (D217)	

Descripción 218

3-(1-Metiletil)-7-nitro-1*H*-indol-5-carboxilato de etilo (D218)

A una solución de 3-bromo-4-[(3-metil-2-buten-1-il)-(trifluoroacetil)amino]-5-nitrobenzoato de etilo (D215) (12.9 g, 28.5 mmol, 1 eq.) en DMF (130 ml), se le agregó HCOONa (1.94 g, 28.5 mmol, 1 eq.), Na_2CO_3 (7.54 g, 71.2 mmol, 2.5 eq.), Bu_4NCl (8.7 g, 31.3 mmol, 1.1 eq.) y acetato de paladio (II) (320 mg, 1.42 mmol, 0.05 eq.), y la mezcla resultante se agitó bajo nitrógeno durante 1 h; después se enfrió a temperatura ambiente y se concentró al vacío. El residuo se dividió entre AcOEt y H_2O y las dos capas se separaron. El material insoluble en la fase acuosa se separó por filtración a través de una almohadilla de celite y la capa acuosa se extrajo dos veces con AcOEt. La capa orgánica combinada se lavó con salmuera, se secó sobre $MgSO_4$ y se concentró al vacío, para dar 3-(1-metiletil)-7-nitro-1*H*-indol-5-carboxilato de metilo (D218) (10.1 g, 128%), como un sólido negro que se usó en el siguiente paso sin mayor purificación.

Descripciones 219-220 (D219-220)

Los siguientes compuestos se obtuvieron de manera análoga, usando el precursor apropiado:

Descripción	Precursor
3-Etil-7-nitro-1*H*-indol-5-carboxilato de etilo (D219)	D216
3-Metil-7-nitro-1*H*-indol-5-carboxilato de etilo (D220)	D217

Descripción 221

7-Amino-3-(1-metiletil)-1*H*-indol-5-carboxilato de etilo (D221)

A una solución de 3-(1-metiletil)-7-nitro-1*H*-indol-5-carboxilato de etilo crudo (D218) (10.1 g, 28.5 mmol, 1 eq.) en MeOH (250 ml) y H_2O (25 ml), se le agregó paladio al 10% sobre carbón (50% en húmedo, 1.5 g, 8% p/p) y NH_4COOH (17 g, 280 mmol, 10 eq.), y la mezcla resultante se agitó a 70°C durante 3 h; después se enfrió a temperatura ambiente. El catalizador se separó por filtración a través de una almohadilla de celite y la mayor parte del MeOH se removió al vacío. El residuo se diluyó con AcOEt y la capa orgánica se lavó con una solución acuosa saturada de $NaHCO_3$, se secó sobre $MgSO_4$ y se concentró al vacío. La purificación del residuo por cromatografía de vaporización instantánea sobre gel de sílice (iso-hexano/AcOEt: 3/1 a 1/1), dio 7-amino-3-(1-metiletil)-1*H*-indol-5-carboxilato de metilo (D221) (1.47 g, 21 %) como un sólido blanco.

Descripciones 222-223 (D222-223)

Los siguientes compuestos se obtuvieron de manera análoga al

procedimiento de la descripción 221, usando el precursor apropiado:

Descripción	Precursor
7-Amino-3-etil-1*H*-indol-5-carboxilato de etilo (D222)	D219
7-Amino-3-metil-1*H*-indol-5-carboxilato de etilo (D223)	D220

Descripciones 224-230 (D224-230)

Los siguientes compuestos se obtuvieron de sus precursores correspondientes de manera análoga al procedimiento de la descripción 2 (D2):

Descripción	Precursor	$[M+H]^+$	t.r. (min)
7-[(4-Clorobutanoil)amino]-3-metil-1*H*-indol-5-carboxilato de etilo (D224)	D223		
7-[(4-Clorobutanoil)amino]-3-etil-1*H*-indol-5-carboxilato de etilo (D225)	D222		
7-[(4-Clorobutanoil)amino]-3-(1-metiletil)-1*H*-indol-5-carboxilato de etilo (D226)	D221		
4-[(4-Clorobutanoil)amino]-1-etil-1*H*-benzoimidazol-6-carboxilato de metilo (D227)	D207		
4-[(4-Clorobutanoil)amino]-1*H*-indol-6-carboxilato de metilo (D228)	D201	295.0	2.63
4-[(4-Clorobutanoil)amino]-1-etil-1*H*-indazol-6-carboxilato de metilo (D229)	D199	324.3	2.70
8-[(4-Clorobutanoil)amino]-4-etil-1,2,3,4-tetrahidro-6-quinoxalincarboxilato de metilo (D230)	D211	340.2	2.73

Descripción 231

4-(1,1-Dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-1*H*-indol-6-carboxilato de metilo (D231)

El 4-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-1*H*-indol-6-carboxilato de metilo (D231) se obtuvo de ácido 4-(1,1-dioxidotetrahidro-2*H*-

337
339

1,2-tiazin-2-il)-1*H*-indol-6-carboxílico (A155), de manera análoga a la descripción 25 (D25).

Descripción 232

6-Metil-4-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-1*H*-indol-1,6-dicarboxilato de 1-(1,1-dimetiletilo) (D232)

A una solución de 4-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-1*H*-indol-6-carboxilato de metilo (D231) (308 mg, 1.0 mmol, 1 eq.) en CH_2Cl_2 (10 ml), se le agregó NEt_3 (166 µl, 1.2 mmol, 1.2 eq.), dicarbonato de bis(1,1-dimetiletilo) (251 mg, 1.15 mmol, 1.15 eq.) y DMAP (12 mg, 0.1 mmol, 0.1 eq.), y la mezcla resultante se agitó a temperatura ambiente durante 30 min. La fase orgánica se lavó con una solución acuosa de HCl 2N y una solución acuosa saturada de $NaHCO_3$, se secó sobre $MgSO_4$ y se concentró al vacío. La trituración en Et_2O/iso-hexano dio 6-metil-4-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-1*H*-indol-1,6-dicarboxilato de 1-(1,1-dimetiletilo) (D232) (150 mg, 37%), como un sólido blanco que se usó en el siguiente paso sin mayor purificación. $[M+H+NH_3]^+$ = 426.2, t.r. = 3.38 min.

Descripción 233

6-Metil-4-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-2,3-dihidro-1*H*-indol-1,6-dicarboxilato de 1-(1,1-dimetiletilo) (D233)

El 6-metil-4-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-2,3-dihidro-1*H*-indol-1,6-dicarboxilato de 1-(1,1-dimetiletilo) (D233) se obtuvo de 6-metil-4-

338
340

(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-1*H*-indol-1,6-dicarboxilato de 1-(1,1-dimetiletilo) (D232), de manera análoga al procedimiento descrito para el éster 116 (B116). Sin ion molecular, t.r. = 3.23 min.

Descripción 234

Sal clorhidrato de 4-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-2,3-dihidro-1*H*-indol-6-carboxilato de metilo (D234)

Se disolvió 6-metil-4-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-2,3-dihidro-1*H*-indol-1,6-dicarboxilato de 1-(1,1-dimetiletilo) (D233) (500 mg, 1.2 mmol, 1 eq.) en una solución de HCl 4N en Et_2O (10 ml, 40 mmol, exceso), y la solución resultante se agitó a temperatura ambiente 1 h; después se concentró al vacío. La trituración del residuo con Et_2O dio la sal clorhidrato de 4-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-2,3-dihidro-1*H*-indol-6-carboxilato de metilo (D234) (430 mg, 100%), como un sólido blanco que se usó en el siguiente paso sin mayor purificación. $[M+H]^+$ = 311.0, t.r. = 2.16 min.

Descripción 235

1-Acetil-4-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-2,3-dihidro-1*H*-indol-6-carboxilato de metilo (D235)

A una solución de la sal clorhidrato de 4-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-2,3-dihidro-1*H*-indol-6-carboxilato de metilo (D234) (350 mg, 1.0 mmol, 1 eq.) en AcOEt (5 ml), se le agregó NEt_3 (140 ml, 1.0 mmol, 1 eq.) y anhídrido acético (0.5 ml, 5.6 mmol, 5.6 eq.), y la mezcla resultante se agitó

a 50°C durante 30 min; después se enfrió a temperatura ambiente y se lavó con una solución acuosa de HCl 2N, seguido por una solución acuosa saturada de $NaHCO_3$; después se secó sobre $MgSO_4$ y se concentró al vacío, para dar 1-acetil-4-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-2,3-dihidro-1*H*-indol-6-carboxilato de metilo (D235) como un sólido blanco, que se usó en el siguiente paso sin mayor purificación. $[M+H]^+$ = 353.2, t.r. = 2.24 min.

Descripción 236

4-{bis[(3-Cloropropil)sulfonil]amino}-1-etil-1*H*-indol-6-carboxilato de metilo (D236)

A una solución de la sal clorhidrato de 4-amino-1-etil-1*H*-indol-6-carboxilato de metilo (D202) (1.7 g, 6.68 mmol, 1 eq.) en CH_2Cl_2 (50 ml), se le agregó NEt_3 (4.2 ml, 30 mmol, 4.5 eq.) y después cloruro de 3-cloro-1-propanosulfonilo (1.8 ml, 15.0 mmol, 2.2 eq.), y la mezcla resultante se agitó durante 2 h. La fase orgánica se lavó con una solución acuosa de HCl 2N y una solución acuosa saturada de $NaHCO_3$, se secó sobre $MgSO_4$ y se concentró al vacío. La purificación del residuo por cromatografía de vaporización instantánea sobre gel de sílice (AcOEt/iso-hexano: 1/1), dio 4-{bis[(3-cloropropil)sulfonil]amino}-1-etil-1*H*-indol-6-carboxilato de metilo (D236) (1.85 g, 55%), como un sólido de color canela claro. $[M-H]^-$ = 498.1, t.r. = 3.51 min.

Descripción 237

4-{bis[(3-Cloropropil)sulfonil]amino}-1-etil-1*H*-indazol-6-carboxilato de metilo (D237)

El 4-{bis[(3-cloropropil)sulfonil]amino}-1-etil-1*H*-indazol-6-carboxilato de metilo (D237) se obtuvo de 4-amino-1-etil-1*H*-indazol-6-carboxilato de metilo, de manera análoga al procedimiento descrito para 4-{bis[(3-cloropropil)sulfonil]amino}-1-etil-1*H*-indol-6-carboxilato de metilo (D236). $[M+H]^+$ = 500.1, t.r. = 3.50 min.

Descripción 238

8-{bis[(3-Cloropropil)sulfonil]amino}-4-etil-1,2,3,4-tetrahidro-6-quinoxalincarboxilato de metilo (D238)

El 8-{bis[(3-cloropropil)sulfonil]amino}-4-etil-1,2,3,4-tetrahidro-6-quinoxalincarboxilato de metilo (D238) se obtuvo de 8-amino-4-etil-1,2,3,4-tetrahidro-6-quinoxalincarboxilato de metilo (D211), de manera análoga al procedimiento descrito para 4-{bis[(3-cloropropil)sulfonil]amino}-1-etil-1*H*-indol-6-carboxilato de metilo (D236). $[M+H]^+$ = 517.2, t.r. = 3.32 min.

Descripción 239

4-{bis[(3-Cloropropil)sulfonil]amino}-1-etil-1*H*-benzoimidazol-6-carboxilato de metilo (D239)

El 4-{bis[(3-cloropropil)sulfonil]amino}-1-etil-1*H*-benzoimidazol-6-carboxilato de metilo (D239) se obtuvo de 4-amino-1-etil-1*H*-benzoimidazol-6-

carboxilato de metilo (D207), de manera análoga al procedimiento descrito para 4-[bis[(3-cloropropil)sulfonil]amino)-1-etil-1*H*-indol-6-carboxilato de metilo (D236). $[M+H]^+$ = 500.3, t.r. = 3.20 min.

Descripción 240

Acido 4-[1(3-Cloropropil)sulfonil]amino)-1-etil-1*H*-indol-6-carboxílico (D240)

A una solución de 4-[bis[(3-cloropropil)sulfonil]amino)-1-etil-1*H*-indol-6-carboxilato de metilo (D236) (1.8 g, 3.6 mmol, 1 eq.) en MeOH (100 ml), se le agregó una solución acuosa de NaOH 2N (20 ml, 40 mmol, exceso), y la mezcla resultante se agitó durante 1 h. La mayor parte del MeOH se removió al vacío y el residuo se dividió entre AcOEt y una solución acuosa de HCl 2N. Las dos capas se separaron y la fase acuosa se secó sobre $MgSO_4$ y se concentró al vacío para dar ácido 4-[[(3-cloropropil)sulfonil]amino)-1-etil-1*H*-indol-6-carboxílico (D240) (930 mg, 75%), como un aceite pardo que se usó en el siguiente paso sin mayor purificación.

Descripción 241

4-[[(3-Cloropropil)sulfonil]amino)-1-etil-1*H*-indol-6-carboxilato de metilo (D241)

El 4-[[(3-cloropropil)sulfonil]amino)-1-etil-1*H*-indol-6-carboxilato de metilo (D241) se obtuvo de ácido 4-[[(3-cloropropil)sulfonil]amino)-1-etil-1*H*-indol-6-carboxílico (D240), de manera análoga a la descripción 25 (D25).

$[M+H]^+$ = 359.2, t.r. = 3.12 min.

Descripción 242

7-{[(4-Clorobutil)sulfonil]amino}-3-etil-1*H*-indol-5-carboxilato de etilo (D242)

A una solución de 7-amino-3-etil-1*H*-indol-5-carboxilato de etilo (D222) (150 mg, 0.65 mmol, 1 eq.) en CH_2Cl_2 (10 ml), a temperatura ambiente, se le agregó piridina (115 µl, 1.42 mmol, 2.2 eq.), cloruro de 4-cloro-1-butanosulfonilo (D20) (259 mg, 1.36 mmol, 2.1 eq.) y DMAP (8 mg, 0.065 mmol, 0.1 eq.), y la mezcla resultante se agitó durante 1 h; entonces se diluyó con AcOEt y se lavó con una solución acuosa de HCl 2N y salmuera; después se secó sobre $MgSO_4$ y se concentró al vacío para dar 7-{[(4-clorobutil)sulfonil]amino}-3-etil-1*H*-indol-5-carboxilato de etilo (D242) (230 mg, 92%), como un aceite púrpura que se usó en el siguiente paso sin mayor purificación. $[M+H]^+$ = 387.3, t.r. = 3.35 min.

Descripción 243

7-{[(3-cloropropil)sulfonil]amino}-3-etil-1*H*-indol-5-carboxilato de etilo (D243)

El 7-{[(3-cloropropil)sulfonil]amino}-3-etil-1*H*-indol-5-carboxilato de etilo (D243) se obtuvo de 7-amino-3-etil-1*H*-indol-5-carboxilato de etilo (D222), de manera análoga al procedimiento de la descripción 242 (D242), usando cloruro de 3-cloro-1-propanosulfonilo en lugar de cloruro de 4-cloro-1-

butanosulfonilo (D20). $[M+H]^+$ = 373.0, t.r. = 3.49 min.

Descripción 244

Acido 3,4-diamino-5-nitrobenzoico (D244)

A una solución de ácido 4-amino-3,5-dinitrobenzoico (10 g, 44 mmol, 1 eq.) en DME (100 ml) y $CHCl_3$ (10 ml), bajo nitrógeno, se le agregó paladio al 10% sobre carbón (50% en húmedo, 1 g, 5% p/p), y la suspensión resultante se agitó bajo una atmósfera de nitrógeno (2.45 kg/cm^2) durante 15 h. Se le agregó paladio al 10% sobre carbón (50% en húmedo, 1 g, 5% p/p) y la suspensión resultante se agitó bajo una atmósfera de hidrógeno (2.45 kg/cm^2) otras 15 h. El catalizador se separó por filtración a través de una almohadilla de celite y la solución se concentró al vacío, para dar ácido 3,4-diamino-5-nitrobenzoico (D244) (9.85 g, 113%), como un sólido rojo que se usó en el siguiente paso sin mayor purificación. $[M-H]^-$ = 196.1, t.r. = 2.15 min.

Descripción 245

3,4-Diamino-5-nitrobenzoato de metilo (D245)

El 3,4-diamino-5-nitrobenzoato de metilo (D245) se preparó de manera análoga a la descripción 25, a partir de ácido 3,4-diamino-5-nitrobenzoico (D244). $[M+H]^+$ = 212.2, t.r. = 2.40 min.

Descripción 246

4-Nitro-1*H*-1,2,3-benzotriazol-6-carboxilato de metilo (D246)

A una solución de 3,4-diamino-5-nitrobenzoato de metilo (D245) (2.5 g, 12 mmol, 1 eq.) en AcOH (10 ml), a temperatura ambiente, se le agregó $NaNO_2$ (900 mg, 13 mmol, 1.1 eq.) y la mezcla resultante se agitó a 60°C durante 1 h; se enfrió a temperatura ambiente y se concentró al vacío. El residuo se dividió entre AcOEt y una solución acuosa de ácido cítrico al 5%, y las capas se separaron. La fase orgánica se lavó con salmuera, se secó sobre $MgSO_4$ y se concentró al vacío. La trituración del residuo en Et_2O/iso-hexano dio 4-nitro-1*H*-1,2,3-benzotriazol-6-carboxilato de metilo (D246) (2.08 g, 78%), como un sólido naranja que se usó en el siguiente paso sin mayor purificación. $[M+H]^+$ = 223.3, t.r. = 2.31 min.

Descripción 247

4-Amino-1*H*-1,2,3-benzotriazol-6-carboxilato de metilo (D247)

El 4-amino-1*H*-1,2,3-benzotriazol-6-carboxilato de metilo (D247) se obtuvo de 4-nitro-1*H*-1,2,3-benzotriazol-6-carboxilato de metilo (D246), de manera análoga al procedimiento descrito para 5-amino-2-fluoro-3-(2-oxo-1-pirrolidinil)benzoato de metilo (D150). $[M+H]^+$ = 193.3, t.r. = 2.01 min.

Descripción 248

4-[(4-Clorobutanoil)amino]-1*H*-1,2,3-benzotriazol-6-carboxilato de metilo (D248)

El 4-[(4-clorobutanoil)amino]-1*H*-1,2,3-benzotriazol-6-carboxilato de metilo (D248) se obtuvo de 4-amino-1*H*-1,2,3-benzotriazol-6-carboxilato de metilo (D247), de manera análoga al procedimiento de la descripción 2 (D2). Sin ion molecular, t.r. = 3.19 min.

Descripción 249

4-(2-Oxo-1-pirrolidinil)-1*H*-1,2,3-benzotriazol-6-carboxilato de metilo (D249)

El 4-(2-oxo-1-pirrolidinil)-1*H*-1,2,3-benzotriazol-6-carboxilato de metilo (D249) se obtuvo de 4-[(4-clorobutanoil)amino]-1*H*-1,2,3-benzotriazol-6-carboxilato de metilo (D248), de manera análoga al procedimiento descrito para el éster 27 (B27). $[M+H]^+$ = 261.2, t.r. = 2.25 min.

Descripción 250

4-Nitro-1*H*-benzoimidazol-6-carboxilato de metilo (D250)

Una solución de 3,4-diamino-5-nitrobenzoato de metilo (D245) (1.3 g, 6.16 mmol, 1 eq.) en HCOOH (20 ml) se agitó a 100°C durante 1 h; después se enfrió a temperatura ambiente y se concentró al vacío. El residuo se dividió entre AcOEt y una solución acuosa de NaOH 2N, y las capas se separaron. La fase orgánica se secó sobre $MgSO_4$ y se concentró al vacío,

para dar 4-nitro-1*H*-benzoimidazol-6-carboxilato de metilo (D250) (1.5 g, 110%) como un sólido pardo claro, que se usó en el siguiente paso sin mayor purificación. $[M+H]^+$ = 222.3, t.r. = 2.29 min.

Descripción 251

4-Amino-1*H*-benzoimidazol-6-carboxilato de metilo (D251)

El 4-amino-1*H*-benzoimidazol-6-carboxilato de metilo (D251) se obtuvo de 4-nitro-1*H*-benzoimidazol-6-carboxilato de metilo (D250), de manera análoga al procedimiento descrito para 5-amino-2-fluoro-3-(2-oxo-1-pirrolidinil)benzoato de metilo (D150). $[M+H]^+$ = 192.3, t.r. = 1.55 min.

Descripción 252

4-{[(4-Clorobutil)sulfonil]amino}-1*H*-benzoimidazol-6-carboxilato de metilo (D252)

A una solución de 4-amino-1*H*-benzoimidazol-6-carboxilato de metilo (D251) (1.1 g, 5.76 mmol, 1 eq.) en CH_2Cl_2 (80 ml), a temperatura ambiente, se le agregó piridina (1.02 ml, 12.67 mmol, 2.2 eq.), cloruro de 4-cloro-1-butanosulfonilo (D20) (2.31 g, 12.1 mmol, 2.1 eq.) y DMAP (704 mg, 5.76 mmol, 1 eq.), y la mezcla resultante se agitó durante 1 h; después se concentró al vacío. El residuo se diluyó con AcOEt y la fase orgánica se lavó con una solución acuosa de HCl 2N y salmuera, entonces se secó sobre $MgSO_4$ y se concentró al vacío. La purificación del residuo por cromatografía de vaporización instantánea sobre gel de sílice (AcOEt/iso-hexano: 2/3), dio 4-

347
349

{[(4-clorobutil)sulfonil]amino}-1*H*-benzoimidazol-6-carboxilato de metilo (D252) (1 g, 50%), como un aceite incoloro. $[M+H]^+$ = 346.1, t.r. = 2.97 min.

Descripción 253

4-(1,1-Dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-1*H*-benzoimidazol-6-carboxilato de metilo (D253)

A una solución de 4-{[(4-clorobutil)sulfonil]amino}-1*H*-benzoimidazol-6-carboxilato de metilo (D252) (1 g, 3.23 mmol, 1 eq.) en EtOH (50 ml), se le agregó NEt_3 (2 ml, exceso), y la solución resultante se agitó a 70°C durante 2 días. Después se enfrió a temperatura ambiente y se concentró al vacío. El residuo se disolvió en AcOEt y la fase orgánica se lavó con una solución acuosa de ácido cítrico al 5%. La fase acuosa se saturó con NaCl y se extrajo dos veces con AcOEt. La fase orgánica combinada se secó sobre $MgSO_4$ y se concentró al vacío. La purificación del residuo por cromatografía de vaporización instantánea sobre gel de sílice (CH_2Cl_2/MeOH: 96/4 a 90/10), dio 4-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-1*H*-benzoimidazol-6-carboxilato de metilo (D253) (250 mg, 25%), como un sólido amarillo claro. $[M+H]^+$ = 310.3, t.r. =2.11 min.

Descripción 254

4-Hidroxi-3,5-diyodobenzoato de metilo (D254)

El 4-hidroxi-3,5-diyodobenzoato de metilo (D254) se preparó de manera análoga a la descripción 25 (D25), partiendo de ácido 4-hidroxi-3,5-

348
350

diyodobenzoico, disponible comercialmente.

Descripción 255

4-[(2*E*/*Z*)-2-Buten-1-iloxi]-3,5-diyodobenzoato de metilo (D255)

A una solución de 4-hidroxi-3,5-diyodobenzoato de metilo (D254) (26.9 g, 66.7 mmol, 1 eq.) en acetona (250 ml), a temperatura ambiente, se le agregó K_2CO_3 (13.8 g, 100 mmol, 1.5 eq.) y 1-bromo-2-buteno (8.25 ml, 80 mmol, 1.2 eq.), y la suspensión resultante se agitó a 55°C durante 15 h; después se enfrió a temperatura ambiente y se concentró al vacío. El residuo se dividió entre AcOEt y H_2O y las dos capas se separaron. La fase orgánica se lavó con una solución acuosa de NaOH 2N y salmuera, se secó sobre $MgSO_4$ y se concentró al vacío, para dar 4-[(2*E*/*Z*)-2-buten-1-iloxi]-3,5-diyodobenzoato de metilo (D255) (28.6 g, 94%), como un sólido blanco que se usó en el siguiente paso sin mayor purificación.

Descripción 256

3,5-Diyodo-4-(2-propen-1-iloxi)benzoato de metilo (D256)

El 3,5-diyodo-4-(2-propen-1-iloxi)benzoato de metilo (D256) se obtuvo de 4-hidroxi-3,5-diyodobenzoato de metilo (D254), de manera análoga al procedimiento de la descripción 255 (D255), usando 3-bromo-1-propeno en lugar de 1-bromo-2-buteno.

Descripción 257

4-(3-Buten-1-iloxi)-3,5-diyodobenzoato de metilo (D257)

El 4-(3-buten-1-iloxi)-3,5-diyodobenzoato de metilo (D257) se obtuvo de 4-hidroxi-3,5-diyodobenzoato de metilo (D254), de manera análoga al procedimiento de la descripción 255 (D255), usando 4-bromo-1-buteno en lugar de 1-bromo-2-buteno. $[M+H]^+$= 458.8, t.r. = 4.05 min.

Descripción 258

4-[(2*E/Z*)-2-Buten-1-iloxi]-3-yodo-5-(2-oxo-1-pirrolidinil)benzoato de metilo (D258)

A una solución de 4-[(2*E/Z*)-2-buten-1-iloxi]-3,5-diyodobenzoato de metilo (D255) (5 g, 11 mmol, 1 eq.) en tolueno (50 ml), se le agregó 2-pirrolidinona (1.08 g, 13 mmol, 1.2 eq.), K_3PO_4 (4.46 g, 21 mmol, 2 eq.), CuI (105 mg, 0.55 mmol, 0.05 eq.) y dimetiletilendiamina (117 µl, 1.1 mmol, 0.1 eq.), y la mezcla resultante se agitó a 100°C durante 15 h; después se enfrió a temperatura ambiente y se concentró al vacío. El residuo se dividió entre AcOEt y H_2O y las capas se separaron. La fase orgánica se secó bajo $MgSO_4$ y se concentró al vacío. La purificación del residuo por cromatografía de vaporización instantánea sobre gel de sílice (AcOEt/iso-hexano: 1/1), dio 4-[(2*E/Z*)-2-buten-1-iloxi]-3-yodo-5-(2-oxo-1-pirrolidinil)benzoato de metilo (D258) (1.4 g, 31%), como un aceite incoloro. $[M+H]^+$ = 415. 9, t.r. = 3.27 min.

Descripción 259

3-Yodo-5-(2-oxo-1-pirrolidinil)-4-(2-propen-1-iloxi)benzoato de metilo (D259)

El 3-yodo-5-(2-oxo-1-pirrolidinil)-4-(2-propen-1-iloxi)benzoato de metilo (D259) se obtuvo de 3,5-diyodo-4-(2-propen-1-iloxi)benzoato de metilo (D256), de manera análoga al procedimiento de la descripción 258 (D258).

Descripción 260

4-(3-Buten-1-iloxi)-3-yodo-5-(2-oxo-1-pirrolidinil)benzoato de metilo (D260)

El 4-(3-buten-1-iloxi)-3-yodo-5-(2-oxo-1-pirrolidinil)benzoato de metilo (D260) se obtuvo de 4-(3-buten-1-iloxi)-3,5-diyodobenzoato (D257) de metilo, de manera análoga al procedimiento de la descripción 258 (D258). $[M+H]^+$ = 416.0, t.r. = 3.02 min.

Descripción 261

4-Metil-8-(2-oxo-1-pirrolidinil)-2*H*-cromeno-6-carboxilato de metilo y 4-(etiloxi)-3-[etil(propanoil)amino]-5-(1-metiletenil)benzoato de metilo (D261)

El 4-metil-8-(2-oxo-1-pirrolidinil)-2*H*-cromeno-6-carboxilato de metilo y 4-(etiloxi)-3-[etil(propanoil)amino]-5-(1-metiletenil)benzoato de metilo (D261), se obtuvieron de 4-(3-buten-1-iloxi)-3-yodo-5-(2-oxo-1-pirrolidinil)-benzoato de metilo (D260), de manera análoga al procedimiento descrito para

3-etil-7-(2-oxo-1-pirrolidinil)-1-benzofuran-5-carboxilato de metilo (B163). $[M+H]^+$ = 288.1, t.r. = min.

Descripción 262

3-Bromo-5-(1,1-dioxido-2-isotiazolidinil)benzoato de metilo (D262)

El 3-bromo-5-(1,1-dioxido-2-isotiazolidinil)benzoato de metilo (D262) se obtuvo de 3-bromo-5-yodobenzoato de metilo (D8a), de manera análoga al procedimiento de la descripción 17 (D17), usando D8a en lugar de D8b como material de partida.

Descripción 263

3-Bromo-5-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)benzoato de metilo (D263)

El 3-bromo-5-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)benzoato de metilo (D263) se obtuvo de 3-bromo-5-yodobenzoato de metilo (D8a), de manera análoga al procedimiento de la descripción 18 (D18), usando D8a en lugar de D8b como material de partida.

Descripción 264

3-(3-Ciclopenten-1-il)-5-(1,1-dioxido-2-isotiazolidinil)benzoato de metilo; 3-(2-ciclopenten-1-il)-5-(1,1-dioxido-2-isotiazolidinil)benzoato de metilo; 3-(1-ciclopenten-1-il)-5-(1,1-dioxido-2-isotiazolidinil)benzoato de metilo (D264)

El 3-(3-ciclopenten-1-il)-5-(1,1-dioxido-2-isotiazolidinil)benzoato de metilo, 3-(2-ciclopenten-1-il)-5-(1,1-dioxido-2-isotiazolidinil)benzoato de metilo y 3-(1-ciclopenten-1-il)-5-(1,1-dioxido-2-isotiazolidinil)benzoato de metilo (D264), se obtuvieron de 3-bromo-5-(1,1-dioxido-2-isotiazolidinil)-benzoato de metilo (D262), de manera análoga al procedimiento de la descripción 73 (D73).

Descripción 265

3-(1-Ciclopenten-1-il)-5-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-benzoato de metilo; 3-(2-ciclopenten-1-il)-5-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)benzoato de metilo; 3-(3-ciclopenten-1-il)-5-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)benzoato de metilo (D265)

El 3-(1-ciclopenten-1-il)-5-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)benzoato de metilo, 3-(2-ciclopenten-1-il)-5-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)benzoato de metilo, y 3-(3-ciclopenten-1-il)-5-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)benzoato de metilo (D265), se obtuvieron de 3-bromo-5-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)benzoato de metilo (D263), de manera análoga al procedimiento de la descripción 73 (D73).

Descripción 266

3-(1,1-Dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-nitrobenzoato de metilo (D266)

El 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-nitrobenzoato de metilo (D266) se obtuvo de 3-bromo-5-nitrobenzoato de metilo (D11), de manera análoga al procedimiento de la descripción 15 (D15), usando el compuesto de la descripción 22b (D22b) en lugar del compuesto de la descripción D22a (D22a).

Descripción 267

3-Amino-5-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)benzoato de metilo (D267)

El 3-amino-5-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)benzoato de metilo (D267) se obtuvo de 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-nitrobenzoato de metilo (D266), de manera análoga al procedimiento de la descripción 16 (D16).

Descripción 268

3-(1,1-Dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-hidroxibenzoato de metilo (D268)

A una solución de 3-amino-5-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)benzoato de metilo (D267) (7.5 g, 26.4 mol, 1 eq.) en una solución acuosa de HCl 2N (75 ml) y MeOH (75 ml), a 0°C, se le agregó en porciones $NaNO_2$

(4.0 g, 58.1 mmol, 2.2 eq.) durante 20 min. Se le agregó MeOH (50 ml) y H_2O (200 ml) y la mezcla resultante se agitó a 95°C durante 1 h; después se enfrió a temperatura ambiente. La mayor parte del MeOH se removió al vacío y la fase acuosa resultante se extrajo con AcOEt. El material insoluble se separó por filtración para dar 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-hidroxibenzoato de metilo (D) (0.63 g, 8%). La fase orgánica se lavó con salmuera, se secó sobre $MgSO_4$ y se concentró al vacío, para dar un residuo pardo que se volvió a disolver en AcOEt. La fase orgánica se extrajo con una solución acuosa saturada de Na_2CO_3 y la fase acuosa se extrajo tres veces con Et_2O; después se acidificó a pH 1 y se volvió a extraer tres veces con AcOEt. La fase orgánica combinada se lavó con salmuera, se secó sobre $MgSO_4$ y se concentró al vacío, para dar 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-hidroxibenzoato de metilo (D268) (2.2 g, 30%).

Descripción 269

5-(1-Ciclopenten-1-il)-3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-2-fluorobenzoato de metilo; 5-(2-ciclopenten-1-il)-3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-2-fluorobenzoato de metilo; y 5-(3-ciclopenten-1-il)-3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-2-fluorobenzoato de metilo (D269)

El 5-(1-ciclopenten-1-il)-3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-2-fluorobenzoato de metilo, 5-(2-ciclopenten-1-il)-3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-2-fluorobenzoato de metilo, y 5-(3-ciclopenten-1-il)-3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-2-fluorobenzoato de metilo (D269), se

obtuvieron de la descripción 158 (D158), de manera análoga al procedimiento de la descripción 73 (D73)

Descripción 270

2-Metil-2-[3-(trifluorometil)fenil]propanoato de etilo (D270)

El 2-metil-2-[3-(trifluorometil)fenil]propanoato de etilo (D270) se obtuvo de [3-(trifluorometil)fenil]acetato de etilo, de manera análoga al procedimiento de la descripción 98 (D98).

Descripción 271

Acido 2-metil-2- [3-(trifluorometil)fenil]propanoico (D271)

El ácido 2-metil-2-[3-(trifluorometil)fenil]propanoico (D271) se obtuvo de 2-metil-2-[3-(trifluorometil)fenil]propanoato de etilo (D270), de manera análoga al procedimiento de la descripción 99 (D99).

Descripción 272

{1-Metil-1-[3-(trifluorometil)fenil]etil}carbamato de fenilmetilo (D272)

El {1-metil-1-[3-(trifluorometil)fenil]etil}carbamato de fenilmetilo (D272) se obtuvo de ácido 2-metil-2-[3-(trifluorometil)fenil]propanoico (D271), de manera análoga al procedimiento de la descripción 100 (D100).

Descripción 273

Metanosulfonato de 2-({[(1,1-dimetiletil)oxi]carbonil}amino)-2-metilpropilo (D273)

A una solución de (2-hidroxi-1,1-dimetiletil)carbamato de 1,1-dimetiletilo (5.1 g, 27 mmol, 1 eq.) en CH_2Cl_2 (100 ml), a temperatura ambiente, se le agregó NEt_3 (11.3 ml, 81 mmol, 3 eq.) y cloruro de metanosulfonilo (28.3 mmol, 2.2 ml, 1.05 eq.), y la solución resultante se agitó durante 2 h; después se dividió entre AcOEt y una solución acuosa saturada de $NaHCO_3$. Las dos capas se separaron, y la fase orgánica se secó sobre $MgSO_4$ y se concentró al vacío para dar metanosulfonato de 2-({[(1,1-dimetiletil)oxi]carbonil}amino)-2-metilpropilo (D273) (7.8 g, 108%), como un aceite amarillo que se usó en el siguiente paso sin mayor purificación.

Descripción 274

[1,1-Dimetil-2-(feniloxi)etil]carbamato de 1,1-dimetiletilo (D274)

A una solución de fenol (2.1 g, 22.4 mmol, 3 eq.) en DMF (10 ml), a temperatura ambiente, se le agregó NaH (dispersión en aceite mineral, 60%, 360 mg, 9.0 mmol, 1.2 eq.) y después de 10 min se le agregó metanosulfonato de 2-({[(1,1-dimetiletil)oxi]carbonil}amino)-2-metilpropilo (D273) (2 g, 7.5 mmol, 1 eq.); la solución resultante se agitó a 50°C durante 2 h y después se enfrió a temperatura ambiente y se concentró al vacío. La purificación del residuo por cromatografía de vaporización instantánea sobre gel de sílice (iso-hexano/AcOEt: 9/1 a 6/1), dio [1,1-dimetil-2-

(feniloxi)etil]carbamato de 1,1-dimetiletilo (D274) (180 mg, 9%), como un aceite amarillo.

Descripción 275

{1,1-Dimetil-2-[(fenilmetil)oxi]etil}carbamato de 1,1-dimetiletilo (D275)

El {1,1-dimetil-2-[(fenilmetil)oxi]etil}carbamato de 1,1-dimetiletilo (D275) se preparó a partir de metanosulfonato de 2-({[(1,1-dimetiletil)oxi]carbonil}amino)-2-metilpropilo (D273), de manera análoga al [1,1-dimetil-2-(feniloxi)etil]carbamato de 1,1-dimetiletilo (D274), usando fenilmetanol en lugar de fenol.

Descripción 276

{1,1-Dimetil-2-[(2-metilpropil)tio]etil}carbamato de 1,1-dimetiletilo (D276)

El {1,1-dimetil-2-[(2-metilpropil)tio]etil}carbamato de 1,1-dimetiletilo (D276) se preparó de metanosulfonato de 2-({[(1,1-dimetiletil)oxi]carbonil}amino)-2-metilpropilo (D273), de manera análoga al [1,1-dimetil-2-(feniloxi)etil]carbamato de 1,1-dimetiletilo (D274), usando 2-metil-1-propanotiol en lugar de fenol.

Descripción 277

(4,4-Difluorociclohexil)carbamato de 1,1-dimetiletilo (D277)

A una solución de (4-oxociclohexil)carbamato de 1,1-dimetiletilo (1 g, 4.69 mmol, 1 eq.) en CH_2Cl_2 (15 ml), se le agregó DAST (1.05 ml, 7.98 mmol, 1.7 eq.), y la mezcla resultante se agitó durante 15 h. Se le agregó una solución acuosa saturada de $NaHCO_3$ y la mezcla bifásica resultante se agitó vigorosamente durante 1 h. Las dos capas se separaron y la fase acuosa se extrajo con CH_2Cl_2. La fase orgánica combinada se secó sobre $MgSO_4$ y se concentró al vacío, para dar (4,4-difluorociclohexil)carbamato de 1,1-dimetiletilo (D277) (1.03 g, 93%), como un sólido de color beige que se usó en el siguiente paso sin mayor purificación.

Descripciones 278-281 (D278-281)

Los siguientes ácidos se obtuvieron por alquilación de ácido ciclobutanocarboxílico como se describe en: K. Tani, A. Naganawa, A. Ishida, K. Sagawa, H. Harada, M. Ogawa, T., Maruyama, S. Ohuchida, H. Nakai, K. Kondo, M. Toda, *Bio. Med. Chem.* 2002, 10, 1093-1106:

Descripción
Acido 1-etilciclobutanocarboxílico (D278)
Acido 1-propilciclobutanocarboxílico (D279)
Acido 1-(1-metiletil)ciclobutanocarboxílico (D280)
Acido 1-[(3-clorofenil)metil]ciclobutanocarboxílico (D281)

Descripciones 282-285 (D282-285)

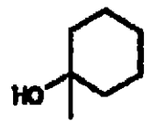
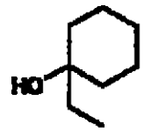
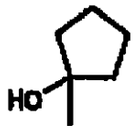
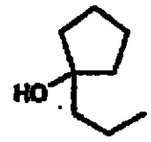
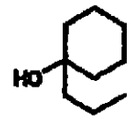
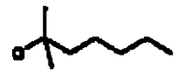
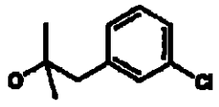
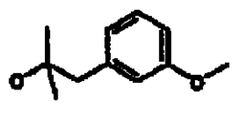
Los siguientes compuestos se obtuvieron de sus precursores, de manera análoga al procedimiento de la descripción 100 (D100):

Descripción	Precursor
(1-Etilciclobutil)carbamato de fenilmetilo (D282)	D278
(1-Propilciclobutil)carbamato de fenilmetilo (D283)	D279
[1-(1-Metiletil)ciclobutil]carbamato de fenilmetilo (D284)	D280
{1-[(3-Clorofenil)metil]ciclobutil}carbamato de fenilmetilo (D285)	D281

360
362

Descripciones 286-293 (D286-293)

Las siguientes amidas se obtuvieron por medio de una reacción de Ritter como se describe en: M. Mousseron, *Bull. Soc. Chim. Fr.* 1957, 596:

Descripción	Precursor
N-(1-Metilciclohexil)acetamida (D286)	
N-(1-Etilciclohexil)acetamida (D287)	
N-(1-Metilciclopentil)acetamida (D288)	
N-(1-Propilciclopentil)acetamida (D289)	
N-(1-Propilciclohexil)acetamida (D290)	
N-(1,1-Dimetilhexil)acetamida (D291)	
N-[2-(3-Clorofenil)-1,1-dimetiletil]acetamida (D292)	
N-[1,1-Dimetil-2-[3-(metiloxi)fenil]etil]acetamida (D293)	

Descripción 294

4,4-Dimetilciclohexanona (D294)

La 4,4-dimetilciclohexanona (D294) se obtuvo de 4,4-dimetil-2-ciclohexen-1-ona, de manera análoga al procedimiento descrito para el éster 116 (B116).

Descripción 295

3,3-Dimetilciclopentanona (D295)

La 3,3-dimetilciclopentanona (D295) se obtuvo de 4,4-dimetil-2-ciclopenten-1-ona, de manera análoga al procedimiento descrito para 4,4-dimetilciclohexanona (D294).

Descripción 296

Oxima de 4,4-dimetilciclohexanona (D296)

A una solución de 4,4-dimetilciclohexanona (D294) (9.2 g, 73 mmol, 1 eq.) en EtOH (50 ml) y H_2O (50 ml), se le agregó $NH_2OH.HCl$ (6.6 g, 94.5 mmol, 1.3 eq.) y Na_2CO_3 (10.06 g, 94.5 mmol, 1.3 eq.), y la solución turbia resultante se puso en reflujo durante 2 h; después se enfrió a temperatura ambiente. La mayor parte del EtOH se removió al vacío y la fase acuosa se extrajo dos veces con AcOEt. La fase orgánica combinada se secó sobre $MgSO_4$ y se concentró al vacío, para dar la oxima de 4,4-dimetilciclohexanona (D296) (10 g, 97%), como un sólido incoloro que se usó en el siguiente paso sin purificación.

Descripciones 297-298 (D297-298)

Las siguientes oximas se obtuvieron de sus precursores, de manera análoga al procedimiento de la descripción (D296).

Descripción	Precursor
Oxima de (1*E/Z*)-2,2-dimetilciclohexanona (D297)	D294
Oxima de (1*E/Z*)-3,3-dimetilciclopentanona (D298)	D295

Descripciones 299-311 (D299-311)

Los siguientes compuestos se obtuvieron de (2S)-2-(1-metiletil)-3,6-bis(metiloxi)-2,5-dihidropirazina, de acuerdo con el procedimiento general descrito en: P. dalla Croce, C. la Rosa, E. Pizzatti, *Tetrahedron : Asymmetry* 2000, 11, 2635-2642:

Descripción
3,5-Difluoro-L-fenilalaninato (D299)
3-Fluoro-L-fenilalaninato (D300)
3,4-Difluoro-L-fenilalaninato (D301)
2-Cloro-L-fenilalaninato (D302)
Metil-3-cloro-L-fenilalaninato (D303)
Metil-4-cloro-L-fenilalaninato (D304)
Metil-3-(2-tienil)-L-alaninato (D305)
Metil-3-(3-tienil)-L-alaninato (D306)
Metil-3-(2-furanil)-L-alaninato (D307)
Metil-3-(2-piridinil)-L-alaninato (D308)
Metil-3-(1,3-tiazol-2-il)-L-alaninato (D309)
Metil-3-(1H-pirazol-1-il)-L-alaninato (D310)
Metil-3-(3-piridinil)-L-alaninato (D311)

Descripciones 312-313 (D312-313)

Los compuestos de las descripciones 312-313 se prepararon de manera análoga al ejemplo 1, a partir del ácido y las aminas apropiadas que

se indican en el cuadro siguiente

Descripción	Acido	Amina	$[M+H]^+$	t.r. (min)
3-(1,1-Dioxido-6,7-dihidro-1,2-tiazepin-2(3H)-il)-N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-({[3-(trifluorometil)fenil]metil}amino)propil]-5-propilbenzamida (D312)	A117	C16	630.4	2.89
3-(1,1-Dioxido-6,7-dihidro-1,2-tiazepin-2(3H)-il)-N-[(1S,2R)-2-hidroxi-3-({[3-(metiloxi)fenil]metil)amino)-1-(fenilmetil)propil]-5-propilbenzamida (D313	A117	C14	592.4	2.75

Descripción 314

1-[3-(Metiloxi)fenil]ciclohexanol (D314)

A una solución de bromuro de 3-metoxifenil-magnesio (1 M en THF, 61 ml, 61 mmol, 1 eq.), a 0°C, se le agregó lentamente ciclohexanona (6g, 61 mmol, 1 eq.) en Et_2O (30 ml). La mezcla resultante se agitó a temperatura ambiente durante 4 h y después se vació en H_2O a 0°C. Las dos capas se separaron y la fase acuosa se extrajo tres veces con Et_2O. La fase orgánica combinada se lavó con salmuera, se secó sobre $MgSO_4$ y se concentró al vacío, para dar 1-[3-(metiloxi)fenil]ciclohexanol (D314) (12.4 g, 100%) como un aceite amarillo claro, que se usó en el siguiente paso sin mayor purificación.

Descripción 315

1-(1-Azidociclohexil)-3-(metiloxi)benceno (D315)

A una solución de 1-[3-(metiloxi)fenil]ciclohexanol (2.93 g, 14.22

mmol, 1 eq.) en CH_2Cl_2 (25 ml), bajo nitrógeno y a 0°C, se le agregó azida de sodio (1.85 g, 28.44 mmol, 2 eq.) y después TFA (4.4 ml, 56.89 mmol, 4 eq.), lentamente. Después se le agregaron 40 ml de CH_2Cl_2 y la suspensión resultante se agitó a temperatura ambiente durante 16 h; después se dividió entre Et_2O y H_2O. Las dos capas se separaron y la fase orgánica se lavó con H_2O y una solución acuosa de NaOH 1N, entonces se secó sobre $MgSO_4$ y se concentró al vacío, para dar 1-(1-azidociclohexil)-3-(metiloxi)benceno (D315) (2.78 g, 85%), como un aceite transparente que se usó en el siguiente paso sin mayor purificación.

Descripción 316

Oxima de (1*E/Z*)-propanal (D316)

La oxima de (1*E/Z*)-propanal se obtuvo de propanal, de manera similar al procedimiento de la descripción 296 (D296).

Descripción 317

2-Propin-1-ilcarbamato de 1,1-dimetiletilo (D317)

A una solución de 2-propin-1-amina (2 g, 36.4 mmol, 1 eq.) en CH_2Cl_2 (20 ml), se le agregó NEt_3 (5.3 ml, 38.18 mmol, 1.05 eq.) y dicarbonato de bis(1,1-dimetiletilo) (8.32 g, 38.18 mmol, 1.05 eq.). La mezcla resultante se agitó a temperatura ambiente durante 3 h y después de vació en una solución acuosa de HCl 2N. Las dos capas se separaron y la fase orgánica se lavó con una solución acuosa saturada de $NaHCO_3$, entonces se secó sobre

$MgSO_4$ y se concentró al vacío, para dar 2-propin-1-ilcarbamato de 1,1-dimetiletilo (D317) (4.05 g, 72%) como un cristal incoloro.

Descripción G33

Ester *ter*-butílico del ácido ((1S,2R)-2-hidroxi-1-isobutilcarbamoil-pentil)-carbámico (G33)

El éster metílico del ácido (2S,3R)-2-*ter*-butoxicarbonilamino-3-hidroxi-hexanoico (D94) (1.57g, 6.02 mmol, 1 eq.) se puso en reflujo en isobutilamina (10 ml) durante 2 h. La solución se concentró al vacío y el residuo se purificó por cromatografía de vaporización instantánea sobre gel de sílice, para dar el éster *ter*-butílico del ácido ((1S,2R)-2-hidroxi-1-isobutilcarbamoil-pentil)-carbámico (G33) (1.52g, 84%) como un sólido blanco.

Los siguientes compuestos se obtuvieron de manera análoga a la descripción 96a, usando el ácido (disponible comercialmente) y la amina apropiada:

Nombre
Ester *ter*-butílico del ácido ((S)-1-ciclohexilcarbamoil-3-metilsulfanil-propil)-carbámico (G6)
Ester *ter*-butílico del ácido [(S)-1-(3,3-dimetil-butilcarbamoil)-etil]-carbámico (G36)

Descripción G38

Ester ter-butílico del ácido ((S)-1-isobutilcarbamoil-3-metanosulfonil-propil)-carbámico (G38)

Al éster *ter*-butílico del ácido ((S)-1-isobutilcarbamoil-3-

metilsulfanil-propil)-carbámico (D96) (1.19 g, 3.9 mmol, 1 eq.) en CH_2Cl_2 (25 ml), a 0°C, se le agregó en porciones ácido *m*-cloroperbenzoico (50-55%, 4.0 g, 11.6 mmol, 3 eq.). La mezcla resultante se agitó 2 h a 0°C y entonces se diluyó con AcOEt y se lavó con una solución acuosa saturada de $NaHCO_3$; se secó sobre $MgSO_4$ y se concentró al vacío, para dar el éster *ter*-butílico del ácido ((S)-1-isobutilcarbamoil-3-metanosulfonil-propil)-carbámico (G38) (1.06 g, 81 %), como un sólido incoloro.

Descripción G157

[(3-Etil-5-isoxazolil)metil]carbamato de 1,1-dimetiletilo (G157)

A una solución de oxima de (1*E/Z*)-propanal (D316) (4g, 54.8 mmol, 1 eq.) en CH_2Cl_2 (200 ml), a temperatura ambiente, se le agregó *N*-cloro-succinamida (7.44 g, 55.8 mmol, 1.02 eq.), y la solución resultante se agitó a esta temperatura durante 2.5 h; después se le agregó NEt_3 (20 ml, exceso) y la mezcla resultante se agitó 2 h. Se le agregó DIPEA (9.52 mmol, 55.8 mmol, 1.02 eq.) y 2-propin-1-ilcarbamato de 1,1-dimetiletilo (D317) (1.34 g, 8.76 mmol, 0.16 eq.), y la solución se agitó 48 h; después se vació en una solución acuosa de HCl 1M. Las dos capas se separaron y la fase orgánica se lavó con una solución acuosa saturada de $NaHCO_3$, entonces se secó sobre $MgSO_4$ y se concentró al vacío. La purificación del residuo por cromatografía de vaporización instantánea sobre gel de sílice (iso-hexano/AcOEt: 4/1 a 3/1), dio [(3-etil-5-isoxazolil)metil]carbamato de 1,1-dimetiletilo (G157) (1.28 g, 63%).

Descripción F5

1,1,5-Trimetil-hexilamina (F5)

El compuesto de la descripción F5 se obtuvo de acuerdo con S. S. Berg y D. T. Cowling, *J. Chem. Soc.* (C) 1971, 1653-1658.

Descripción F33

Sal clorhidrato de la isobutil-amida del ácido (2S,3R)-2-amino-3-hidroxi-hexanoico (F33)

Se disolvió el éster metílico de ácido (2S,3R)-2-*ter*-butoxicarbonilamino-3-hidroxi-hexanoico (G33) (235 mg, 0.86 mmol, 1 eq.) en HCl 4M en dioxano (4 ml), y la solución se agitó durante 1 h a temperatura ambiente; después se concentró al vacío. El residuo se trituró con Et_2O para dar la sal clorhidrato de la isobutil-amida del ácido (2S,3R)-2-amino-3-hidroxi-hexanoico (F33) (176 mg, 95%), como un sólido blanco.

Los siguientes compuestos se obtuvieron (como sus sales clorhidrato) del precursor apropiado, como se indica en el cuadro siguiente, de acuerdo con una forma análoga a la Descripción F33:

Nombre	Precursor
(S)-2-Amino-*N*-ciclohexil-propionamida (F6)	G6
Isobutil-amida del ácido (S)-2-amino-hexanoico (F36)	G36

Descripción F15

1-(3-Metoxi-fenil)-1-metil-etilamina (F15)

Un matraz se cargó con éster bencílico del ácido [1-(3-metoxi-

fenil)-1-metil-etil]-carbámico (D100) (1 g, 3.34 mmol, 1 eq.), paladio al 10% sobre carbón (50% en húmedo, 100 mg, 10% p/p), NH_4COOH (2.1 g, 33 mmol, 10 eq.), EtOH (40 ml) y H_2O (8 ml). La mezcla resultante se agitó a 80°C durante 2 h, se enfrió a temperatura ambiente y el catalizador se separó por filtración usando una almohadilla de celite. La mayor parte del EtOH se removió al vacío y el residuo se diluyó con solución acuosa de HCl 1 N. La fase acuosa se extrajo con AcOEt y después se basificó a pH 13 y se extrajo dos veces con AcOEt. La capa orgánica combinada se secó sobre $MgSO_4$ y se concentró al vacío para producir 1-(3-metoxi-fenil)-1-metil-etilamina (F15) (290 mg, 53%) como una goma amarilla.

Descripción F40

2-[3-(Trifluorometil)fenil]-2-propanamina (F40)

La 2-[3-(trifluorometil)fenil]-2-propanamina (F40) se obtuvo de {1-metil-1-[3-(trifluorometil)fenil]etil}carbamato de fenilmetilo (D272), de manera análoga al procedimiento de la descripción F15 (F15).

Descripción F41

{1-13-(Metiloxi)fenil]ciclohexil}amina (F41)

A una solución de 1-(1-azidociclohexil)-3-(metiloxi)benceno (D315) (2.78 g, 12.0 mmol, 1 eq.) en THF (20 ml), a temperatura ambiente, se le agregó $LiAlH_4$ (1 M en THF, 36 ml, 36 mmol, 3 eq.), y la mezcla resultante se agitó a esta temperatura durante 4 h. Después, la mezcla se inactivó

cuidadosamente con una solución acuosa de NaOH 1 N (6 ml, 60 mmol, 1 eq.) y después H_2O. La mezcla se filtró a través de una almohadilla de celite; después se acidificó con una solución acuosa de HCl 2N (50 ml). Las dos capas se separaron y el pH de la fase acuosa se ajustó a 9 usando una solución acuosa de NaOH 2N. La fase acuosa se extrajo tres veces con Et_2O y la fase orgánica combinada se secó sobre $MgSO_4$; después se concentró al vacío para dar {1-[3-(metiloxi)fenil]ciclohexil}amina (F41) (1.55 g, 63%) como un aceite transparente, que se usó en el siguiente paso sin mayor purificación. $[M+H]^+$ = 189.0, t.r. = 1.90 min.

Descripciones F48, F61, F81 y F110-114

Las siguientes aminas se obtuvieron de sus amidas correspondientes, de manera análoga al procedimiento de la descripción F5 (F5):

Descripción	Precursor
2-Metil-2-heptanamina (F48)	D291
2-Metil-1-[3-(metiloxi)fenil]-2-propanamina (F61)	D293
1-Metilciclohexanamina (F81)	D286
1-Metilciclohexanamina (F110)	D287
1-Metilciclopentanamina (F111)	D288
1-Propilciclopentanamina (F112)	D289
1-Propilciclohexanamina (F113)	D290
1-(3-Clorofenil)-2-metil-2-propanamina (F114)	D292

Descripción F52

7-(Metiloxi)-1,2,3,4-tetrahidro-1-naftalenamina (F52)

La 7-(metiloxi)-1,2,3,4-tetrahidro-1-naftalenamina (F52) se

370
372

obtuvo de 7-(metiloxi)-3,4-dihidro-1(2*H*)-naftalenona, de manera análoga al procedimiento descrito en la patente de E.U.A. No. 4,132,737.

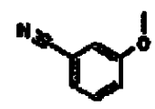
Descripciones F54-56 y F155

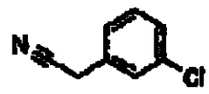
Las siguientes aminas se prepararon de su precursor, de manera análoga al procedimiento descrito para la amina 1 (C1):

Descripción	Precursor
Cloruro ácido de 2-metil-1-(2-metilpropil)tio]-2-propanamina (F54)	D276
Cloruro ácido de 2-metil-1-(feniloxi)-2-propanamina (F55)	D274
Cloruro ácido de 2-metil-1-[(fenilmetil)oxi]-2-propanamina (F56)	D275
Clorhidrato de 4,4-difluorociclohexanamina (F155)	D277

Descripciones F63, F73-75 y F77-80

Las siguientes aminas se prepararon de sus nitrilos correspondientes de acuerdo con el método general descrito en: P. Bertus, J. Szymoniak, *Chem. Comm.*, 2001, 1792:

Descripción	Precursor
1-[3-(Metiloxi)fenil]ciclopropanamina (F63)	
1-(4-Metilpentil)ciclopropanamina (F73)	
1-Etilciclopropanamina (F74)	
1-(1-Metiletil)ciclopropanamina (F75)	

Descripción	Precursor
1-Propilciclopropanamina (F77)	
1-(3-metilbutil)ciclopropanamina (F78)	
1-(2-metilpropil)ciclopropanamina (F79)	
1-[(3-Clorofenil)metil]ciclopropanamina (F80)	

Descripciones F69 y F148-150

Los siguientes compuestos se obtuvieron de sus precursores, de manera análoga al procedimiento de la descripción F15 (F15):

Descripción	Precursor
1-Etilciclobutanamina (F69)	D282
1-Propilciclobutanamina (F148)	D283
1-(1-Metiletil)ciclobutanamina (F149)	D284
1-[(3-Clorofenil)metil]ciclobutanamina (F150)	D285

Descripción F70

2-Metil-1-[(2-metilpropil)oxi]-2-propanamina (F70)

La 2-metil-1-[(2-metilpropil)oxi]-2-propanamina (F70) se obtuvo de 2-metil-1-[(2-metil-2-propen-1-il)oxi]-2-propanamina (F71), de manera análoga al procedimiento descrito para el éster 166 (B116).

Descripción F71

2-Metil-1-[(2-metil-2-propen-1-il)oxi]-2-propanamina (F71)

A una solución de NaH (dispersión en aceite mineral, 60%, 2.0 g, 50 mmol, 1 eq.) en DMF, a 0°C, se le agregó 2-amino-2-metil-1-propanol (4.8 ml, 50 mmol, 1 eq.) y después de 1 h, 3-bromo-2-metil-1-propeno (5.5 ml, 55 mmol, 1.1 eq.). La solución resultante se agitó a temperatura ambiente durante 15 h y después se dividió entre AcOEt y H_2O. Las dos capas se separaron y la fase orgánica se lavó con H_2O y salmuera, se secó sobre $MgSO_4$ y se destiló (45°C, P = 150 mbar), para dar 2-metil-1-[(2-metil-2-propen-1-il)oxi]-2-propanamina (F71), como un sólido rosa claro.

Descripción F83

4,4-Dimetilciclohexanamina (F83)

La oxima de 4,4-dimetilciclohexanona (D296) (10 g, 71 mmol, 1 eq.) en EtOH (100 ml), se agitó con Ni de Raney (1 g, 10% p/p) bajo una atmósfera de H_2 (3.5 kg/cm^2) durante 4 días. El catalizador se separó por filtración a través de una almohadilla de celite y se le agregó HCl (1 M en Et_2O, 100 ml, 100 mmol, 1.4 eq.). El precipitado formado se separó por filtración y se disolvió en agua. La fase acuosa se lavó con Et_2O y se hizo fuertemente básica con pellas de KOH; después se extrajo dos veces con CH_2Cl_2. La fase orgánica combinada se secó sobre $MgSO_4$ y se concentró al vacío, para dar 4,4-dimetilciclohexanamina (F83) (8 g, 89%) como un aceite transparente, que se usó en el siguiente paso sin mayor purificación.

Descripciones F86 y F92

Las siguientes aminas se obtuvieron de su precursor, de manera análoga al procedimiento descrito para 4,4-dimetilciclohexanamina (F83):

Amina	Precursor
2,2-Dimetil-ciclohexanamina (F86)	D297
3,3-Dimetil-ciclopentanamina (F92)	D298

Descripción F157

[(3-Etil-5-isoxazolil)metil]amina (F157)

La [(3-etil-5-isoxazolil)metil]amina (F157) se obtuvo de [(3-etil-5-isoxazolil)metil]carbamato de 1,1-dimetiletilo (G157), de manera análoga al procedimiento descrito en la descripción F33 (F33).

Preparación de ésteres

Ester 1

Ester metílico del ácido 3-metilsulfanil-5-(2-oxo-pirrolidin-1-il)-benzoico (B1)

A una solución del éster metílico del ácido 3-(4-cloro-butanoilamino)-5-metilsulfanil-benzoico crudo (D64) (0.17 g, 0.56 mmol, 1 eq.), en THF (2 ml), a 0°C, se le agregó en porciones NaH (60% en aceite mineral, 24.6 mg, 0.616 mmol, 1.1 eq.) durante 2 min. La mezcla resultante se agitó a temperatura ambiente durante 40 min y se le agregó una gota de MeOH para destruir el NaH remanente. La mezcla resultante se diluyó entonces con AcOEt, se lavó secuencialmente con solución acuosa de HCl 2N, solución

acuosa saturada de $NaHCO_3$ y salmuera; se secó sobre Na_2SO_4 y se concentró al vacío. La purificación por cromatografía de vaporización instantánea sobre gel de sílice (iso-hexano/AcOEt: 1/1), dio el éster metílico del ácido 3-(4-cloro-butanoilamino)-5-metilsulfanil-benzoico (B1) (122 mg, 82%), como un sólido blanco. $[M+H]^+$ = 266.0, t.r. = 2.86 min.

Ester 2

Ester etílico del ácido 3-etilsulfanil-5-(2-oxo-pirrolidin-1-il)-benzoico (B2)

El éster 2 se preparó de 177 mg (0.54 mmol) de éster etílico de ácido 3-(4-cloro-butanoilamino)-5-etilsulfanil-benzoico (D65), de manera análoga que para el éster 1, produciendo 129 mg (82%) del éster etílico de ácido 3-etilsulfanil-5-(2-oxo-pirrolidin-1-il)-benzoico (B2) como una goma incolora transparente, después de purificación por cromatografía de vaporización instantánea sobre gel de sílice (iso-hexano/AcOEt: 60/40). $[M+H]^+$ = 294.1, t.r. = 3.23 min

Ester 3

Ester metílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-metilsulfanil-benzoico (B3)

A una solución de éster metílico del ácido 3-(3-cloro-propano-1-sulfonilamino)-5-metilsulfanil-benzoico (D66) (183 mg, 0.54 mmol, 1 eq.) en MeOH (3 ml), se le agregó NEt_3 (150 µl, 1.08 mmol, 2 eq.). La mezcla

resultante se agitó a 70 °C durante 2 h y después se dejó enfriar a temperatura ambiente durante la noche. Se le agregó una porción más de NEt_3 (75 µl, 0.54 mmol, 1 eq.) y la mezcla se agitó a 80 °C durante 3 h, cuando se le agregó otra porción de NEt_3 (75 µl, 0.54 mmol, 1 eq.). Después de otras 2 h a 80 °C, la solución se enfrió a temperatura ambiente y se concentró al vacío. El residuo se dividió entre AcOEt y solución acuosa de HCl 2N. La capa orgánica se lavó con salmuera, se secó sobre Na_2SO_4 y se concentró al vacío. La purificación por cromatografía de vaporización instantánea sobre gel de sílice (iso-hexano/AcOEt: 60/40), dio éster metílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-metilsulfanil-benzoico (B3) (150 mg, 92%). $[M+H]^+$ = 302.0 t.r. = 2.89 min.

<u>Ester 4</u>

<u>Ester etílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-etilsulfanil-benzoico (B4)</u>

El éster 4 se preparó de 190 mg (0.52 mmol) de éster etílico de ácido 3-(3-cloro-propano-1-sulfonilamino)-5-etilsulfanil-benzoico (D67), de una manera análoga al éster 3, produciendo 154 mg (90%) de éster etílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-etilsulfanil-benzoico (B4), después de purificación por cromatografía de vaporización instantánea sobre gel de sílice (iso-hexano/AcOEt: 60/40). $[M+H]^+$ = 330.0, t.r. = 3.24 min

Ester 11

Ester metílico del ácido 3-etoxi-5-(2-oxo-pirrolidin-1-il)-benzoico (B11)

A éster metílico del ácido 3-hidroxi-5-(2-oxo-pirrolidin-1-il)-benzoico (D37) (0.80 g, 3.4 mmol, 1 eq.) disuelto en DMF (10 ml), se le agregó K_2CO_3 (0.94 g, 6.8 mmol, 2 eq.) y yoduro de etilo (1.1 g, 6.8 mmol, 2 eq.). La mezcla resultante se calentó a 50 °C durante 4 h; se enfrió a temperatura ambiente, se diluyó con solución acuosa de HCl 2N (50 ml) y se extrajo con Et_2O (50 ml). La fase orgánica se lavó entonces con agua (50 ml), se secó sobre $MgSO_4$ y se concentró al vacío, para dar el éster metílico del ácido 3-etoxi-5-(2-oxo-pirrolidin-1-il)-benzoico (B11) (0.85 g, 95%), como un aceite pardo que solidificó lentamente hasta quedar un sólido de color canela.

Ester 11 (Procedimiento alternativo)

Ester metílico del ácido 3-etoxi-5-(2-oxo-pirrolidin-1-il)-benzoico (B11):

El éster metílico del ácido 3-(4-cloro-butanoilamino)-5-etoxi-benzoico (D51) (7 g, 20 mmol, 1 eq.) en THF (50 ml), se trató en porciones con NaH (60% en aceite mineral, 0.88 g, 22 mmol, 1.1 eq.) durante 15 min a temperatura ambiente. La mezcla resultante se agitó durante 30 min y entonces se diluyó con AcOEt (300 ml). La solución resultante se lavó con una solución acuosa de HCl 2N (200 ml), se secó sobre $MgSO_4$ y se concentró al vacío. La recristalización del residuo de Et_2O/hexano, dio el éster

metílico del ácido 3-etoxi-5-(2-oxo-pirrolidin-1-il)-benzoico (B11) (3.5 g, 66%) como un sólido blanco.

Los siguientes ésteres se prepararon de manera análoga al éster 11 de D37, usando un reactivo apropiado disponible comercialmente:

Ester
Ester metílico del ácido 3-metoxi-5-(2-oxo-pirrolidin-1-il)-benzoico (B9)
Ester metílico del ácido 3-(2-oxo-pirrolidin-1-il)-5-propoxi-benzoico (B10)
Ester metílico del ácido 3-isopropoxi-5-(2-oxo-pirrolidin-1-il)-benzoico (B12)
Ester metílico del ácido 3-(2-oxo-pirrolidin-1-il)-5-pentiloxi-benzoico (B13)

Ester 14

El siguiente éster se preparó de manera análoga a la descripción 38 a partir del compuesto de la descripción 37, usando el alcohol apropiado indicado en el cuadro siguiente:

Ester	Alcohol
Ester metílico del ácido 3-(2-metoxi-etoxi)-5-(2-oxo-pirrolidin-1-il)-benzoico (B14)	

Ester 15

Eter metílico del ácido 3-(3-hidroxi-propoxi)-5-(2-oxo-pirrolidin-1-il)-benzoico (B15)

El éster metílico del ácido 3-(3-benciloxi-propoxi)-5-(2-oxo-pirrolidin-1-il)-benzoico (D38) en MeOH (15 ml), se hidrogenó inicialmente con Pd 10% sobre carbón (50% en húmedo, 0.25 g, 0.25 eq. p/p), a presión

atmosférica durante 24 h, y después se le agregaron 0.25 g más de Pd 10% sobre carbón (50% en húmedo, 0.25 g, 0.25 eq. p/p), y la mezcla se hidrogenó a 3.5 kg/cm^2 por 48 h más. La mezcla se filtró a través de celite y se concentró al vacío. La purificación por cromatografía de vaporización instantánea sobre gel de sílice (AcOEt/iso-hexano: 1/1), dio el éster metílico del ácido 3-(3-hidroxi-propoxi)-5-(2-oxo-pirrolidin-1-il)-benzoico (B15) (260 mg, 69%, 2 pasos). $[M+H]^+ = 294.0$

Ester 17

Ester metílico del ácido 3-(3-metoxi-propoxi)-5-(2-oxo-pirrolidin-1-il)-benzoico (B17)

El éster metílico del ácido 3-(3-hidroxi-propoxi)-5-(2-oxo-pirrolidin-1-il)-benzoico (B15) (127 mg, 0.43 mmol, 1 eq.) en CH_2Cl_2 (2 ml), se trató con esponja de protón (279 mg, 1.30 mmol, 3 eq.) y tetrafluoroborato de trimetiloxonio (192 mg, 1.30 mmol, 3 eq.). Después de 3 h, se le agregó más esponja de protón (93 mg, 0.43 mmol, 1 eq.) y tetrafluoroborato de trimetiloxonio (65 mg, 0.43 mmol, 1 eq.) y la agitación se continuó 2 h más. La mezcla se dividió después entre AcOEt y solución acuosa de HCl 2N. Las dos capas se separaron y la fase acuosa se extrajo con AcOEt. La capa orgánica combinada se lavó con una solución acuosa saturada de $NaHCO_3$, solución acuosa de HCl 2N y salmuera, y después se secó sobre $Na2SO_4$ y se concentró al vacío. La purificación por cromatografía de vaporización instantánea sobre gel de sílice (acetato de etilo/iso-hexano: 1/4 a 1/3), dio el

éster metílico del ácido 3-(3-metoxi-propoxi)-5-(2-oxo-pirrolidin-1-il)-benzoico (B17) (76 mg, 58%). $[M+H]^+ = 308.1$

Ester 18

Ester metílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-etoxi-benzoico (B18)

El éster metílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-hidroxi-benzoico (D41) (0.80 g, 3.0 mmol, 1 eq.) se disolvió en DMF (10 ml) y se le agregó K_2CO_3 (0.94 g, 6.8 mmol, 2 eq.) y yoduro de etilo (1.1g, 6.8 mmol, 2 eq.); la mezcla resultante se calentó a 50 °C durante 4 h; después se enfrió a temperatura ambiente y se diluyó con solución acuosa de HCl 2N (50 ml). La fase acuosa se extrajo con Et_2O (50 ml). La fase orgánica se lavó con H_2O (50 ml), se secó sobre $MgSO_4$ y se concentró al vacío. La purificación por cromatografía de vaporización instantánea sobre gel de sílice (AcOEt/iso-hexano: 1/1), dio el éster metílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-etoxi-benzoico (B18) (220 mg, 25%) como un aceite amarillo claro.

Ester 18 (Procedimiento alternativo)

Ester metílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-etoxi-benzoico (B18)

Una solución de éster metílico del ácido 3-(3-cloro-propano-1-sulfonilamino)-5-etoxi-benzoico (D53) (6.7 g, 20 mmol, 1 eq.) en EtOH (100 ml), se trató con NEt_3 (4.0 g, 40 mmol, 2 eq.). La mezcla resultante se puso

en reflujo durante 4 h, se enfrió a temperatura ambiente y se concentró al vacío. El residuo se disolvió en AcOEt (200 ml), y la solución resultante se lavó con una solución acuosa de HCl 2N (100 ml), seguido por solución acuosa saturada de $NaHCO_3$ (100 ml); después se secó sobre $MgSO_4$ y se concentró al vacío, para dar un aceite pardo. La cristalización de Et_2O/hexano dio el éster metílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-etoxi-benzoico (B18) (4.7 g, 78%), como un sólido de color canela claro.

Ester 19

Ester metílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-isopropoxi-benzoico (B19)

El éster metílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-hidroxi-benzoico (D41) (0.30 g, 1.1 mmol, 1 eq.) se disolvió en DMF (5 ml) y se le agregó K_2CO_3 (0.306 g, 2.2 mmol, 2 eq.) y 2- yodopropano (374 mg, 2.2 mmol, 2 eq.); la mezcla se calentó a 50 °C durante 4 h y después se enfrió a temperatura ambiente y se diluyó con solución acuosa de HCl 2N (50 ml). La fase acuosa se extrajo con Et_2O (50 ml) y la fase orgánica se lavó con H_2O (50 ml), se secó sobre $MgSO_4$ y se concentró al vacío, para dar el éster metílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-isopropoxi-benzoico (B19) (290 mg, 88%), como un aceite amarillo claro.

Los siguientes ésteres se prepararon de la descripción 41, de manera análoga al procedimiento descrito para el éster 19, usando los reactivos apropiados disponibles comercialmente:

Ester
Ester metílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-metoxi-benzoico (B20)
Ester metílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-propoxi-benzoico (B21)
Ester metílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-pentiloxi-benzoico (B22)

Los siguientes ésteres se prepararon de manera análoga al procedimiento de la descripción 30, a partir del bromuro de arilo y amina apropiados indicados en el cuadro siguiente:

Ester	Bromuro de arilo	Amina	$[M+H]^+$	t.r. (min)
Ester metílico del ácido 3-(2-oxo-pirrolidin-1-il)-5-pirrolidin-1-il-benzoico (B113)	D9a		289.1	3.03
Ester metílico del ácido 3-morfolin-4-il-5-(2-oxo-pirrolidin-1-il)-benzoico (B29)	D9a		305.0	2.59
Ester metílico del ácido 3-(4-metil-piperazin-1-il)-5-(2-oxo-pirrolidin-1-il)-benzoico (B115)	D9a		318.1	1.91
Ester metílico del ácido 3-(2-oxo-pirrolidin-1-il)-5-piperidin-1-il-benzoico (B28)	D9a		303.1	2.93
Ester metílico del ácido 3-(2-oxo-piperidin-1-il)-5-pirrolidin-1-il-benzoico (B54)	D10		345.2	3.35

Ester	Bromuro de arilo	Amina	$[M+H]^+$	t.r. (min)
Ester metílico del ácido 3-morfolin-4-il-5-(2-oxo-piperidin-1-il)-benzoico (B56)	D10		361.2	2.95
Ester metílico del ácido 3-(2-oxo-piperidin-1-il)-5-piperidin-1-il-benzoico (B55)	D10		359.2	3.35
Ester metílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-pirrolidin-1-il-benzoico (B114)	D17		67.1	3.43
Ester metílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-morfolin-4-il-benzoico (B61)	D17		383.1	3.04

Ester 24

Ester metílico del ácido 3,5-bis-(2-oxo-pirrolidin-1-il)benzoico (B24)

A una solución de éster metílico del ácido 3-bromo-5-yodobenzoico (D8a) (588 mg, 1.72 mmol, 1.5 eq.) en dioxano (10 ml) se le agregó pirrolidin-2-ona (120 µl, 1.14 mmol, 1 eq.), Cs_2CO_3 (720 mg, 2.21 mmol, 2 eq.), Xantphos (51 mg, 0.09 mmol, 0.08 eq.) y tris(dibencilidenacetona)dipaladio (0) (28 mg, 0.03 mmol, 0.026 eq.). La mezcla de reacción se agitó a 100 °C durante 16 h y después se enfrió a temperatura ambiente; se filtró a través de una almohadilla de celite y se

concentró al vacío. La purificación por cromatografía en columna sobre gel de sílice (EtOAc) produjo el éster metílico del ácido 3,5-bis-(2-oxo-pirrolidin-1-il)benzoico (B24) (411 mg, 79%), como un sólido amarillo claro. $[M+H]^+$ = 303.2.

Los siguientes ésteres se prepararon de manera análoga al éster 23, a partir de las materias primas apropiadas indicadas en el cuadro siguiente:

Ester	Precursor
Ester metílico del ácido 4-cloro-3,5-bis-(2-oxo-pirrolidin-1-il)-benzoico (B25)	D28a
Ester metílico del ácido 4-metoxi-3,5-bis-(2-oxo-pirrolidin-1-il)-benzoico (B26)	D28b

Ester 27

Ester metílico del ácido 3-nitro-5-(2-oxo-pirrolidin-1-il)-benzoico (B27)

A una solución de éster metílico del ácido 3-(4-cloro-butanoilamino)-5-nitro-benzoico (D2) (56 g, 186 mmol, 1 eq.) en THF (500 ml), bajo nitrógeno, se le agregó en porciones NaH (60% p/p, en aceite mineral, 8 g, 200 mmol, 1.07 eq.) durante 10 min. La mezcla resultante se agitó a temperatura ambiente durante 1 h y después se enfrió a 0 °C, y se le agregó a gotas MeOH hasta que terminó el burbujeo. La solución se concentró al vacío y el residuo se diluyó con AcOEt. La fase orgánica se lavó con H_2O, se secó sobre $MgSO_4$ y se concentró al vacío. El residuo se trituró con iso-hexano para dar el éster metílico del ácido 3-nitro-5-(2-oxo-pirrolidin-1-il)-benzoico

(B27) (38.5 g, 78%), como un sólido de color canela claro.

Ester 30

Ester metílico del ácido 3-(2-oxo-pirrolidin-1-il)-5-fenilamino-benzoico (B30)

Un matraz se cargó bajo nitrógeno con éster metílico del ácido 3-bromo-5-(2-oxo-pirrolidin-1-il)-benzoico (D9a) (298 mg, 1 mmol, 1 eq.), Cs_2CO_3 (488 mg, 1.5 mmol, 1.5 eq.), tris(dibencilidenacetona)dipaladio (0) (18.3 mg, 0.02 mmol, 0.02 eq.), 2-(di-*ter*-butilfosfino)bifenilo (18 mg, 0.06 mmol, 0.06 eq.) y DME (8 ml). Después se le agregó anilina (136, µl, 1.5 mmol, 1.5 eq.) por medio de una jeringa y la mezcla resultante se agitó a 100 °C durante 16 h; después se enfrió a temperatura ambiente, se diluyó con H_2O y AcOEt. Las capas se separaron y la fase acuosa se extrajo con AcOEt. La fase orgánica combinada se secó sobre $MgSO_4$ y se concentró al vacío. La purificación del residuo por cromatografía de vaporización instantánea sobre gel de sílice (iso-hexano/AcOEt: 3/1 a 1/1), dio el éster metílico del ácido 3-(2-oxo-pirrolidin-1-il)-5-fenilamino-benzoico (B30) (100 mg, 32%), como un sólido blanco. $[M+H]^+$ = 311.0, t.r. = 3.14 min

Ester 31

Ester *ter*-butílico del ácido 3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzoico (B31)

Un matraz se cargó con éster *ter*-butílico del ácido (bencil-etil-

amino)-2-oxo-pirrolidin-1-il)-benzoico (D30) (3 g, 7.6 mmol, 1 eq.), Pd 10% sobre carbón (50% en húmedo, 600 mg, 10% p/p), NH_4COOH (4.8 g, 76 mmol, 10 eq.), MeOH (30 ml) y H_2O (50 ml). La mezcla resultante se agitó a 50°C durante 16 h, se enfrió a temperatura ambiente y el catalizador se separó por filtración usando una almohadilla de celite. La mayor parte del MeOH se removió al vacío y el residuo se diluyó con solución acuosa saturada de $NaHCO_3$. La fase acuosa se extrajo dos veces con AcOEt. La fase orgánica combinada se secó sobre $MgSO_4$ y se concentró al vacío para dar el éster *ter*-butílico del ácido 3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzoico (B31) (2.2 g, 95%), como un aceite amarillo. $[M+H]^+$ = 305.2, t.r. = 3.11 min

Los siguientes ésteres se prepararon de manera análoga al procedimiento descrito para el éster 31 (B31) a partir del precursor de bencilanilina apropiado, indicado en el cuadro siguiente:

Ester	Precursor	$[M+H]^+$	t.r. (min)
Ester *ter*-butílico del ácido 3-metilamino-5-(2-oxo-pirrolidin-1-il)-benzoico (B32)	D31	291.1	2.96
Ester *ter*-butílico del ácido 3-metilamino-5-(2-oxo-piperidin-1-il)-benzoico (B57)	D32	249.1 (-*t*Bu)	2.91
Ester *ter*-butílico del ácido 3-etilamino-5-(2-oxo-piperidin-1-il)-benzoico (B59)	D33	319.2	3.10
Ester *ter*-butílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-metilamino- benzoico (B62)	D34		
éster *ter*-butílico del ácido 3-(1,1-dioxo-1λ^6-[1,2]tiazinan-2-il)-5-etilamino-benzoico (B73)	D35	355.2	3.32

Ester 33

Ester metílico del ácido dietilamino-(2-oxo-pirrolidin-1-il)-benzoico (B33)

A una solución de éster metílico del ácido 3-amino-5-(2-oxo-pirrolidin-1-il)-benzoico (D4a) (100 mg, 0.43 mmol, 1 eq.) en $(CH_2Cl)_2$ (1.5 ml), se le agregó acetaldehído (0.072 ml, 1.29 mmol, 3 eq.) y triacetoxiborohidruro de sodio (273 mg, 1.29 mmol, 3 eq.). La solución resultante se agitó a temperatura ambiente durante 1 h, se diluyó con AcOEt (20 ml) y se lavó con una solución acuosa 2N de NaOH (20 ml); se secó sobre $MgSO_4$ y se concentró al vacío, para dar el éster metílico del ácido dietilamino-(2-oxo-pirrolidin-1-il)-benzoico (B33) (110 mg, 98%), como un aceite amarillo claro.

Los siguientes ésteres se prepararon de manera análoga al procedimiento descrito para el éster 33 (B33), usando el aldehído apropiado y la anilina apropiada indicada en el cuadro siguiente:

Ester	Anilina	$[M+H]^+$	t.r. (min)
Ester metílico del ácido dimetilamino-(2-oxo-pirrolidin-1-il)-benzoico (B34)	D4a	263.0	2.63
Ester metílico del ácido dietilamino-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-benzoico (B63)	D16	327.0	2.96
Ester metílico del ácido dietilamino-(2-oxo-piperidin-1-il)-benzoico (B60)	D4b		

Ester 35

Ester metílico del ácido 3-(2-oxo-pirrolidin-1-il)-5-propilamino-benzoico (B35)

A una solución de éster metílico del ácido 3-amino-5-(2-oxo-

pirrolidin-1-il)-benzoico (D4a) (500 mg, 2,14 mmol, 1 eq.) en $(CH_2Cl)_2$ (10 ml), se le agregó triacetoxiborohidruro de sodio (640 mg, 3.02 mmol, 1.4 eq.), propionaldehído (0.156 ml, 2.14 mmol, 1 eq.) y CH_3COOH (0.125 ml, 2.18 mmol, 1.02 eq.). La mezcla resultante se agitó a temperatura ambiente durante 2 h, se diluyó con CH_2Cl_2 (20 ml) y se lavó con una solución acuosa saturada de $NaHCO_3$ (20 ml); se secó sobre $MgSO_4$ y se concentró al vacío. La purificación del residuo por cromatografía de vaporización instantánea sobre gel de sílice (iso-hexano/AcOEt: 3/2), dio el éster metílico del ácido 3-(2-oxo-pirrolidin-1-il)-5-propilamino-benzoico (B35) (250 mg, 42%), como un aceite incoloro.

Los siguientes ésteres se obtuvieron de manera análoga al procedimiento que se describe para el éster 35 (B35), usando el aldehído apropiado y la anilina apropiada indicada en el cuadro siguiente:

Ester	Anilina	$[M+H]^+$	t.r. (min)
Ester metílico del ácido 3-bencilamino-5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-benzoico (B64)	D16		
Ester metílico del ácido 3-butilamino-5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-benzoico (B65)	D16	327.0	3.10
Ester metílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-(3-metil-butilamino)-benzoico (B66)	D16	341.1	3.26
Ester metílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-fenetilamino-benzoico (B67)	D16	375.0	3.23
Ester metílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-pentilamino-benzoico (B68)	D16	341.1	3.29
Ester metílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-propilamino-benzoico (B69)	D16	313.0	2.90
Ester metílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-etilamino-benzoico (B70)	D16	299.0	2.91
Ester metílico del ácido 3-(ciclopropilmetil-amino)-5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-benzoico (B71)	D16	325.0	2.91

Ester	Anilina	$[M+H]^+$	t.r. (min)
Ester metílico del ácido 3-isobutilamino-5-(2-oxo-pirrolidin-1-il)-benzoico (B36)	D4a	291.1	3.03
Ester metílico del ácido 3-bencilamino-5-(2-oxo-pirrolidin-1-il)-benzoico (B37)	D4a		
Ester metílico del ácido 3-(3-metil-butilamino)-5-(2-oxo-pirrolidin-1-il)-benzoico (B38)	D4a		
Ester metílico del ácido 3-(2-oxo-pirrolidin-1-il)-5-pentilamino-benzoico (B39)	D4a		
Ester metílico del ácido 3-butilamino-5-(2-oxo-pirrolidin-1-il)-benzoico (B40)	D4a		
Ester metílico del ácido 3-(2,2-dimetil-propilamino)-5-(2-oxo-pirrolidin-1-il)-benzoico (B41)	D4a	305.0	3.22
Ester metílico del ácido 3-(ciclopropilmetil-amino)-5-(2-oxo-pirrolidin-1-il)-benzoico (B42)	D4a		
Ester metílico del ácido 3-(2-oxo-piperidin-1-il)-5-propilamino-benzoico (B58)	D4b		

Ester 43

Ester metílico del ácido 3-(1-etil-propilamino)-5-(2-oxo-pirrolidin-1-il)-benzoico (B43)

A una solución de éster metílico del ácido 3-amino-5-(2-oxo-pirrolidin-1-il)-benzoico (D4a) (200 mg, 0.87 mmol, 1 eq.) en $(CH_2Cl)_2$ (5 ml), se le agregó triacetoxiborohidruro de sodio (1.536 g, 5.22 mmol, 6 eq.), 3-pentanona (0.546 ml, 5.22 mmol, 6 eq.) y AcOH (0.050 ml, 0.87 mmol, 1 eq.). La mezcla resultante se agitó a temperatura ambiente durante 48 h, se diluyó con CH_2Cl_2 (20 ml) y se lavó con una solución acuosa saturada de $NaHCO_3$ (20 ml); se secó sobre $MgSO_4$ y se concentró al vacío. La purificación del residuo por cromatografía de vaporización instantánea sobre gel de sílice (isohexano/AcOH: 3/2), dio el éster metílico del ácido 3-(1-etil-propilamino)-5-(2-

oxo-pirrolidin-1-il)-benzoico (B43) (106 mg, 40%) como un aceite incoloro. $[M+H]^+$ = 305.0, t.r. = 3.19.

Los siguientes ésteres se obtuvieron de manera análoga al éster 43 (B43), usando la cetona apropiada y la anilina apropiada indicada en el cuadro siguiente:

Ester	Anilina	$[M+H]^+$	t.r. (min)
Ester metílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-isopropilamino-benzoico (B72)	D16	313.0	2.82
Ester metílico del ácido 3-isopropilamino-5-(2-oxo-pirrolidin-1-il)-benzoico (B44)	D4a	227.0	2.75
Ester metílico del ácido 3-ciclopentilamino-5-(2-oxo-pirrolidin-1-il)-benzoico (B45)	D4a		
Ester metílico del ácido 3-ciclohexilamino-5-(2-oxo-pirrolidin-1-il)-benzoico (B46)	D4a		

Ester 47

Ester *ter*-butílico del ácido (acetil-metil-amino)-(etil-propionil-amino)-benzoico (B47)

A una solución de éster *ter*-butílico del ácido 3-metilamino-5-(2-oxo-pirrolidin-1-il)-benzoico (B32) (200 mg, 0.69 mmol, 1 eq.) en CH_2Cl_2 (5 ml), se le agregó NEt_3 (278 µl, 2 mmol, 2.9 eq.) y anhídrido acético (195 µl, 2 mmol, 2.9 eq.). La mezcla resultante se agitó a temperatura ambiente durante 16h, se diluyó con CH_2Cl_2, y se lavó con una solución acuosa saturada de $NaHCO_3$; se secó sobre $MgSO_4$ y se concentró al vacío, para dar el éster *ter*-butílico del ácido (acetil-metil-amino)-(etil-propionil-amino)-benzoico (B47) (203 mg, 89%), como un aceite amarillo claro que se usó en el siguiente paso

sin mayor purificación. $[M+H]^+$ = 333.1, t.r. = 2.76 min.

Los siguientes ésteres se prepararon de manera análoga al procedimiento que se describe para el éster 47, a partir de la amina apropiada:

Ester	Amina
Ester metílico del ácido (acetil-propil-amino)-(2-oxo-pirrolidin-1-il)-benzoico (B48)	B35
Ester metílico del ácido acetil-isopropil-amino)-(2-oxo-pirrolidin-1-il)-benzoico (B49)	B44

Ester 50

Ester metílico del ácido 3-acetilamino-5-(2-oxo-pirrolidin-1-il)-benzoico (B50)

A una solución de éster metílico del ácido 3-amino-5-(2-oxo-pirrolidin-1-il)-benzoico (D4a) (80 mg, 0.34 mmol, 1 eq.) en CH_2Cl_2 (10 ml), se le agregó NEt_3 (0.142 ml, 1.02 mmol, 2 eq.) y anhídrido acético (0.078 ml, 0.82 mmol, 2.4 eq.). La mezcla resultante se agitó a temperatura ambiente durante 16h. La reacción se diluyó entonces con AcOEt (20 ml), se lavó con una solución acuosa de HCl 2N (20ml), se secó sobre $MgSO_4$, y se concentró al vacío para dar el éster metílico del ácido 3-acetilamino-5-(2-oxo-pirrolidin-1-il)-benzoico (B50) (67 mg, 71%), como una espuma de color amarillo claro.

Ester 51

Ester *ter*-butílico del ácido (metanosulfonil-metil-amino)-(2-oxo-pirrolidin-1-il)-benzoico (B51)

A una solución de éster *ter*-butílico del ácido 3-metilamino-5-(2-oxo-pirrolidin-1-il)-benzoico (B32) (200 mg, 0.69 mmol, 1 eq.) en CH_2Cl_2 (5 ml), se le agregó NEt_3 (278111, 2 mmol, 2.9 eq.) y cloruro de metanosulfonilo (162 µl, 2 mmol, 2.9 eq.). La mezcla resultante se agitó a temperatura ambiente durante 16 h, se diluyó con CH_2Cl_2, y se lavó con una solución acuosa saturada de $NaHCO_3$; se secó sobre $MgSO_4$ y se concentró al vacío, para dar el éster *ter*-butílico del ácido (metanosulfonil-metil-amino)-(2-oxo-pirrolidin-1-il)-benzoico (B51) (203 mg, 89%), como un aceite amarillo claro. $[M+H]^+$ = 313.0, t.r. = 2.95 min.

Ester 52

Ester metílico del ácido (metanosulfonil-propil-amino)-(2-oxo-pirrolidin-1-il)-benzoico (B52)

El éster 52 se preparó de éster metílico del ácido 3-(2-oxo-pirrolidin-1-il)-5-propilamino-benzoico (B35), de manera análoga a la descrita para el éster 51 (B51).

Ester 53

Ester metílico del ácido 3-metanosulfonilamino-5-(2-oxo-pirrolidin-1-il)-benzoico (B53)

A una solución de éster metílico del ácido 3-amino-5-(2-oxo-pirrolidin-1-il)-benzoico (D4a) (200 mg, 0.85 mmol, 1 eq.) en CH_2Cl_2 (5 ml) y DMF (5 ml), se le agregó NEt_3 (0.181 ml, 1.3 mmol, 1.5 eq.) y cloruro de metanosulfonilo (0.071 ml, 1 mmol, 1.2 eq.). La mezcla resultante se agitó a temperatura ambiente durante 1 h, se diluyó con AcOEt (30 ml) y se lavó con una solución acuosa de HCl 2N (30 ml); se secó sobre $MgSO_4$ y se concentró al vacío. El residuo se trituró con Et_2O y después se filtró para dar el éster metílico del ácido 3-metanosulfonilamino-5-(2-oxo-pirrolidin-1-il)-benzoico (B53), como un sólido amarillo claro (100 mg, 38%).

Ester 74

Ester 3-metílico 1-*ter*-butílico del ácido 5-(2-oxo-pirrolidin-1-il)-isoftálico (B74)

Una solución de éster 1-*ter*-butílico éster 3-metílico (D80) (4.5 g, 12.7 mmol, 1 eq.) en THF (60 ml), se trató en porciones con NaH (60%, suspensión en aceite mineral, 560 mg, 14 mmol, 1.1 eq.) durante 5 min a temperatura ambiente. La mezcla resultante se agitó durante 1 h, después se le agregó MeOH (5 ml) y la mezcla se concentró al vacío. El residuo se diluyó con AcOEt (200 ml) y la fase orgánica se lavó con H_2O (100 ml), se secó sobre $MgSO_4$ y se concentró al vacío, para dar el éster 1-*ter*-butílico éster 3-

metílico de ácido 5-(2-oxo-pirrolidin-1-il)-isoftálico (B74) (3.9 g, 97%), como un sólido blanco.

Ester 76

Ester metílico del ácido 3-hidroximetil-5-(2-oxo-pirrolidin-1-il)-benzoico (B76)

Una suspensión de éster monometílico del ácido 5-(2-oxo-pirrolidin-1-il)-isoftálico (A75) (200 mg, 0.76 mmol, 1 eq.) en THF (20 ml), se enfrió a 0 °C y se trató con BH_3-Me_2S (solución 2M en THF, 0.64 ml, 1.28 mmol, 1.3 eq.). La mezcla resultante se puso en reflujo durante 1 h y después se enfrió a temperatura ambiente. Se le agregó MeOH (5 ml) y la mezcla resultante se concentró al vacío. El residuo se diluyó con AcOEt (50 ml) y la solución resultante se lavó con una solución acuosa saturada de $NaHCO_3$ (30 ml) y solución acuosa de HCl 2N (30 ml), se secó sobre $MgSO_4$ y se concentró al vacío, para dar el éster metílico del ácido 3-hidroximetil-5-(2-oxo-pirrolidin-1-il)-benzoico (B76) (70 mg, 37%), como un aceite amarillo claro.

Ester 77

Ester metílico del ácido 5-(2-oxo-pirrolidin-1-il)-*N*-propil-isoftalámico (B77)

Una suspensión de éster monometílico del ácido 5-(2-oxo-pirrolidin-1-il)-isoftálico (A75) (200 mg, 76 mmol, 1 eq.) en CH_2C1_2 (20 ml), a temperatura ambiente, se trató con unas gotas de DMF, seguida por $(COCl)_2$

(100 mg, 0.8 mmol, 1.1 eq.). La mezcla resultante se agitó durante 1 h y después se le agregó propilamina (140 mg, 2.4 mmol, 3.3 eq.); la solución resultante se agitó durante 30 min. La solución se lavó entonces con solución acuosa de HCl 2N (30 ml) y solución acuosa saturada de $NaHCO_3$ (30 ml); se secó sobre $MgSO_4$ y se concentró al vacío, para dar el éster metílico del ácido 5-(2-oxo-pirrolidin-1-il)-*N*-propil-isoftalámico (B77) (127 mg, 55%), como un sólido ceroso cremoso.

Los siguientes compuestos se prepararon de manera análoga a la que se describe para el éster 77, a partir de éster monometílico del ácido 5-(2-oxo-pirrolidin-1-il)-isoftálico (A75) y la amina apropiada:

Ester
Ester metílico del ácido *N,N*-dimetil-5-(2-oxo-pirrolidin-1-il)-isoftalámico (B78)
Ester metílico del ácido *N*-metil-5-(2-oxo-pirrolidin-1-il)-isoftalámico (B79)

Ester 80

Ester metílico del ácido 5-(2-oxo-pirrolidin-1-il)-*N,N*-dipropil-isoftalámico (B80)

Una solución de éster metílico del ácido 5-(4-cloro-butanoilamino)-*N,N*-dipropil-isoftalámico (D89) (1.7 g, 4.4 mmol, 1 eq.) en THF (20 ml), se trató en porciones con NaH (dispersión en aceite mineral, 60%, 180 mg, 4.5 mmol, 1.1 eq.), y la mezcla resultante se agitó durante 1 h y entonces se diluyó con AcOEt (100 ml). La solución resultante se lavó con una solución acuosa de HCl 2N (50 ml), se secó sobre $MgSO_4$ y se concentró

al vacío, para dar el éster metílico del ácido 5-(2-oxo-pirrolidin-1-il)-*N,N*-dipropil-isoftalámico (B80) (1.38 g, 91 %), como un aceite incoloro.

Ester 81

Ester metílico del ácido 5-(2-oxo-piperidin-1-il)-*N,N*-dipropil-isoftalámico (B81)

El éster 81 se preparó de manera análoga al éster 80 a partir de éster metílico del ácido 5-(5-cloro-pentanoilamino)-*N,N*-dipropil-isoftalámico (D90).

Ester 82

Ester metílico del ácido 3-nitro-5-(2-oxo-piperidin-1-il)-benzoico (B82)

Se agregó en porciones NaH (60% p/p en aceite mineral, 680 mg, 17 mmol, 0.9 eq.) a una solución de éster metílico del ácido 3-(5-cloro-pentanoilamino)-5-nitro-benzoico (D3) (6 g, 19 mmol, 1 eq.) en THF (40 ml), bajo nitrógeno. La mezcla resultante se agitó a temperatura ambiente durante 1 h y después se le agregó a gotas MeOH. La solución se concentró al vacío y el residuo se diluyó con AcOEt. La fase orgánica se lavó con H_2O, se secó sobre $MgSO_4$ y se concentró al vacío. La purificación por cromatografía de vaporización instantánea sobre gel de sílice (AcOEt/iso-hexano: 1/2), dio el éster metílico del ácido 3-nitro-5-(2-oxo-piperidin-1-il)-benzoico (B82) (2.8 g, 53%), como un aceite naranja claro.

Ester 83

Ester metílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-fluorometil-benzoico (B83)

Una solución de éster metílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-hidroximetil-benzoico (D84) (400 mg, 1.4 mmol, 1 eq.) en CH_2Cl_2 (40 ml), a 0 °C, se trató con trifluoruro de (dietilamino)azufre (240 mg, 1.5 mmol, 1.1 eq.). La mezcla se agitó a 0 °C durante 1 h y después se dejó calentar a temperatura ambiente. La solución se lavó con una solución acuosa de HCl 2N (40 ml), se secó sobre $MgSO_4$ y se concentró al vacío, para dar el éster metílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-fluorometil-benzoico (B83) (250 mg, 62%), como un sólido blanco.

Ester 84

Ester metílico del ácido 3-dimetilaminometil-5-(dioxo-1λ^6-isotiazolidin-2-il)-benzoico (B84)

Una solución de éster metílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-metanosulfoniloximetil-benzoico (D85) (200 mg, 0.55 mmol, 1 eq.) en EtOH (3 ml), se trató con dimetilamina (33% en EtOH, 3 ml, exceso). La mezcla resultante se agitó durante 15 min y después se concentró al vacío y se reevaporó con tolueno (5 ml). El residuo se disolvió en AcOEt (50 ml) y la solución resultante se lavó con una solución acuosa saturada de $NaHCO_3$ (50 ml), se secó sobre $MgSO_4$ y se concentró al vacío, para dar el éster metílico del ácido 3-dimetilaminometil-5-(dioxo-1λ^6-isotiazolidin-2-il)-benzoico (B84)

(170 mg, 99%), como un sólido ceroso amarillo.

Ester 85

Ester metílico del ácido 3-azidometil-5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-benzoico (B85)

Una solución de éster metílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-metanosulfoniloximetil-benzoico (D85) (200 mg, 0.55 mmol, 1 eq.) en DMF (2 ml), se trató con NaN_3 (39 mg, 0.6 mmol, 1.1 eq.), y la mezcla resultante se agitó durante 1 h a temperatura ambiente, entonces se diluyó con AcOEt (50 ml). La solución resultante se lavó secuencialmente con solución acuosa de HCl 2N (30 ml), solución acuosa saturada de $NaHCO_3$ (30 ml) y H_2O (50 ml), se secó sobre $MgSO_4$ y se concentró al vacío, para dar el éster metílico del ácido 3-azidometil-5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-benzoico (B85), como un sólido blanco (129 mg, 76%).

Ester 89

Ester metílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-(Z)-propenil-benzoico (B89)

Una suspensión de bromuro de (etil)trifenilfosfonio (371 mg, 1.0 mmol, 1.4 eq.) en THF (20 ml) se trató con KOtBu (112 mg, 1.0 mmol, 1.4 eq.), y la mezcla resultante se agitó durante 15 min a temperatura ambiente. Se le agregó una solución de éster metílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-formil-benzoico (D86) (200 mg, 0.7 mmol, 1 eq.) en THF

(10 ml), y la mezcla resultante se agitó durante 1 h a temperatura ambiente; después se diluyó con AcOEt (100 ml). La solución resultante se lavó con una solución acuosa de HCl 2N (100 ml), se secó sobre $MgSO_4$ y se concentró al vacío. La purificación por cromatografía de vaporización instantánea sobre gel de sílice (EtOAc/iso-hexano: 1/1), dio el éster metílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-(E/Z)-propenil-benzoico (B89) (135 mg, 65%) como un aceite incoloro.

Los siguientes compuestos se prepararon de manera análoga al procedimiento descrito para el éster 89, a partir de éster metílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-formil-benzoico (D86) y la materia prima apropiada disponible comercialmente:

Ester
Ester metílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-vinil-benzoico (B88)
Ester metílico del ácido (Z/E)-but-1-enil-(etanosulfonil-etil-amino)-benzoico (B90)
Ester metílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-(2-metil-propenil)-benzoico (B91)

Ester 92

Ester metílico del ácido 5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-isoftalámico (B92)

Una suspensión de éster monometílico del ácido 5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-isoftálico (D83) (750 mg, 2.5 mmol, 1 eq.) en CH_2Cl_2 (30 ml), se trató con $(COCl)_2$ 2M en CH_2Cl_2 (1.5 ml, 3.0 mmol, 1.2 eq.), seguido por unas gotas de DMF. La mezcla resultante se agitó durante 30 min y

después se le agregó amoniaco acuoso al 32% (5 ml, exceso). La mezcla resultante se agitó durante 15 min y entonces se diluyó con CH_2Cl_2 (50 ml) y se lavó con una solución acuosa de HCl 2N (50 ml). El precipitado blanco resultante se filtró para dar el éster metílico del ácido 5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-isoftalámico B92 (650 mg, 87%), como un sólido blanco.

Ester 93

Ester metílico del ácido 3-ciano-5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-benzoico (B93)

Una suspensión de éster metílico del ácido 5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-isoftalámico (B92) (500 mg, 1.68 mmol, 1 eq.) en CH_2Cl_2 (100 ml), se trató con NEt_3 (404 mg, 4.0 mmol, 2.4 eq.) y anhídrido trifluoroacético (378 mg, 1.8 mmol, 1.1 eq.). La mezcla resultante se agitó durante 1 h a temperatura ambiente y después se trató con porciones adicionales de NEt_3 (404 mg, 4.0 mmol, 2.4 eq.) y anhídrido trifluoroacético (378 mg, 1.8 mmol, 1.1 eq.), y se agitó otros 45 min. La solución resultante se lavó con una solución acuosa de HCl 2N (50 ml) y solución acuosa saturada de $NaHCO_3$ (50 ml), se secó sobre $MgSO_4$, y se concentró al vacío. El residuo se trituró con Et_2O para dar el éster metílico del ácido 3-ciano-5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-benzoico (B93) (350 mg, 75%), como un sólido blanco.

Ester 94

Ester metílico del ácido 5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-*N,N*-dipropil-isoftalámico (B94)

Una solución de éster metílico del ácido 5-(3-cloro-propano-1-sulfonilamino)-*N,N*-dipropil-isoftalámico (D91) (1.7 g, 4.0 mmol, 1 eq.) en EtOH (20 ml), se trató con NEt_3 (799 mg, 7.9 mmol, 2 eq.), y la mezcla se puso en reflujo durante 3 h; después se enfrió a temperatura ambiente y se concentró al vacío. El residuo se disolvió en AcOEt (100 ml) y la fase orgánica se lavó con una solución acuosa de HCl 2N (50 ml), se secó sobre $MgSO_4$ y se concentró al vacío. El residuo se trituró con Et_2O para dar el éster metílico del ácido 5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-*N,N*-dipropil-isoftalámico (B94) (1.2 g, 78%), como un sólido blanco.

Ester 95

Ester metílico del ácido 5-(1,1-dioxo-1λ^6-[1,2]-tiazinan-2-il)-*N,N*-dipropil-isoftalámico (B95)

El éster 95 se preparó de manera análoga al éster 94 a partir de éster metílico del ácido 5-(4-cloro-butano-1-sulfonilamino)-*N,N*-dipropil-isoftalámico (D92).

1600
A03

Ester 100

Ester metílico del ácido fluoro-(2-oxo-pirrolidin-1-il)-trifluorometil-benzoico (B100)

El éster metílico del ácido 3-bromo-2-fluoro-5-trifluorometilbenzoico (D29a) (500 mg, 1.95 mmol, 1 eq.), Cs_2CO_3 (950 mg, 2.92 mmol, 1.5 eq.), pirrolidin-2-ona (248 mg, 2.92 mmol, 1.5 eq.), Xantphos (68 mg, 0.117 mmol, 0.06 eq.) y tris(dibencilidenacetona)dipaladio (0) (36 mg, 0.039 mmol, 0.02 eq.), se pusieron en reflujo bajo argón en dioxano (7 ml) durante 18h. Después de enfriar, la mezcla se filtró y se evaporó al vacío. La purificación por cromatografía de vaporización instantánea sobre gel de sílice (AcOEt/iso-hexano: 1/4 a 1/2), dio el éster metílico del ácido fluoro-(2-oxo-pirrolidin-1-il)-trifluorometil-benzoico (B100) (195 mg, 32%). $[M+H]^+$ 306.2.

Los siguientes compuestos (ésteres 101-102) se prepararon de manera análoga a la descripción 68 a partir del bromuro de arilo apropiado indicado en el cuadro siguiente, usando el complejo de 2,4,6-trialquenilciclotriboroxano-piridina apropiado, como lo describen F. Kerins y D. F. O'Shea, en *J. Org. Chem*, 2002, 67, 4968-4971:

Descripción	Bromuro de arilo	$[M+H]^+$	t.r. (min)
Ester metílico del ácido 3-(2-metil-propenil)-5-(2-oxo-pirrolidin-1-il)benzoico (B101)	D9a	274.1	3.14
Ester metílico del ácido 3-(2-oxo-pirrolidin-1-il)-5-((E)-estiril)-benzoico (B102)	D9a		

Los siguientes compuestos se prepararon de manera análoga al procedimiento descrito para éster *ter*-butílico del ácido 3-(2-oxo-piperidin-1-il)-

5-propil-benzoico (B116):

Ester	Alqueno	$[M+H]^+$	t.r. (min)
Ester metílico del ácido 3-isopropil-5-(2-oxo-pirrolidin-1-il)-benzoico (B104)	D71	248.1	2.77
Ester metílico del ácido 3-(2-oxo-pirrolidin-1-il)-5-propil-benzoico B106	D72	262.1	3.04
Ester metílico del ácido 3-ciclopentil-5-(2-oxo-pirrolidin-1-il)-benzoico (B107)	D74	288.1	3.26
Ester metílico del ácido 3-ciclohexil-5-(2-oxo-pirrolidin-1-il)-benzoico (B108)	D74		
Ester *ter*-butílico del ácido 3-(1,1-dioxo-1λ^6-[1,2]tiazinan-2-il)-5-propil-benzoico (B112)	D69		

Ester 109

Ester *ter*-butílico del ácido 3-etinil-5-(2-oxo-pirrolidin-1-il)-benzoico (B109)

El éster 109 se preparó de manera análoga al procedimiento descrito para el éster 111, de 300 mg (mmol) de éster *ter*-butílico del ácido 3-(3-hidroxi-3-metil-but-1-inil)-5-(2-oxo-pirrolidin-1-il)-benzoico (D76), produciendo 220 mg (88%) del éster *ter*-butílico del ácido 3-etinil-5-(2-oxo-pirrolidin-1-il)-benzoico (B109), como un sólido blanquecino.

Ester 111

Ester *ter*-butílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-etinil-benzoico (B111)

A una solución de éster *ter*-butílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-(3-hidroxi-3-metil-but-1-inil)-benzoico (D75) (142 mg, 0.37

mmol, 1 eq.) en tolueno (20 ml), se le agregó NaH (dispersión en aceite mineral, 60%, 4 mg, 0.1 mmol, 0.3 eq.). La mezcla resultante se agitó a 110°C durante 30 min, se enfrió a temperatura ambiente y se diluyó con AcOEt. La fase orgánica se lavó con una solución acuosa saturada de $NaHCO_3$, se secó sobre $MgSO_4$ y se concentró al vacío, para dar el éster *ter*-butílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-etinil-benzoico (B111) (142 mg, 118%), como un aceite amarillo claro.

Ester 116

Ester *ter*-butílico del ácido 3-(2-oxo-piperidin-1-il)-5-propil-benzoico (B116)

A una solución de éster *ter*-butílico del ácido 3-(2-oxo-piperidin-1-il)-5-(E/Z)-propenil-benzoico (D68) (485 mg, 1.5 mmol, 1 eq.) en EtOH (10 ml) y H_2O (2 ml), se le agregó paladio al 10% sobre carbón (50% en húmedo, 485 mg, 5% p/p) y NH_4COOH (945 mg, 15 mmol, 10 eq.). La mezcla resultante se agitó a 65 °C durante 1h y después se enfrió a temperatura ambiente. La mayor parte del EtOH se removió al vacío y el residuo se disolvió en AcOEt. La fase orgánica se lavó con H_2O, se secó sobre $MgSO_4$ y se concentró al vacío, para dar el éster *ter*-butílico del ácido 3-(2-oxo-piperidin-1-il)-5-propil-benzoico (B116) (300 mg, 70%), como un aceite incoloro.

Ester 117

3-(1,1-Dioxido-6,7-dihidro-1,2-tiazepin-2(3*H*)-il)-5-propilbenzoato de metilo (B117)

A una solución de 3-[(3-buten-1-ilsulfonil)(2-propen-1-il)amino]-5-propilbenzoato de metilo (D135) (1 g, 2.8 mmol, 1 eq.) en CH_2Cl_2 (200 ml), se le agregó dicloruro de bis(triciclohexilfosfino)bencilideno-rutenio (IV) (117 mg, 0.14 mmol, 0.05 eq.), y la solución resultante se agitó a temperatura ambiente durante 48 h; después se concentró al vacío. La purificación del residuo por cromatografía de vaporización instantánea sobre gel de sílice (iso-hexano/AcOEt: 9:1), dio 3-(1,1-dioxido-6,7-dihidro-1,2-tiazepin-2(3*H*)-il)-5-propilbenzoato de metilo (B117) (700 mg, 76%), como un aceite púrpura claro. $[M+H]^+$ = 324.4, t.r. = 3.10 min.

Ester 118

5-(Etilamino)-2-fluoro-3-(2-oxo-1-pirrolidinil)benzoato de metilo (B118)

A una solución de 5-(etil[4-(metiloxi)fenil]metil}amino)-2-fluoro-3-(2-oxo-1-pirrolidinil)benzoato de metilo (D155) (7 g, 17.5 mmol, 1 eq.) en EtOH (150 ml), se le agregó paladio al 10% sobre carbón (50% en húmedo, 1.4 g, 10% p/p), y la mezcla resultante se agitó bajo una atmósfera de hidrógeno (1 atm) durante 3 h. El catalizador se separó por filtración a través de una almohadilla de celite y la solución se concentró al vacío. El residuo se trituró con AcOEt/iso-hexano, para dar 5-(etilamino)-2-fluoro-3-(2-oxo-1-

pirrolidinil)benzoato de metilo (B118) (4.8 g, 98%) como un sólido verdoso claro, que se usó en el siguiente paso sin mayor purificación. $[M+H]^+$ = 281.2, t.r. = 2.35 min.

Los siguientes ésteres se obtuvieron del precursor apropiado de manera análoga al procedimiento descrito para el éster 35 (B35), usando acetaldehído en lugar de propionaldehído.

Ester	Precursor	$[M+H]^+$	t.r.(min)
3-(1,1-Dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-2-fluorobenzoato (B119)	D152	331.2	2.80
3-(1,1-Dioxido-2-isotiazolidinil)-5-(etilamino)-2-fluorobenzoato de metilo (B122)	D151	317.1	2.64
3-(1,1-Dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-2-(metiloxi)benzoato de metilo (B139)	D153	343.2	2.64

Los siguientes compuestos se prepararon de manera análoga al procedimiento descrito para el éster *ter*-butílico del ácido 3-(2-oxo-piperidin-1-il)-5-propil-benzoico (B116), partiendo de su precursor apropiado:

Ester	Precursor	$[M+H]^+$	t.r.(min)
2-Fluoro-3-(2-oxo-1-pirrolidinil)-5-propilbenzoato de metilo (B120)	D159	280.2	2.73
3-(1,1-Dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-2-fluoro-5-propilbenzoato de metilo (B173)	D161	330.2	2.91
3-(1,1-Dioxido-2-isotiazolidinil)-2-fluoro-5-propilbenzoato de metilo (B174)	D160	-	2. 74

Ester 121

3-(2-Oxo-5-fenil-1-piperidinil)-5-propilbenzoato de 1,1-dimetiletilo (B121)

El 3-(2-oxo-5-fenil-1-piperidinil)-5-propilbenzoato de 1,1-dimetiletilo (B121) se preparó de 3-(2-oxo-5-fenil-1-piperidinil)-5-[(1*E/Z*)-1-propen-1-il]benzoato de 1,1-dimetiletilo (D192), de manera análoga al procedimiento descrito para éster *ter*-butílico del ácido 3-(2-oxo-piperidin-1-il)-5-propil-benzoico (B116). $[M+H]^+$ = 394.3, t.r. = 3.88 min.

Ester 123

3-(1,1-Dioxido-4-feniltetrahidro-2*H*-1,2-tiazin-2-il)-5-nitrobenzoato de metilo (B123)

Un matraz se cargó bajo nitrógeno con 3-bromo-5-nitrobenzoato de metilo (D11) (136 mg, 0.52 mmol, 1,1 eq.), Cs_2CO_3 (216 mg, 0.66 mmol, 1.4 eq.), tris(dibencilidenacetona)dipaladio (0) (22 mg, 0.023 mmol, 0.05 eq.), Xantphos (27 mg, 0.047 mmol, 0.1 eq.) y tolueno (10 ml). Después se agregó 1,1-dióxido de 4-feniltetrahidro-2*H*-1,2-tiazina (J. Morris, D. G. Wishka, *J. Org. Chem.* 1991, 56, 3549-3556; 100 mg, 0.47 mmol, 1 eq.), y la mezcla resultante se agitó a 120°C durante 5 h; después se enfrió a temperatura ambiente y se concentró al vacío. El residuo se dividió entre H_2O y AcOEt y la fase acuosa se volvió a extraer con AcOEt. La solución orgánica combinada se secó sobre $MgSO_4$ y se concentró al vacío. La purificación del residuo por cromatografía de vaporización instantánea sobre gel de sílice (iso-hexano/AcOEt: 7/3), dio 3-

(1,1-dioxido-4-feniltetrahidro-2*H*-1,2-tiazin-2-il)-5-nitrobenzoato de metilo (B123) (110 mg, 60%), como un aceite amarillo. $[M+H+NH_3]^+$ = 408.3, t.r. = 3.24 min.

Ester 124

3-Amino-5-(1,1-dioxido-4-feniltetrahidro-2*H*-1,2-tiazin-2-il)benzoato de metilo (B124)

El 3-amino-5-(1,1-dioxido-4-feniltetrahidro-2*H*-1,2-tiazin-2-il)-benzoato de metilo (B124) se obtuvo de 3-(1,1-dioxido-4-feniltetrahidro-2*H*-1,2-tiazin-2-il)-5-nitrobenzoato de metilo (B123), de manera análoga al procedimiento de la descripción 16 (D16). $[M+H]^+$ = 361.3, t.r. = 2.91 min.

Ester 125

3-(1,1-Dioxido-4-feniltetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-benzoato de metilo (B125)

El 3-(1,1-dioxido-4-feniltetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-benzoato de metilo (B125) se obtuvo de 3-amino-5-(1,1-dioxido-4-feniltetrahidro-2*H*-1,2-tiazin-2-il)benzoato de metilo (B124), de manera análoga al procedimiento descrito para el éster 35 (B35), usando acetaldehído en lugar de propionaldehído. $[M+H]^+$ = 389.4, t.r. = 3.23 min.

467
410

Ester 126

3-Ciclopentil-5-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)benzoato de metilo (B126)

El 3-ciclopentil-5-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-benzoato de metilo (B126) se obtuvo de 3-(1-ciclopenten-1-il)-5-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)benzoato de metilo, 3-(2-ciclopenten-1-il)-5-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)benzoato de metilo, y 3-(3-ciclopenten-1-il)-5-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)benzoato de metilo (D265), de manera análoga al procedimiento descrito para el éster 107 (B107).

Ester 127

3-(1,1-Dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-[(1-metiletil)amino]-benzoato de metilo (B127)

El 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-[(1-metiletil)-amino]benzoato de metilo (B127) se obtuvo de 3-amino-5-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)benzoato de metilo (D194), de manera análoga al procedimiento descrito para el éster 35 (B35), usando acetona en lugar de propionaldehído. $[M+H]^+$ = 327.2, t.r. = 2.82 min.

Ester 128

3-[Etil(metil)amino]-5-(2-oxo-1-pirrolidinil)benzoato de 1,1-dimetiletilo (B128)

El 3-[etil(metil)amino]-5-(2-oxo-1-pirrolidinil)benzoato de 1,1-

dimetiletilo (B128) se obtuvo de 3-(metilamino)-5-(2-oxo-1-pirrolidinil)benzoato de 1,1-dimetiletilo (B32), de manera análoga al procedimiento que se describe para el éster 35 (B35), usando acetaldehído en lugar de propionaldehído. $[M+H]^+$ = 319.4, t.r. = 3.17 min.

Los siguientes compuestos se obtuvieron de sus precursores correspondientes de manera análoga al procedimiento descrito para el éster 35 (B35), usando acetaldehído en lugar de propionaldehído y el precursor apropiado indicado en el cuadro siguiente.

Ester	Precursor	$[M+H]^+$	t.r.(min)
3-(Etilamino)-4-metil-5-(2-oxo-1-pirrolidinil)benzoato de metilo (B129)	D184	277.1	2.63
3-(1,1-Dioxido-2-isotiazolidinil)-5-(etilamino)-4-metilbenzoato de metilo (B130)	D186	313.1	2.79
3-(1,1-Dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-4-metilbenzoato de metilo (B131)	D188	327.1	2.93
3-(1,1-Dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-4-(metiloxi)benzoato de metilo (B132)	D187	343.1	2.90
3-(Etilamino)-4-(metiloxi)-5-(2-oxo-1-pirrolidinil)benzoato de metilo (B133)	D183	293.1	2.64
3-(1,1-Dioxido-2-isotiazolidinil)-5-etilamino)-4-(metiloxi)benzoato de metilo (B134)	D185	329.1	2.79

Ester 135

3-(Dietilamino)-5-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-4-metilbenzoato de metilo (B135)

El 3-(dietilamino)-5-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-4-metilbenzoato de metilo (B135) se obtuvo como un subproducto durante la síntesis de 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-4-metil-

409
412

benzoato de metilo (B131) a partir de 3-amino-5-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-4-metilbenzoato de metilo (D188). $[M+H]^+$ = 355.1, t.r. = 2.95 min.

Ester 136

3-(1,1-Dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-4-(metiloxi)-5-[(1*E/Z*)-1-propen-1-il]benzoato de metilo (B136)

A una solución de 3-[[(4-clorobutil)sulfonil]amino]-4-(metiloxi)-5-[(1*E/Z*)-1-propen-1-il]benzoato de metilo (D170) (650 mg, 1.72 mmol, 1 eq.) en EtOH (50 ml), se le agregó NEt_3 (500 µl, 3.6 mmol, 2.1 eq.) y la solución resultante se puso en reflujo durante 6 h; después se enfrió a temperatura ambiente y se concentró al vacío. El residuo se disolvió en AcOEt y la fase orgánica se lavó con una solución acuosa de HCl 2N y una solución acuosa saturada de $NaHCO_3$, se secó sobre $MgSO_4$ y se concentró al vacío. La purificación del residuo por cromatografía de vaporización instantánea sobre gel de sílice (iso-hexano/AcOEt: 3/1), dio 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-4-(metiloxi)-5-[(1*E/Z*)-1-propen-1-il]benzoato de metilo (B136) (450 mg, 77%), como un aceite amarillo claro. $[M+H]^+$ = 340.0, t.r. = 3.14 min.

Ester 138

3-(1,1-Dioxido-2-isotiazolidinil)-5-(2-oxo-1-pirrolidinil)benzoato de metilo (B138)

El 3-(1,1-dioxido-2-isotiazolidinil)-5-(2-oxo-1-pirrolidinil)benzoato de metilo (B138) se obtuvo de 3-[(4-clorobutanoil)amino]-5-(1,1-dioxido-2-

410
413

isotiazolidinil)benzoato de metilo (D195), de manera análoga al procedimiento descrito para el éster 27 (B27). $[M+H]^+$ = 339.0, t.r. = 2.41 min.

Ester 140

1-Etil-4-(2-oxo-1-pirrolidinil)-1*H*-indol-6-carboxilato de metilo (B140)

A una solución de 4-(2-oxo-1-pirrolidinil)-1*H*-indol-6-carboxilato de metilo (B154) (500 mg, 1.94 mmol, 1 eq.) en DMF (10 ml), a temperatura ambiente, se le agregó NaH (dispersión en aceite mineral, 60%, 84 mg, 2.1 mmol, 1.1 eq.), y la mezcla resultante se agitó 15 min. Se le agregó yoduro de etilo (200 µl, 2.5 mmol, 1.3 eq.) y la solución resultante se agitó durante 30 min y después se concentró al vacío. El residuo se disolvió en AcOEt y la fase orgánica se lavó con una solución acuosa de HCl 2N, se secó sobre $MgSO_4$ y se concentró al vacío. La purificación del residuo por cromatografía de vaporización instantánea sobre gel de sílice (AcOEt/iso-hexano: 1/4 a 1/1), dio 1-etil-4-(2-oxo-1-pirrolidinil)-1*H*-indol-6-carboxilato de metilo (B140) (400 mg, 72%), como un sólido blanquecino. $[M+H]^+$ = 287.0, t.r. = 2.73 min.

Los siguientes compuestos se obtuvieron de sus precursores correspondientes de manera análoga al procedimiento de la descripción 2 (D2):

Ester	Precursor	$[M+H]^+$	t.r.(min)
3-Etil-7-(2-oxo-1-pirrolidinil)-1*H*-indol-5-carboxilato de etilo (B141)	D225		
1-Etil-4-(2-oxo-1-pirrolidinil)-1*H*-benzoimidazol-6-carboxilato de metilo (B149)	D227		
1-Etil-4-(2-oxo-1-pirrolidinil)-1*H*-indazol-6-carboxilato de metilo (B152)	D229	288.4	2.20
4-(2-Oxo-1-pirrolidinil)-1*H*-indol-6-carboxilato de metilo (B154)	D228	259.0	2.22
3-Metil-7-(2-oxo-1-pirrolidinil)-1*H*-indol-5-carboxilato de etilo (B160)	D224		
3-(1-Metiletil)-7-(2-oxo-1-pirrolidinil)-1*H*-indol-5-carboxilato de etilo (B161)	D226		
4-Etil-8-(2-oxo-1-pirrolidinil)-1,2,3,4-tetrahidro-6-quinoxalincarboxilato de metilo (B171)	D230	304.3	2.52

Ester 142

3-Etil-1-metil-7-(2-oxo-1-pirrolidinil)-1*H*-indol-5-carboxilato de etilo (B142)

A una solución de 3-etil-7-(2-oxo-1-pirrolidinil)-1*H*-indol-5-carboxilato de etilo (B141) (658 mg, 2.3 mmol, 1 eq.) en DMF (10 ml), a temperatura ambiente, se le agregó NaH (dispersión en aceite mineral, 60%, 120 mg, 3.0 mmol, 1.3 eq.), y la mezcla resultante se agitó 15 min a esta temperatura. Se le agregó yoduro de etilo (187 µl, 3.0 mmol, 1.3 eq.) y la solución resultante se agitó durante 30 min y después se concentró al vacío. El residuo se disolvió en AcOEt y la fase orgánica se lavó con H_2O, se secó sobre $MgSO_4$ y se concentró al vacío. El residuo se trituró con iso-hexano para dar 3-etil-1-metil-7-(2-oxo-1-pirrolidinil)-1*H*-indol-5-carboxilato de etilo (620 mg, 90%) como un sólido amarillo, que se usó en el siguiente paso sin mayor purificación.

Ester 143

4-(1,1-Dioxido-2-isotiazolidinil)-1-etil-1*H*-indol-6-carboxilato de metilo (B143)

A una solución de 4-[[(3-cloropropil)sulfonil]amino]-1-etil-1*H*-indol-6-carboxilato de metilo (D241) (900 mg, 2.5 mmol, 1 eq.) en EtOH (100 ml), se le agregó NEt_3 (1 ml, 7.3 mmol, 3 eq.), y la solución resultante se puso en reflujo durante 1.5 h; después se enfrió a temperatura ambiente y se concentró al vacío. El residuo se disolvió en AcOEt y la fase orgánica se lavó con una solución acuosa de HCl 2N; se secó sobre $MgSO_4$ y se concentró al vacío, para dar 4-(1,1-dioxido-2-isotiazolidinil)-1-etil-1*H*-indol-6-carboxilato de metilo (B143) (386 mg, 48%) como un aceite pardo, que se usó en el siguiente paso sin mayor purificación.

Ester 144

7-(1,1-Dioxido-2-isotiazolidinil)-3-etil-1*H*-indol-5-carboxilato de etilo (B144)

El 7-(1,1-dioxido-2-isotiazolidinil)-3-etil-1*H*-indol-5-carboxilato de etilo (B144) se obtuvo de 7-[[(3-cloropropil)sulfonil]amino]-3-etil-1*H*-indol-5-carboxilato de etilo (D243), de manera análoga al procedimiento descrito para 4-(1,1-dioxido-2-isotiazolidinil)-1-etil-1*H*-indol-6-carboxilato de metilo (B143). $[M+H]^+$ = 337.1, t.r. = 3.23 min.

Ester 145

4-(1,1-Dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-1-etil-2,3-dihidro-1*H*-indol-6-carboxilato de metilo (B145)

A una solución de 1-acetil-4-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-2,3-dihidro-1*H*-indol-6-carboxilato de metilo (D235) (300 mg, 0.85 mmol, 1 eq.) en THF (20 ml), a temperatura ambiente, se le agregó BH_3 (1.5 M en THF, 2 ml, 3 mmol, 3.5 eq.) y la mezcla resultante se agitó a temperatura ambiente durante 15 h. Se le agregó EtOH (5 ml) y la mezcla resultante se concentró al vacío después de 5 min. El residuo se dividió entre una solución acuosa de HCl 2N (20 ml) y CH_2Cl_2 (20 ml), y la mezcla bifásica se agitó vigorosamente durante 3 h. Las dos capas se separaron y la fase orgánica se secó sobre $MgSO_4$ y se concentró al vacío. La purificación del residuo por cromatografía de vaporización instantánea sobre gel de sílice (AcOEt/iso-hexano: 1/2), dio 4-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-1-etil-2,3-dihidro-1*H*-indol-6-carboxilato de metilo (B145) (200 mg, 70%) como un sólido de color amarillo muy claro. $[M+H]^+$ = 339.2, t.r. = 2.92 min.

Ester 146

7-(1,1-Dioxido-2-isotiazolidinil)-3-etil-1-metil-1*H*-indol-5-carboxilato de etilo (B146)

El 7-(1,1-dioxido-2-isotiazolidinil)-3-etil-1-metil-1*H*-indol-5-carboxilato de etilo (B146) se preparó de 7-(1,1-dioxido-2-isotiazolidinil)-3-etil-1*H*-indol-5-carboxilato de etilo (B144), de manera análoga al procedimiento

descrito para el éster 142 (B142).

Ester 147

4-(1,1-Dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-1-etil-1*H*-indol-6-carboxilato de metilo (B147)

A una solución de 4-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-1*H*-indol-6-carboxilato de metilo (D231) (180 mg, 0.58 mmol, 1 eq.) en DMF (3 ml), a temperatura ambiente, se le agregó NaH (dispersión en aceite mineral, 60%, 24 mg, 0.6 mmol, 1 eq.) y la mezcla resultante se agitó 15 min a esta temperatura. Se le agregó yoduro de etilo (64 µl, 0.8 mmol, 1.4 eq.) y la solución resultante se agitó durante 1 h; después se concentró al vacío. El residuo se disolvió en AcOEt y la fase orgánica se lavó con una solución acuosa de HCl 2N, se secó sobre $MgSO_4$ y se concentró al vacío. La purificación del residuo por cromatografía de vaporización instantánea sobre gel de sílice, dio 4-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-1-etil-1*H*-indol-6-carboxilato de metilo (B147) (110 mg, 51 %), como un sólido amarillo que se usó en el siguiente paso sin mayor purificación. $[M+H]^+$ = 337.0, t.r. = 2.82 min.

Ester 148

7-(1,1-Dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-3-etil-1*H*-indol-5-carboxilato de etilo (B148)

A una solución de 7-{[(4-clorobutil)sulfonil]amino}-3-etil-1*H*-indol-

5-carboxilato de etilo (D242) (230 mg, 0.59 mmol, 1 eq.) en EtOH (10 ml), se le agregó NEt_3 (249 µl, 1.78 mmol, 3 eq.), y la solución resultante se agitó a 70°C durante 3 h. Se le agregó NEt_3 (1 ml, exceso), y la solución se agitó a la misma temperatura durante 15 h; después se enfrió a temperatura ambiente y se concentró al vacío. El residuo se disolvió en AcOEt y la fase orgánica se lavó con una solución acuosa de HCl 2N, se secó sobre $MgSO_4$ y se concentró al vacío. La purificación del residuo por cromatografía de vaporización instantánea sobre gel de sílice (AcOEt/iso-hexano: 3/7), dio 7-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-3-etil-1*H*-indol-5-carboxilato de etilo (B148) (150 mg, 72%), como un aceite incoloro. [M-H]⁻ = 349.3, t.r. = 3.10 min.

Ester 150

4-(1,1-Dioxido-2-isotiazolidinil)-1-etil-1*H*-benzoimidazol-6-carboxilato de metilo (B150)

El 4-(1,1-dioxido-2-isotiazolidinil)-1-etil-1*H*-benzoimidazol-6-carboxilato de metilo (B150) se obtuvo de 4-{bis[(3-cloropropil)sulfonil]amino}-1-etil-1*H*-benzoimidazol-6-carboxilato de metilo (D239), de manera análoga al procedimiento descrito para 4-(1,1-dioxido-2-isotiazolidinil)-1-etil-1*H*-indazol-6-carboxilato de metilo (B153). $[M+H]^+$ = 324.5, t.r. = 2.10 min.

Ester 151

4-(1,1-Dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-1-etil-1*H*-benzoimidazol-6-carboxilato de metilo (B151)

A una solución de 4-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-1*H*-benzoimidazol-6-carboxilato de metilo (D253) (230 mg, 0.74 mmol, 1 eq.) en DMF (10 ml), a temperatura ambiente, se le agregó NaH (dispersión en aceite mineral, 60%, 33 mg, 0.82 mmol, 1.1 eq.), y la mezcla resultante se agitó 5 min a esta temperatura. Se le agregó yoduro de etilo (66 µl, 0.82 mmol, 1.1 eq.), y la solución resultante se agitó durante 30 min a 60°C; después se enfrió a temperatura ambiente y se concentró al vacío. El residuo se dividió entre AcOEt y una solución acuosa de ácido cítrico al 5%. Las dos capas se separaron y la fase acuosa se saturó con NaCl y se extrajo dos veces con AcOEt. La fase orgánica combinada se secó sobre $MgSO_4$ y se concentró al vacío, para dar 4-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-1-etil-1*H*-benzoimidazol-6-carboxilato de metilo (B151) (400 mg, 160%) como un aceite viscoso de color amarillo claro, que se usó en el siguiente paso sin mayor purificación. $[M+H]^+$ = 338.1, t.r. = 2.43 min.

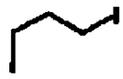
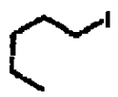
Ester 153

4-(1,1-Dioxido-2-isotiazolidinil)-1-etil-1*H*-indazol-6-carboxilato de metilo (B153)

A una solución de 4-{bis[(3-cloropropil)sulfonil]amino}-1-etil-1*H*-indazol-6-carboxilato de metilo (D237) (1.5 g, 3 mmol, 1 eq.) en EtOH (20 ml),

se le agregó NEt_3 (920 µl, 6.6 mmol, 2.2 eq.), y la solución resultante se puso en reflujo durante 3 h; después se enfrió a temperatura ambiente y se concentró al vacío. El residuo se disolvió en AcOEt y la fase orgánica se lavó con una solución acuosa de HCl 2N, se secó sobre $MgSO_4$ y se concentró al vacío. El residuo se trituró con AcOEt/iso-hexano, para dar 4-(1,1-dioxido-2-isotiazolidinil)-1-etil-1*H*-indazol-6-carboxilato de metilo (B153) como un sólido pardo claro que se usó en el siguiente paso sin mayor purificación. $[M+H]^+$ = 324.5, t.r. = 2.35 min.

Los siguientes compuestos se obtuvieron del éster 154 (B154) de manera análoga al procedimiento descrito para el éster 140 (B140), usando el reactivo de alquilación apropiado:

Ester	Reactivo de alquilación	$[M+H]^+$	t.r.(min)
1-Metil-4-(2-oxo-1-pirrolidinil)-1*H*-indol-6-carboxilato de metilo (B156)		273.0	2.52
1-Butil-4-(2-oxo-1-pirrolidinil)-1*H*-indol-6-carboxilato de metilo (B157)		315.1	3.10
4-(2-Oxo-1-pirrolidinil)-1-pentil-1*H*-indol-6-carboxilato de metilo (B158)			

418
421

Ester 159

3-Metil-7-(2-oxo-1-pirrolidinil)-1-benzofuran-5-carboxilato de metilo (B159)

El 3-metil-7-(2-oxo-1-pirrolidinil)-1-benzofuran-5-carboxilato de metilo (B159) se obtuvo de 3-yodo-5-(2-oxo-1-pirrolidinil)-4-(2-propen-1-iloxi)benzoato de metilo (D259), de manera análoga al procedimiento descrito para el éster 163 (B163). $[M+H]^+$ = 274.0, t.r. = 2.97 min.

Ester 162

1-Metil-3-(1-metiletil)-7-(2-oxo-1-pirrolidinil)-1*H*-indol-5-carboxilato de etilo (B162)

El 1-metil-3-(1-metiletil)-7-(2-oxo-1-pirrolidinil)-1*H*-indol-5-carboxilato de etilo (B162) se obtuvo de 3-(1-metiletil)-7-(2-oxo-1-pirrolidinil)-1*H*-indol-5-carboxilato etilo (B161), usando un procedimiento análogo al de 3-etil-1-metil-7-(2-oxo-1-pirrolidinil)-1*H*-indol-5-carboxilato etilo (B142).

Ester 163

3-Etil-7-(2-oxo-1-pirrolidinil)-1-benzofuran-5-carboxilato de metilo (B163)

A una solución de 4-[(2*E/Z*)-2-buten-1-iloxi]-3-yodo-5-(2-oxo-1-pirrolidinil)benzoato de metilo (D258) (1.4 g, 3.37 mmol, 1 eq.) en DMF (20 ml), a temperatura ambiente y bajo nitrógeno, se le agregó $Pd(OAc)_2$ (38 mg, 0.17 mmol, 0.05 eq.), NaCOOH (688 mg, 10.1 mmol, 3 eq.), Na_2CO_3 (893 mg,

8.4 mmol, 2.5 eq.) y NBu_4Cl (845 mg, 3.71 mmol, 1.1 eq.). La suspensión resultante se agitó bajo nitrógeno a 120°C durante 1 h; después se enfrió a temperatura ambiente y se concentró al vacío. El residuo se dividió entre AcOEt y H_2O y las dos fases se separaron. La fase orgánica se lavó con salmuera, se secó sobre $MgSO_4$ y se concentró al vacío. La purificación del residuo por cromatografía de vaporización instantánea sobre gel de sílice (iso-hexano/AcOEt: 1/1), dio 3-etil-7-(2-oxo-1-pirrolidinil)-1-benzofuran-5-carboxilato de metilo (B163) (250 mg, 26%) como un sólido blanco. $[M+H]^+$ = 288.1, t.r. = 3.02 min.

Ester 164

4-(Etiloxi)-3-[etil(propanoil)amino]-5-(1-metiletil)benzoato de metilo (B164)

El 4-(etiloxi)-3-[etil(propanoil)amino]-5-(1-metiletil)benzoato de metilo (B164) se obtuvo de 4-metil-8-(2-oxo-1-pirrolidinil)-2*H*-cromeno-6-carboxilato de metilo y 4-(etiloxi)-3-[etil(propanoil)amino]-5-(1-metiletenil)benzoato de metilo (D261), de manera análoga al procedimiento descrito para éster *ter*-butílico del ácido 3-(2-oxo-piperidin-1-il)-5-propil-benzoico (B116).

Ester 165

3-Etil-7-(2-oxo-1-piperidinil)-1*H*-indol-5-carboxilato de etilo (B165)

A una solución de 3-etil-7-yodo-1*H*-indol-5-carboxilato de etilo

(D190) (1 g, 2.91 mmol, 1 eq.) en tolueno (10 ml), se le agregó 2-piperidinona (346 mg, 3.50 mmol, 1.2 eq.), K_3PO_4 (1.24 g, 5.83 mmol, 2 eq.), CuI (56 mg, 0.29 mmol, 0.1 eq.) y dimetiletilendiamina (62 µl, 0.58 mmol, 0.2 eq.), y la mezcla resultante se agitó a 100°C durante 15 h; después se enfrió a temperatura ambiente y se concentró al vacío. El residuo se dividió entre AcOEt y H_2O y las capas se separaron. La fase orgánica se secó bajo $MgSO_4$ y se concentró al vacío. La purificación del residuo por cromatografía de vaporización instantánea sobre gel de sílice (AcOEt/iso-hexano: 1/0), dio 3-etil-7-(2-oxo-1-piperidinil)-1*H*-indol-5-carboxilato de etilo (B165) (250 mg, 27%) como un sólido blanquecino. $[M+H]^+ = 315.4$, t.r. = 2.98 min.

Ester 166

3-Etil-7-(2-oxo-4-fenil-1-pirrolidinil)-1*H*-indol-5-carboxilato de etilo (B166)

El 3-etil-7-(2-oxo-4-fenil-1-pirrolidinil)-1*H*-indol-5-carboxilato de etilo (B166) se obtuvo de 3-etil-7-yodo-1*H*-indol-5-carboxilato de etilo (D166), de manera análoga al procedimiento descrito para 3-bromo-5-(2-oxo-5-fenil-1-piperidinil)benzoato de 1,1-dimetiletilo (D190), usando 4-fenil-2-pirrolidinona (Koelsch, *J. Am. Chem. Soc.* 1943, (65), p. 2093) en lugar de 5-fenil-2-piperidinona. $[M+H]^+ = 377.2$, t.r. = 3.60 min.

Ester 167

1-Etil-4-(2-oxo-1-pirrolidinil)-1*H*-1,2,3-benzotriazol-6-carboxilato de metilo (B167)

A una solución de 4-(2-oxo-1-pirrolidinil)-1*H*-1,2,3-benzotriazol-6-carboxilato de etilmetilo (D249) (400 mg, 1.54 mmol, 1 eq.) en DMF (10 ml), a temperatura ambiente, se le agregó NaH (dispersión en aceite mineral, 60%, 68 mg, 1.69 mmol, 1.1 eq.), y la mezcla resultante se agitó 5 min a esta temperatura. Se le agregó yoduro de etilo (135 µl, 1.69 mmol, 1.1 eq.) y la solución resultante se agitó durante 2 h y después se concentró al vacío. El residuo se disolvió en AcOEt y la fase orgánica se lavó con H_2O, se secó sobre $MgSO_4$ y se concentró al vacío. La purificación del residuo por cromatografía de vaporización instantánea sobre gel de sílice (AcOEt/iso-hexano: 100/0), dio 1-etil-4-(2-oxo-1-pirrolidinil)-1*H*-1,2,3-benzotriazol-6-carboxilato de metilo (270 mg, 61%), como un aceite amarillo claro. $[M+H]^+$ = 289.3, t.r. = 2.47 min.

Ester 168

3-(1,1-Dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etiloxi)benzoato de metilo (B168)

El 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etiloxi)benzoato de metilo (B168) se obtuvo de 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-hidroxibenzoato de metilo (D268), de manera análoga al procedimiento descrito para el éster 18 (B18) de la descripción 41 (D41).

Ester 169

3-Ciclopentil-5-(1,1-dioxido-2-isotiazolidinil)benzoato de metilo (B169)

El 3-ciclopentil-5-(1,1-dioxido-2-isotiazolidinil)benzoato de metilo (B169) se obtuvo de 3-(3-ciclopenten-1-il)-5-(1,1-dioxido-2-isotiazolidinil)benzoato de metilo, 3-(2-ciclopenten-1-il)-5-(1,1-dioxido-2-isotiazolidinil)benzoato de metilo y 3-(1-ciclopenten-1-il)-5-(1,1-dioxido-2-isotiazolidinil)benzoato de metilo (D264), de manera análoga al procedimiento descrito para el éster 107 (B107).

Ester 170

3-(1,1-Dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-[(1-metiletil)oxi]-benzoato de metilo (B170)

El 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-[(1-metiletil)oxi]-benzoato de metilo (B170) se obtuvo de 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-hidroxibenzoato de metilo (D268), de manera análoga al procedimiento descrito para el éster 18 (B18) de la descripción 41 (D41), usando 2-yodopropano en lugar de yodoetano.

Ester 172

8-(1,1-Dioxido-2-isotiazolidinil)-4-etil-1,2,3,4-tetrahidro-6-quinoxalinacarboxilato de metilo (B172)

El 8-(1,1-dioxido-2-isotiazolidinil)-4-etil-1,2,3,4-tetrahidro-6-

quinoxalincarboxilato de metilo (B172) se obtuvo de 8-{bis[(3-cloropropil)-sulfonil]amino)-4-etil-1,2,3,4-tetrahidro-6-quinoxalincarboxilato de metilo (D238), de manera análoga al procedimiento descrito para 4-(1,1-dioxido-2-isotiazolidinil)-1-etil-1*H*-indazol-6-carboxilato de metilo (B153). $[M+H]^+$ = 340.2, t.r. = 3.32 min.

Ester 175

3-(1,1-Dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-2-fluoro-5-[(1-metiletil)-amino]benzoato de metilo (B175)

El 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-2-fluoro-5-[(1-metiletil)amino]benzoato de metilo (B175) se obtuvo de la descripción 152 (D152) de manera análoga al procedimiento descrito para el éster 43 (B43), usando acetona en lugar de 3-pentanona.

Ester 176

5-Ciclopentil-3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-2-fluorobenzoato de metilo (B176)

El 5-ciclopentil-3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-2-fluorobenzoato de metilo (B176) se obtuvo de la descripción (D269) de manera análoga al procedimiento descrito para el éster B116 (B116).

Preparación de epóxidos

Epóxido K1

{(1S)-2-(3,5-Difluorofenil)-1-[(2S)-2-oxiranil]etil}carbamato de 1,1-dimetiletilo (K1)

El {(1S)-2-(3,5-difluorofenil)-1-[(2S)-2-oxiranil]etil}carbamato de 1,1-dimetiletilo (K1) se obtuvo de 3,5-difluoro-L-fenilalaninato (D299), de acuerdo con el procedimiento descrito en la patente de E.U.A. No. 2003/0004360 A1.

Los siguientes epóxidos se obtuvieron de manera análoga al procedimiento descrito para el epóxido K1, usando el alaninato apropiado:

Epóxido	Precursor
{(1S)-2-(3-fluorofenil)-1-[(2S)-2-oxiranil]etil}carbamato de 1,1-dimetiletilo (K2)	D300
{(1S)-2-(3,4-difluorofenil)-1-[(2S)-2-oxiranil]etil}carbamato de 1,1-dimetiletilo (K3)	D301
{(1S)-2-(2-clorofenil)-1-[(2S)-2-oxiranil]etil}carbamato de 1,1-dimetiletilo (K4)	D302
{(1S)-2-(3-clorofenil)-1-[(2S)-2-oxiranil]etil}carbamato de 1,1-dimetiletilo (K5)	D303
{(1S)-2-(4-clorofenil)-1-[(2S)-2-oxiranil]etil}carbamato de 1,1-dimetiletilo (K6)	D304
[(1S)-1-[(2S)-2-oxiranil]-2-(2-tienil)etil]carbamato de 1,1-dimetiletilo (K7)	D305
[(1S)-1-[(2S)-2-oxiranil]-2-(3-tienil)etil]carbamato de 1,1-dimetiletilo (K8)	D306
{(1S)-2-(2-furanil)-1-[(2S)-2-oxiranil]etil}carbamato de 1,1-dimetiletilo (K9)	D307
[(1S)-1-[(2S)-2-oxiranil]-2-(2-piridinil)etil]carbamato de 1,1-dimetiletilo (K10)	D308
[(1S)-1-[(2S)-2-oxiranil]-2-(1,3-tiazol-2-il)etil]carbamato de 1,1-dimetiletilo (K11)	D309
[(1S)-1-[(2S)-2-oxiranil]-2-(1*H*-pirazol-1-il)etil]carbamato de 1,1-dimetiletilo (K12)	D310
[(1S)-1-[(2S)-2-oxiranil]-2-(3-piridinil)etil]carbamato de 1,1-dimetiletilo (K13)	D311

Preparación de aminas BOC-protegidas

Amina BOC-protegida 1 (H1)

Ester *ter*-butílico del ácido ((1S,2R)-1-bencil-3-ciclohexilamino-2-hidroxi-propil)-carbámico (H1)

El éster *ter*-butílico del ácido ((S)-(S)-1-oxiranil-2-fenil-etil)-carbámico (D101) (10 g, 38 mmol, 1 eq.) [Chirex 1819W94 Lote #9924382] se disolvió en EtOH (100 ml) y se le agregó ciclohexilamina (13 ml, 114 mmol, 3 eq.). La mezcla resultante se calentó a temperatura de reflujo bajo una atmósfera de nitrógeno durante 12 h. La mezcla se enfrió y el solvente se removió por evaporación al vacío. El sólido blanco resultante se lavó con H_2O y después con Et_2O, antes de secar al vacío, para dar el éster *ter*-butílico del ácido ((1S,2R)-1-bencil-3-ciclohexilamino-2-hidroxi-propil)-carbámico (H1) (9.0 g, 66%). $[M+H]^+ = 363.2$.

Las aminas BOC-protegidas H2-H20, H24-H33 y H36 se prepararon de manera análoga a la amina BOC-protegida H1, sustituyendo la ciclohexilamina con las aminas indicadas en el cuadro siguiente (a menos que las aminas estuvieran disponibles comercialmente):

Amina BOC-protegida	Precursor
Ester *ter*-butílico del ácido ((1S,2R)-1-bencil-3-ciclobutilamino-2-hidroxi-propil)-carbámico (H2)	-
Ester *ter*-butílico del ácido ((1S,2R)-1-bencil-2-hidroxi-3-isobutilamino-propil)-carbámico (H3)	-
Ester *ter*-butílico del ácido ((1S,2R)-1-bencil-2-hidroxi-3-propilamino-propil)-carbámico (H4)	-
Ester *ter*-butílico del ácido [(1S,2R)-1-bencil-2-hidroxi-3-(1,1,5-trimetil-hexilamino)-propil]-carbámico (H5)	F5

Amina BOC-protegida	Precursor
Ester *ter*-butílico del ácido [(1S,2R)-1-bencil-3-((S)-1-ciclohexilcarbamoil-etilamino)-2-hidroxi-propil]-carbámico (H6)	F6
Ester *ter*-butílico del ácido {(1S,2R)-1-bencil-2-hidroxi-3-[(R)-1-(3-metoxi-fenil)-etilamino]-propil}-carbámico (H7)	-
Ester *ter*-butílico del ácido [(1S,2R)-1-bencil-2-hidroxi-3-(1-metil-1-fenil-etilamino)-propil]-carbámico (H8)	-
Ester *ter*-butílico del ácido [(1S,2R)-1-bencil-2-hidroxi-3-(3-metil-butilamino)-propil]-carbámico (H9)	-
Ester *ter*-butílico del ácido ((1S,2R)-1-bencil-3-*ter*-butilamino-2-hidroxi-propil)-carbámico (H10)	-
Ester *ter*-butílico del ácido [(1S,2R)-1-bencil-2-hidroxi-3-(3-trifluorometoxi-bencilamino)-propil]-carbámico (H11)	-
Ester *ter*-butílico del ácido [(1S,2R)-1-bencil-2-hidroxi-3-(2,2,3,3,3-pentafluoro-propilamino)-propil]-carbámico (H12)	-
Ester *ter*-butílico del ácido [(1S,2R)-1-bencil-3-(2,2,3,3,4,4,4-heptafluoro-butilamino)-2-hidroxi-propil]-carbámico (H13)	-
Ester *ter*-butílico del ácido [(1S,2R)-1-bencil-2-hidroxi-3-(3-metoxi-bencilamino)-propil]-carbámico (H14)	-
Ester *ter*-butílico del ácido {(1S,2R)-1-bencil-2-hidroxi-3-[1-(3-metoxi-fenil)-1-metil-etilamino]-propil}-carbámico (H15)	F15
Ester *ter*-butílico del ácido [(1S,2R)-1-bencil-2-hidroxi-3-(3-trifluorometil-bencilamino)-propil]-carbámico (H16)	-
Ester *ter*-butílico del ácido {(1S,2R)-1-bencil-2-hidroxi-3-[(S)-1-(3-metoxi-fenil)-etilamino]-propil}-carbámico (H17)	-
Ester *ter*-butílico del ácido {(1S,2R)-1-bencil-2-hidroxi-3-[(S)-1-(3-metoxi-fenil)-etilamino]-propil}-carbámico (H18)	-
Ester *ter*-butílico del ácido [(1S,2R)-1-bencil-2-hidroxi-3-(5-metil-hexilamino)-propil]-carbámico (H19)	-
Ester *ter*-butílico del ácido [(1S,2R)-1-bencil-3-(1,5-dimetil-hexilamino)-2-hidroxi-propil]-carbámico (H20)	-
Ester *ter*-butílico del ácido ((1S,2R)-1-bencil-3-etilamino-2-hidroxi-propil)-carbámico (H24)	-
Ester *ter*-butílico del ácido [(1S,2R)-1-bencil-3-(bis-trifluorometil-bencilamino)-2-hidroxi-propil]-carbámico (H25)	-
Ester *ter*-butílico del ácido ((1S,2R)-1-bencil-3-ciclopropilamino-2-hidroxi-propil)-carbámico (H26)	-
Ester *ter*-butílico del ácido [(1S,2R)-1-bencil-2-hidroxi-3-(4-metoxi-bencilamino)-propil]-carbámico (H27)	-
Ester *ter*-butílico del ácido ((1S,2R)-1-bencil-2-hidroxi-3-isopropilamino-propil)-carbámico (H28)	-
Ester *ter*-butílico del ácido [(1S,2R)-1-bencil-2-hidroxi-3-(2-metoxi-bencilamino)-propil]-carbámico (H29)	-

Amina BOC-protegida	Precursor
Ester *ter*-butílico del ácido [(1S,2R)-1-bencil-2-hidroxi-3-((S)-1-fenil-etilamino)-propil]-carbámico (H30)	-
Ester *ter*-butílico del ácido [(1S,2R)-1-bencil-2-hidroxi-3-((R)-1-fenil-etilamino)-propil]-carbámico (H31)	-
Ester *ter*-butílico del ácido [(1S,2R)-1-bencil-2-hidroxi-3-(4-metil-pentilamino)-propil]-carbámico (H32)	-
Ester *ter*-butílico del ácido [(1S,2R)-1-bencil-2-hidroxi-3-((R)-2-hidroxi-1-isobutilcarbamoil-pentilamino)-propil]-carbámico (H33)	F33
Ester *ter*-butílico del ácido [(1S,2R)-1-bencil-2-hidroxi-3-((S)-1-isobutilcarbamoil-pentilamino)-propil]-carbámico (H36)	F36

Las aminas BOC-protegidas H40-H114 se prepararon de manera análoga a la amina BOC-protegida H1, sustituyendo la ciclohexilamina con las aminas indicadas en el cuadro siguiente (a menos que las aminas estuvieran disponibles comercialmente):

Amina BOC-protegida	Precursor
[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-({[3-trifluorometil)fenil]metil}amino)propil]carbamato de 1,1-dimetiletilo (H40)	F40
[(1S,2R)-2-hidroxi-3-({1-[3-(metiloxi)fenil]ciclohexil}amino)-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H41)	F41
[(1S,2R)-2-hidroxi-3-{[(1-metil-1*H*-pirazol-4-il)metil]amino}-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H42)	
[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-(tetrahidro-2*H*-piran-4-ilamino)propil]carbamato de 1,1-dimetiletilo (H43)	
[(1S,2R)-3-[(3,3-dimetilbutil)amino]-2-hidroxi-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H44)	
{(1S,2R)-2-hidroxi-1-(fenilmetil)-3-[(1,1,3,3-tetrametilbutil)amino]propil}carbamato de 1,1-dimetiletilo (H45)	
[(1S,2R)-3-[(1,3-dimetilbutil)amino]-2-hidroxi-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H46)	
[(1S,2R)-3-({[4-fluoro-3-(trifluorometil)fenil]metil}amino)-2-hidroxi-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H47)	
[(1S,2R)-3-[(1,1-dimetilhexil)amino]-2-hidroxi-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H48)	F48
[(1S,2R)-2-hidroxi-3-({[2-metil-5-(trifluorometil)fenil]metil}amino)-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H49)	

Amina BOC-protegida	Precursor
[(1S,2R)-3-[(1S)-2,3-dihidro-1*H*-inden-1-ilamino]-2-hidroxi-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H50)	
[(1S,2R)-2-hidroxi-3-{[(1S,2R)-2-hidroxi-2,3-dihidro-1*H*-inden-1-il]amino}-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H51)	
[(1S,2R)-2-hidroxi-3-{[6-(metiloxi)-2,3-dihidro-1*H*-inden-1-il]amino}-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H52	F52
[(1S,2R)-2-hidroxi-3-{[(1R,2S)-2-hidroxi-2,3-dihidro-1*H*-inden-1-il]amino}-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H53)	
[(1S,2R)-3-({1,1-dimetil-2-[(2-metilpropil)tio]etil}amino)-2-hidroxi-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H54)	F54
[(1S,2R)-3-{[1,1-dimetil-2-(feniloxi)etil]amino}-2-hidroxi-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H55)	F55
[(1S,2R)-3-({1,1-dimetil-2-[(fenilmetil)oxi]etil}amino)-2-hidroxi-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H56)	F56
[(1S,2R)-2-hidroxi-3-{[3-(metiloxi)fenil]amino}-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H57)	
[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-({2-[3-trifluorometil)fenil]etil}amino)propil]carbamato de 1,1-dimetiletilo (H58)	
[(1S,2R)-3-[(1,1-dimetil-2-feniletil)amino]-2-hidroxi-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H59)	
[(1S,2R)-2-hidroxi-3-{[2-(1-naftalenil)etil]amino}-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H60)	
[(1S,2R)-3-({1,1-dimetil-2-[3-(metiloxi)fenil]etil}amino)-2-hidroxi-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H61)	F61
[(1S,2R)-2-hidroxi-3-(fenilamino)-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H62)	
[(1S,2R)-2-hidroxi-3-({1-[3-(metiloxi)fenil]ciclopropil}amino)-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H63)	F63
[(1S,2R)-3-[(ciclohexilmetil)amino]-2-hidroxi-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H64)	
{(1S,2R)-2-hidroxi-1-(fenilmetil)-3-[(tetrahidro-2*H*-piran-4-ilmetil)-amino]propil}carbamato de 1,1-dimetiletilo (H65)	
[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-(tetrahidro-2*H*-tiopiran-4-ilamino)propil]carbamato de 1,1-dimetiletilo (H66)	
[(1S,2R)-2-hidroxi-3-[(1-metilpropil)amino]-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H67)	
[(1S,2R)-3-{[4-(1,1-dimetiletil)ciclohexil]amino}-2-hidroxi-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H68)	
[(1S,2R)-3-[(1-etilciclobutil)amino]-2-hidroxi-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H69)	F69
[1S,2R)-3-({1,1-dimetil-2-[(2-metilpropil)oxi]etil}amino)-2-hidroxi-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H70)	F70

Amina BOC-protegida	Precursor
[(1S,2R)-3-({1,1-dimetil-2-[(2-metil-2-propen-1-il)oxi]etil}amino)-2-hidroxi-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H71)	F71
[(1S,2R)-3-[(1R)-2,3-dihidro-1*H*-inden-1-ilamino]-2-hidroxi-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H72)	
[(1S,2R)-2-hidroxi-3-{[1-(4-metilpentil)ciclopropil]amino}-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H73)	F73
[(1S,2R)-3-[(1-etilciclopropil)amino]-2-hidroxi-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H74)	F74
[(1S,2R)-2-hidroxi-3-{[1-(1-metiletil)ciclopropil]amino}-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H75)	F75
[(1S,2R)-3-(butilamino)-2-hidroxi-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H76)	
{(1S,2R)-2-hidroxi-1-(fenilmetil)-3-[(1-propilciclopropil)amino]propil}carbamato de 1,1-dimetiletilo (H77)	F77
[(1S,2R)-2-hidroxi-3-{[1-(3-metilbutil)ciclopropil]amino}-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H78)	F78
[(1S,2R)-2-hidroxi-3-{[1-(2-metilpropil)ciclopropil]amino}-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H79)	F79
[(1S,2R)-3-({1-[(3-clorofenil)metil]ciclopropil}amino)-2-hidroxi-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H80)	F80
[(1S,2R)-2-hidroxi-3-[(1-metilciclohexil)amino]-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H81)	F81
[(1S,2R)-3-[(2S)-biciclo[2.2.1]hept-2-ilamino]-2-hidroxi-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H82)	
[(1S,2R)-3-[(4,4-dimetilciclohexil)amino]-2-hidroxi-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H83)	F83
((1S,2R)-2-hidroxi-1-(fenilmetil)-3-{[(1R)-1,2,2-trimetilpropil]amino}propil)carbamato de 1,1-dimetiletilo (H84)	
((1S,2R)-2-hidroxi-1-(fenilmetil)-3-{[(1S)-1,2,2-trimetilpropil]amino}propil)carbamato de 1,1-dimetiletilo (H85)	
[(1S,2R)-3-[(2,2-dimetilciclohexil)amino]-2-hidroxi-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H86)	F86
[(1S,2R)-2-hidroxi-3-(pentilamino)-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H87)	
[(1S,2R)-3-(hexilamino)-2-hidroxi-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H88)	
[(1S,2R)-3-[(3,3-dimetilbutil)amino]-2-hidroxi-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H89)	
[(1S,2R)-3-[(1,1-dimetilpropil)amino]-2-hidroxi-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H90)	
[(1S,2R)-3-[(ciclopropilmetil)amino]-2-hidroxi-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H91)	

Amina BOC-protegida	Precursor
[(1S,2R)-3-[(3,3-dimetilciclopentil)amino]-2-hidroxi-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H92)	F92
[(1S,2R)-2-hidroxi-3-(metilamino)-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H93)	
[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-(triciclo[3.3.1.1^{3,7}]dec-1-ilamino)propil]carbamato de 1,1-dimetiletilo (H94)	
[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-(1,2,3,4-tetrahidro-1-naftalenilamino)propil]carbamato de 1,1-dimetiletilo (H95)	
[(1S,2R)-2-hidroxi-3-({2-[3-(metiloxi)fenil]etil}amino)-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H96)	
[(1S,2R)-2-hidroxi-3-({2-[4-(metiloxi)fenil]etil}amino)-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H97)	
[(1S,2R)-2-hidroxi-3-({2-[2-(metiloxi)fenil]etil}amino)-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H98)	
[(1S,2R)-3-{[2-(2-clorofenil)etil]amino}-2-hidroxi-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H99)	
[(1S,2R)-3-{[2-(3-clorofenil)etil]amino}-2-hidroxi-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H100)	
[(1S,2R)-3-{[2-(4-clorofenil)etil]amino}-2-hidroxi-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H101)	
[(1S,2R)-2-hidroxi-3-{[2-(4-metilfenil)etil]amino}-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H102)	
[(1S,2R)-2-hidroxi-3-{[2-(2-metilfenil)etil]amino}-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H103)	
[(1S,2R)-3-{[2-(3,4-diclorofenil)etil]amino}-2-hidroxi-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H104)	
[(1S,2R)-3-{[2-(2,4-diclorofenil)etil]amino}-2-hidroxi-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H105)	
[(1S,2R)-3-({2-[3,5-bis(metiloxi)fenil]etil}amino)-2-hidroxi-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H106)	
[(1S,2R)-3-({2-[2,3-bis(metiloxi)fenil]etil}amino)-2-hidroxi-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H107)	
{(1S,2R)-2-hidroxi-1-(fenilmetil)-3-(fenilmetil)amino]propil}carbamato de 1,1-dimetiletilo (H108)	
[(1S,2R)-2-hidroxi-3-[(2-feniletil)amino]-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H109)	
[(1S,2R)-3-[(1-etilciclohexil)amino]-2-hidroxi-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H110)	F110
[(1S,2R)-2-hidroxi-3-[(1-metilciclopentil)amino]-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H111)	F111

Amina BOC-protegida	Precursor
{(1S,2R)-2-hidroxi-1-(fenilmetil)-3-[(1-propilciclopentil)-amino]propil}carbamato de 1,1-dimetiletilo (H112)	F112
{(1S,2R)-2-hidroxi-1-(fenilmetil)-3-[(1-propilciclohexil)-amino]propil}carbamato de 1,1-dimetiletilo (H113)	F113
[(1S,2R)-3-{[2-(3-clorofenil)-1,1-dimetiletil]amino}-2-hidroxi-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H114)	F114

Las siguientes aminas BOC-protegidas H115-H147 se prepararon de manera análoga a la amina BOC-protegida H1, usando el epóxido apropiado y la amina apropiada indicada en el siguiente cuadro (solo se dan las aminas no comerciales):

Amina BOC-protegida	Epóxido	Amina
[(1S,2R)-2-hidroxi-3-({[3-(metiloxi)fenil]metil}amino)-1-(3-piridinilmetil)propil]carbamato de 1,1-dimetiletilo (H115)	K13	
[(1S,2R)-2-hidroxi-3-({[3-(metiloxi)fenil]metil}amino)-1-(1,3-tiazol-2-ilmetil)propil]carbamato de 1,1-dimetiletilo (H116)	K11	
[(1S,2R)-3-(ciclohexilamino)-2-hidroxi-1-(1,3-tiazol-2-ilmetil)propil]carbamato de 1,1-dimetiletilo (H117)	K11	
[(1S,2R)-3-[(1,5-dimetilhexil)amino]-2-hidroxi-1-(1,3-tiazol-2-ilmetil)propil]carbamato de 1,1-dimetiletilo (H118)	K11	
[(1S,2R)-1-(2-furanilmetil)-2-hidroxi-3-({[3-metiloxi)-fenil]metil}amino)propil]carbamato de 1,1-dimetiletilo (H119)	K9	
[(1S,2R)-3-(ciclohexilamino)-1-(2-furanilmetil)-2-hidroxipropil]carbamato de 1,1-dimetiletilo (H120)	K9	
[(1S,2R)-3-[(1,5-dimetilhexil)amino]-1-(2-furanilmetil)-2-hidroxipropil]carbamato de 1,1-dimetiletilo (H121)	K9	
{(1S,2R)-1-(2-furanilmetil)-2-hidroxi-3-[(1,1,5-trimetilhexil)amino]propil}carbamato de 1,1-dimetiletilo (H122)	K9	F5
[(1S,2R)-2-hidroxi-3-({[3-(metiloxi)fenil]metil}amino)-1-(2-piridinilmetil)propil]carbamato de 1,1-dimetiletilo (H123)	K10	
[(1S,2R)-1-[(4-clorofenil)metil]-3-ciclohexilamino)-2-hidroxipropil]carbamato de 1,1-dimetiletilo (H124)	K6	

Amina BOC-protegida	Epóxido	Amina
[(1S,2R)-1-[(4-clorofenil)metil]-2-hidroxi-3-({[3-(metiloxi)fenil]metil}amino)propil]carbamato de 1,1-dimetiletilo (H125)	K6	
[(1S,2R)-1-[(3,5-difluorofenil)metil]-2-hidroxi-3-({[3-(trifluorometil)fenil]metil}amino)propil]carbamato de 1,1-dimetiletilo (H126)	K1	
[(1S,2R)-1-[(3,5-difluorofenil)metil]-2-hidroxi-3-({[3-(metiloxi)fenil]metil}amino)propil]carbamato de 1,1-dimetiletilo (H 127)	K1	
{(1S,2R)-1-[(3,5-difluorofenil)metil]-3-[(1,5-dimetilhexil)amino]-2-hidroxipropil}carbamato de 1,1-dimetiletilo (H128)	K1	
{(1S,2R)-3-(ciclohexilamino)-1-[(3,5-difluorofenil)metil]-2-hidroxipropil}carbamato de 1,1-dimetiletilo (H129)	K1	
{(1S,2R)-1-[(3,5-difluorofenil)metil]-2-hidroxi-3-[(1,1,5-trimetilhexil)amino]propil}carbamato de 1,1-dimetiletilo (H130)	K1	F5
[(1S,2R)-1-[(3,4-difluorofenil)metil]-2-hidroxi-3-({[3-(metiloxi)fenil]metil}amino)propil]carbamato de 1,1-dimetiletilo (H131)	K3	
{(1S,2R)-3-(ciclohexilamino)-1-[(3,4-difluorofenil)metil]-2-hidroxipropil}carbamato de 1,1-dimetiletilo (H132)	K3	
{(1S,2R)-1-[(3,4-difluorofenil)metil]-2-hidroxi-3-[(1,1,5-trimetilhexil)amino]propil}carbamato de 1,1-dimetiletilo (H133)	K3	F5
[(1S,2R)-1-[(3-clorofenil)metil]-2-hidroxi-3-({[3-(metiloxi)fenil]metil}amino)propil]carbamato de 1,1-dimetiletilo (H 134)	K5	
[(1S,2R)-1-[(3-clorofenil)metil]-3-(ciclohexilamino)-2-hidroxipropil]carbamato de 1,1-dimetiletilo (H135)	K5	
[(1S,2R)-1-[(2-clorofenil)metil]-2-hidroxi-3-({[3-(metiloxi)fenil]metil}amino)propil]carbamato de 1,1-dimetiletilo (H136)	K4	
[(1S,2R)-1-[(2-clorofenil)metil]-3-(ciclohexilamino)-2-hidroxipropil]carbamato de 1,1-dimetiletilo (H137)	K4	
{(1S,2R)-1-[(2-clorofenil)metil]-3-[(1,5-dimetilhexil)amino]-2-hidroxipropil}carbamato de 1,1-dimetiletilo (H138)	K4	
{(1S,2R)-1-[(3-clorofenil)metil]-3-[(1,5-dimetilhexil)-amino]-2-hidroxipropil}carbamato de 1,1-dimetiletilo (H139)	K5	
[(1S,2R)-1-[(3-fluorofenil)metil]-2-hidroxi-3-({[3-(metiloxi)-fenil]metil}amino)propil]carbamato de 1,1-dimetiletilo (H140)	K2	

Amina BOC-protegida	Epóxido	Amina
{(1S,2R)-3-[(1,5-dimetilhexil)amino]-1-[(3-fluorofenil)metil]-2-hidroxipropil}carbamato de 1,1-dimetiletilo (H141)	K2	
[(1S,2R)-2-hidroxi-3-({[3-(metiloxi)fenil]metil}amino)-1-(2-tienilmetil)propil]carbamato de 1,1-dimetiletilo (H142)	K7	
[(1S,2R)-3-[(1,5-dimetilhexil)amino]-2-hidroxi-1-(2-tienilmetil)propil]carbamato de 1,1-dimetiletilo (H143)	K7	
[(1S,2R)-2-hidroxi-3-({[3-(metiloxi)fenil]metil}amino)-1-(1*H*-pirazol-1-ilmetil)-propil]carbamato de 1,1-dimetiletilo (H144)	K12	
[(1S,2R)-3-[(1,5-dimetilhexil)amino]-2-hidroxi-1-(1*H*-pirazol-1-ilmetil)propil]carbamato de 1,1-dimetiletilo (H145)	K12	
[(1S,2R)-2-hidroxi-3-({[3-(metiloxi)fenil]metil}amino)-1-(3-tienilmetil)propil]carbamato de 1,1-dimetiletilo (H146)	K8	
[(1S,2R)-3-[(1,5-dimetilhexil)amino]-2-hidroxi-1-(3-tienilmetil)propil]carbamato de 1,1-dimetiletilo (H147)	K8	

Las aminas BOC-protegidas H148-H156 se prepararon de manera análoga a la amina BOC-protegida H1, sustituyendo la ciclohexilamina con las aminas indicadas en el cuadro siguiente (si las aminas no están disponibles comercialmente):

Amina BOC-protegida	Precursor
{(1S,2R)-2-hidroxi-1-(fenilmetil)-3-[(1-propilciclobutil)amino]propil}carbamato de 1,1-dimetiletilo (H148)	F148
[(1S,2R)-2-hidroxi-3-{[1-(1-metiletil)ciclobutil]amino}-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H149)	F149
[(1S,2R)-3-({1-[(3-clorofenil)metil]ciclobutil}amino)-2-hidroxi-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H150)	F150
[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-(triciclo[3.3.1.1^{3,7}]dec-2-ilamino)propil]carbamato de 1,1-dimetiletilo (H151)	

Amina BOC-protegida	Precursor
[(1S,2R)-3-[(1*r*,4*R*)-biciclo[2.2.1]hept-1-ilamino]-2-hidroxi-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H152)	
[(1S,2R)-3-(biciclo[2.2.2]oct-1-ilamino)-2-hidroxi-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H153)	
[(1S,2R)-3-{[(1-etil-1*H*-pirazol-4-il)metil]amino}-2-hidroxi-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H154)	
[(1S,2R)-3-[(4,4-difluorociclohexil)amino]-2-hidroxi-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H155)	F155
[(1S,2R)-3-({(3,4-bis(metiloxi)fenil]metil}amino)-2-hidroxi-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H 156)	

Amina BOC-protegida H157

[(1S,2R)-3-{[(3-Etil-5-isoxazolil)metil]amino}-2-hidroxi-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H157)

El [(1S,2R)-3-[[(3-etil-5-isoxazolil)metil]amino}-2-hidroxi-1-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (H157) se preparó de la descripción F157, de manera análoga al procedimiento descrito para la amina BOC-protegida H1.

Preparación de ácidos

Acido 1

Acido 3-metilsulfanil-5-(2-oxo-pirrolidin-1-il)-benzoico (A1)

A una solución de éster metílico del ácido 3-metilsulfanil-5-(2-oxo-pirrolidin-1-il)-benzoico (B1) (115 mg, 0.433 mmol, 1 eq.) en MeOH (8 ml), se le agregó una solución acuosa de NaOH 2N (0.65 ml, 1.3 mmol, 3 eq.). La mezcla resultante se agitó durante 4 h, se le agregó una solución acuosa de

475
A30

NaOH 2N (1 ml, mmol, eq.), y la solución resultante se agitó durante 16 h; después se concentró al vacío. El residuo se diluyó con H_2O y se extrajo con Et_2O. La capa acuosa se acidificó usando una solución acuosa de HCl 2N, y el precipitado blanco formado se extrajo dos veces con AcOEt. La solución orgánica combinada se secó sobre Na_2SO_4 y se concentró al vacío, para dar ácido 3-metilsulfanil-5-(2-oxo-pirrolidin-1-il)-benzoico (A1) (109 mg, 100%), como un sólido blanco. $[M+H]^+$ = 252.0, t.r. = 2.61 min.

Acido 2

Acido 3-etilsulfanil-5-(2-oxo-pirrolidin-1-il)-benzoico (A2)

El ácido 2 se preparó de 125 mg (0.426 mmol) de éster metílico del ácido 3-metilsulfanil-5-(2-oxo-pirrolidin-1-il)-benzoico (B2), de manera análoga al ácido 1, produciendo 11 mg (98%) de ácido 3-metilsulfanil-5-(2-oxo-pirrolidin-1-il)-benzoico (A2) como un sólido blanco. $[M+H]^+$ = 266.1, t.r. = 2.82 min.

Acido 3

Acido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-metilsulfanil-benzoico (A3)

A una solución de éster metílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-metilsulfanil-benzoico (B3) (144 mg, 0.48 mmol, 1 eq.) en MeOH (10 ml), se le agregó una solución acuosa de NaOH 2N (2.4 ml, 4.8 mmol, 10 eq.). La mezcla resultante se agitó a temperatura ambiente durante

3.5 h y a 40 °C durante 1 h; después se enfrió a temperatura ambiente y se concentró al vacío. El residuo se diluyó con H_2O y se extrajo con Et_2O. La capa acuosa se acidificó con solución acuosa de HCl 2N y el precipitado blanco formado se extrajo dos veces con AcOEt. La solución orgánica combinada se secó sobre Na_2SO_4 y se concentró al vacío, para dar ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-metilsulfanil-benzoico (A3) (136 mg, 100%), como un sólido blanco. $[M+H]^+$ = 288.0, t.r. = 2.63 min

Acido 4

Acido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-etilsulfanil-benzoico (A4)

A una solución de éster etílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-etilsulfanil-benzoico (B4) (145 mg, 0.44 mmol, 1 eq.) en MeOH (5 ml), se le agregó una solución acuosa de NaOH 2N (2.2 ml, 4.4 mmol, 10 eq.). La mezcla resultante se agitó a temperatura ambiente durante 3 h y después se concentró al vacío. El residuo se diluyó con H_2O y se extrajo con Et_2O. La capa acuosa se acidificó con solución acuosa de HCl 2N y el precipitado blanco formado se extrajo dos veces con AcOEt. La solución orgánica combinada se secó sobre Na_2SO_4 y se concentró al vacío, para dar ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-etilsulfanil-benzoico (A4) (133 mg, 100%) como un sólido blanco. $[M+H]^+$ = 302.0, t.r. = 2.83 min.

Acido 5

Acido 3-metanosulfonil-5-(2-oxo-pirrolidin-1-il)-benzoico (A5)

A una solución de ácido 3-metilsulfanil-5-(2-oxo-pirrolidin-1-il)-benzoico (A1) (59 mg, 0.235 mmol, 1 eq.) en MeOH/H_2O (3:1, 24 ml), se le agregó oxona (578 mg, 0.94 mol, 4 eq.). La mezcla resultante se agitó a temperatura ambiente durante 50 min y después se concentró al vacío. El residuo se dividió entre AcOEt y H_2O y las capas se separaron. La capa orgánica se lavó con H_2O y salmuera, se secó sobre Na_2SO_4 y se concentró al vacío, para dar un sólido que se trituró con Et_2O, para dar ácido 3-metanosulfonil-5-(2-oxo-pirrolidin-1-il)-benzoico (A5) (57 mg, 86%) como un sólido blanco. $[M+H]^+$ = 284.0, t.r. = 2.05 min.

Acido 6

Acido 3-etanosulfonil-5-(2-oxo-pirrolidin-1-il)-benzoico (A6)

El ácido 6 se preparó de 59 mg (0.22 mmol) de ácido 3-etilsulfanil-5-(2-oxo-pirrolidin-1-il)-benzoico (A2), de manera análoga al ácido 5, produciendo 59 mg (89%) de ácido 3-etanosulfonil-5-(2-oxo-pirrolidin-1-il)-benzoico (A6) como un sólido blanco. $[M+H]^+$ = 298.0, t.r. = 2.08 min.

Acido 7

Acido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-metanosulfonil-benzoico (A7)

El ácido 7 se preparó de 78 mg (0.27 mmol) de ácido 3-(1,1-

dioxo-1λ^6-isotiazolidin-2-il)-5-metilsulfanil-benzoico (A3), de manera análoga al ácido 6, produciendo 78 mg (90%) de ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-metanosulfonil-benzoico (A7) como un sólido blanco. $[M-H]^-$ = 318.0, t.r. = 2.07 min.

Acido 8

Acido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-etanosulfonil-benzoico (A8)

El ácido 8 se preparó de 72 mg (0.24 mmol) de ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-etilsulfanil-benzoico (A4) (73 mg, 91 %), de manera análoga al ácido 7, produciendo ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-etanosulfonil-benzoico A8, como un sólido blanco. $[M-H]^-$ = 332.0, t.r. = 2.14 min.

Los ácidos A9-A15 se prepararon del éster correspondiente indicado en el cuadro siguiente, usando un procedimiento análogo al que se describe para A113 o A114 (indicado en el cuadro siguiente).

Acido	Procedimiento	Ester
Acido 3-metoxi-5-(2-oxo-pirrolidin-1-il)benzoico (A9)	A113	B9
Acido 3-propoxi-5-(2-oxo-pirrolidin-1-il)benzoico (A10)	A113	B10
Acido 3-etoxi-5-(2-oxo-pirrolidin-1-il)benzoico (A11)	A113	B11
Acido 3-isopropoxi-5-(2-oxo-pirrolidin-1-il)benzoico (A12)	A113	B12
Acido 3-pentoxi-5-(2-oxo-pirrolidin-1-il)benzoico (A13)	A113	B13
Acido 3-(2-metoxi-etoxi)-5-(2-oxo-pirrolidin-1-il)-benzoico (A14)	A113	B14
Acido 3-(3-hidroxi-propoxi)-5-(2-oxo-pirrolidin-1-il)-benzoico (A15)	A113	B15

Acido 16

Acido 3-(2-hidroxi-etoxi)-5-(2-oxo-pirrolidin-1-il)-benzoico (A16)

El ácido 16 se preparó de acuerdo con un procedimiento análogo al que se describe para el éster 15, a partir de ácido 3-(2-benciloxi-etoxi)-5-(2-oxo-pirrolidin-1-il)-benzoico (D40).

Los ácidos A17-A22 y A24-A27 se prepararon del éster correspondiente indicado en el cuadro siguiente, usando un procedimiento análogo al de A113 o A114 (indicado en el cuadro siguiente).

Acido	Procedimiento	Ester
Acido 3-(3-metoxi-propoxi)-5-(2-oxo-pirrolidin-1-il)-benzoico (A17)	A113	B17
Acido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-etoxi-benzoico (A18)	A113	B18
Acido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-isopropoxi-benzoico (A19)	A113	B19
Acido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-metoxi-benzoico (A20)	A113	B20
Acido 3-(1,1-Dioxo-1λ^6-isotiazolidin-2-il)-5-propoxi-benzoico (A21)	A113	B21
Acido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-pentoxi-benzoico (A22)	A113	B22
Acido 3,5-bis-(2-oxo-pirrolidin-1-il)-benzoico (A24)	A113	B24
Acido 4-cloro-3,5-bis-(2-oxo-pirrolidin-1-il)-benzoico (A25)	A113	B25
Acido 4-metoxi-3,5-bis-(2-oxo-pirrolidin-1-il)-benzoico (A26)	A113	B26
Acido 3-nitro-5-(2-oxo-pirrolidin-1-il)-benzoico (A27)	A113	B27

Acido 27 (Procedimiento alternativo)

Acido 3-nitro-5-(2-oxo-pirrolidin-1-il)-benzoico (A27)

Un matraz se cargó, bajo nitrógeno, con ácido 3-bromo-5-nitro-benzoico (D5) (12.3 g, 50 mmol, 1 eq.), Cs_2CO_3 (24.4 g, 75 mmol, 1.5 eq.),

tris(dibencilidenacetona)dipaladio (0) (229 mg, 0.25 mmol, 0.005 eq.), Xantphos (433 mg, 0.75 mmol, 0.015 eq.) y dioxano (120 ml). Después se le agregó 2-pirrolidin-2-ona (5.7 ml, 75 mmol, 1.5 eq.) por medio de una jeringa, y la mezcla resultante se agitó a reflujo durante 60 h; después se enfrió a temperatura ambiente y se concentró al vacío. El residuo se diluyó con H_2O y solución acuosa de NaOH 1 N, y se extrajo dos veces con Et_2O. La fase acuosa se acidificó entonces a pH 1 y se extrajo tres veces con AcOEt. La fase orgánica combinada se secó sobre $MgSO_4$ y se concentró al vacío, para dar ácido 3-nitro-5-(2-oxo-pirrolidin-1-il)-benzoico (A27) (9.3 g, 75%), como un sólido pardo claro.

Los ácidos A28-A74 se prepararon del éster correspondiente indicado en el cuadro siguiente, usando un procedimiento análogo al de A113 o A114 (indicado en el cuadro siguiente).

Acido	Procedimiento	Ester
Acido 3-(2-oxo-pirrolidin-1-il)-5-piperidin-1-il-benzoico (A28)	A113	B28
Acido 3-morfolin-4-il-5-(2-oxo-pirrolidin-1-il)-benzoico (A29)	A113	B29
Acido 3-(2-oxo-pirrolidin-1-il)-5-fenilamino-benzoico (A30)	A113	B30
Acido 3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzoico (A31)	A114	B31
Acido 3-metilamino-5-(2-oxo-pirrolidin-1-il)-benzoico (A32)	A114	B32
Acido 3-dietilamino-5-(2-oxo-pirrolidin-1-il)-benzoico (A33)	A113	B33
Acido 3-dimetilamino-5-(2-oxo-pirrolidin-1-il)-benzoico (A34)	A113	B34
Acido 3-(2-oxo-pirrolidin-1-il)-5-propilamino-benzoico (A35)	A113	B35

Acido	Procedimiento	Ester
Acido 3-isobutilamino-5-(2-oxo-pirrolidin-1-il)-benzoico (A36)	A113	B36
Acido 3-bencilamino-5-(2-oxo-pirrolidin-1-il)-benzoico (A37)	A113	B37
Acido 3-(3-metil-butilamino)-5-(2-oxo-pirrolidin-1-il)-benzoico (A38)	A113	B38
Acido 3-pentilamino-5-(2-oxo-pirrolidin-1-il)-benzoico (A39)	A113	B39
Acido 3-butilamino-5-(2-oxo-pirrolidin-1-il)-benzoico (A40)	A113	B40
Acido 3-(2,2-dimetil-propilamino)-5-(2-oxo-pirrolidin-1-il)-benzoico (A41)	A113	B41
Acido 3-(ciclopropilmetil-amino)-5-(2-oxo-pirrolidin-1-il)-benzoico (A42)	A113	B42
Acido 3-(1-etil-propilamino)-5-(2-oxo-pirrolidin-1-il)-benzoico (A43)	A113	B43
Acido 3-isopropilamino-5-(2-oxo-pirrolidin-1-il)-benzoico (A44)	A113	B44
Acido 3-ciclopentilamino-5-(2-oxo-pirrolidin-1-il)-benzoico (A45)	A113	B45
Acido 3-ciclohexilamino-5-(2-oxo-pirrolidin-1-il)-benzoico (A46)	A113	B46
Acido 3-(acetil-metil-amino)-5-(2-oxo-pirrolidin-1-il)-benzoico (A47)	A113	B47
Acido 3-(acetil-propil-amino)-5-(2-oxo-pirrolidin-1-il)-benzoico (A48)	A114	B48
Acido 3-(acetil-isopropil-amino)-5-(2-oxo-pirrolidin-1-il)-benzoico (A49)	A114	B49
Acido 3-acetilamino-5-(2-oxo-pirrolidin-1-il)-benzoico (A50)	A113	B50
Acido 3-(metanosulfonil-metil-amino)-5-(2-oxo-pirrolidin-1-il)-benzoico (A51)	A113	B51
Acido 3-(metanosulfonil-propil-amino)-5-(2-oxo-pirrolidin-1-il)-benzoico (A52)	A114	B52
Acido 3-metanosulfonilamino-5-(2-oxo-pirrolidin-1-il)-benzoico (A53)	A113	B53
Acido 3-(2-oxo-piperidin-1-il)-5-pirrolidin-1-il-benzoico (A54)	A114	B54
Acido 3-(2-oxo-piperidin-1-il)-5-piperidin-1-il-benzoico (A55)	A114	B55
Acido 3-morfolin-4-il-5-(2-oxo-piperidin-1-il)-benzoico (A56)	A114	B56

Acido	Procedimiento	Ester
Acido 3-metilamino-5-(2-oxo-piperidin-1-il)-benzoico (A57)	A114	B57
Acido 3-propilamino-5-(2-oxo-piperidin-1-il)-benzoico (A58)	A113	B58
Acido 3-etilamino-5-(2-oxo-piperidin-1-il)-benzoico (A59)	A114	B59
Acido 3-dietilamino-5-(2-oxo-piperidin-1-il)-benzoico (A60)	A113	B60
Acido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-morfolin-4-il-benzoico (A61)	A114	B61
Acido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-metilamino-benzoico (A62)	A114	B62
Acido 3-dietilamino-5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-benzoico (A63)	A113	B63
Acido 3-bencilamino-5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-benzoico (A64)	A113	B64
Acido 3-butilamino-5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-benzoico (A65)	A113	B65
Acido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-(3-metil-butilamino)-benzoico (A66)	A113	B66
Acido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-fenetilamino-benzoico (A67)	A113	B67
Acido 3-pentilamino-5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-benzoico (A68)	A113	B68
Acido 3-propilamino-5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-benzoico (A69)	A113	B69
Acido 3-etilamino-5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-benzoico (A70)	A113	B70
Acido 3-(ciclopropilmetil-amino)-5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-benzoico (A71)	A113	B71
Acido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-isopropilamino-benzoico (A72)	A113	B72
Acido 3-(1,1-dioxo-1λ^6-[1,2]tiazinan-2-il)-5-etilamino-benzoico (A73)	A114	B73
Acido 3-ter-butoxi-5-(2-oxo-pirrolidin-1-il)-benzoico (A74)	A113	B74

Los ácidos A75-A85 se prepararon del éster correspondiente indicado en el cuadro siguiente, usando un procedimiento análogo al de A113

o A114 (indicado en el cuadro siguiente).

Acido	Procedimiento	Ester
Acido 3-metoxi-5-(2-oxo-pirrolidin-1-il)-benzoico (A75)	A114	B74
Acido 3-hidroximetil-5-(2-oxo-pirrolidin-1-il)-benzoico (A76)	A113	B76
Acido 5-(2-oxo-pirrolidin-1-il)-N-propil-isoftalámico (A77)	A113	B77
Acido *N,N*-dimetil-5-(2-oxo-pirrolidin-1-il)-isoftalámico (A78)	A113	B78
Acido *N*-metil-5-(2-oxo-pirrolidin-1-il)-isoftalámico (A79)	A113	B79
Acido 5-(2-oxo-pirrolidin-1-il)-*N,N*-dipropil-isoftalámico (A80)	A113	B80
Acido 5-(2-oxo-piperidin-1-il)-*N,N*-dipropil-isoftalámico (A81)	A113	B81
Acido 3-nitro-5-(2-oxo-piperidin-1-il)-benzoico (A82)	A113	B82
Acido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-fluorometil-benzoico (A83)	A113	B83
Acido 3-dimetilaminometil-5-(dioxo-1λ^6-isotiazolidin-2-il)-benzoico (A84)	A113	B84
Acido 3-azidometil-5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-benzoico (A85)	A113	B85

Acido 86

Acido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-metoximetil-benzoico (A86)

Una suspensión de éster metílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-metanosulfoniloximetil-benzoico (D85) (200 mg, 0.55 mmol, 1 eq.) en MeOH (100 ml), se trató con solución acuosa de NaOH 2N (10 ml). La mezcla resultante se agitó durante 4 h a temperatura ambiente y después se concentró al vacío. El residuo se disolvió en AcOEt (100 ml) y la solución resultante se lavó con una solución acuosa de HCl 2N (50 ml), se secó sobre

$MgSO_4$ y se concentró al vacío. El residuo se trituró con Et_2O, para dar el ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-metoximetil-benzoico (A86) (140 mg, 89%), como un sólido blanco.

Acido 87

Acido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-etoximetil-benzoico (A87)

Una suspensión de éster metílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-metanosulfoniloximetil-benzoico (D85) (200 mg, 0.55 mmol, 1 eq.) en EtOH (100 ml), se trató con solución acuosa de NaOH 2N (10 ml). La mezcla resultante se agitó durante 4 h a temperatura ambiente y después se concentró al vacío. El residuo se disolvió en AcOEt (100 ml) y la solución resultante se lavó con una solución acuosa de HCl 2N (50 ml), se secó sobre $MgSO_4$ y se concentró al vacío. El residuo se trituró con Et_2O, para dar el ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-etoximetil-benzoico (A87) (100 mg, 61%), como un sólido blanco.

Los ácidos A88-95 y A100-A102 se prepararon del éster correspondiente indicado en el cuadro siguiente, usando un procedimiento análogo al de A113 o A114 (indicado en el cuadro siguiente).

Acido	Procedimiento	Ester
Acido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-vinil-benzoico (A88)	A113	B88
Acido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-(Z/E)-propenil-benzoico (A89)	A113	B89
Acido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-(Z/E)-butenil-benzoico (A90)	A113	B90
Acido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-(2-metil-propenil)-benzoico (A91)	A113	B91
Acido 5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-isoftalámico (A92)	A113	B92
Acido 3-ciano-5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-benzoico (A93)	A113	B93
Acido 5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-*N,N*-dipropil-isoftalámico (A94)	A113	B94
Acido 5-(1,1-dioxo-1λ^6-[1,2]tiazinan-2-il)-*N,N*-dipropil-isoftalámico (A95)	A113	B95
Acido 2-fluoro-3-(2-oxo-pirrolidin-1-il)-5-trifluorometil-benzoico (A100)	A113	B100
Acido 3-(2-oxo-pirrolidin-1-il)-(2-metil-propenil)-5-benzoico (A101)	A113	B101
Acido 3-(2-oxo-pirrolidin-1-il)-5-((E)-estiril)-benzoico (A102)	A113	B102

Los siguientes compuestos se prepararon del alqueno correspondiente, de manera análoga al procedimiento descrito para el éster *ter*-butílico del ácido 3-(2-oxo-piperidin-1-il)-5-propil-benzoico (B116):

Acido	Alqueno	$[M+H]^+$	t.r. (min)
Ester metílico del ácido 3-(1,1-dioxo-1λ^6-[1,2]tiazinan-2-il)-5-fenetil-benzoico (A103)	A102	310.0	3.12
Acido 3-isobutil-5-(2-oxo-pirrolidin-1-il)-benzoico (A105)	A101	262.1	2.98

Los ácidos A104, A106-A109 y A111-A112 se prepararon del éster correspondiente indicado en el cuadro siguiente, usando un

procedimiento análogo al de A113 o A114 (indicado en el cuadro siguiente).

Acido	Procedimiento	Ester
Acido 3-isopropil-5-(2-oxo-pirrolidin-1-il)-benzoico (A104)	A113	B104
Acido 3-(2-oxo-pirrolidin-1-il)-5-propil-benzoico (A106)	A113	B106
Acido 3-ciclopentil-5-(2-oxo-pirrolidin-1-il)-benzoico (A107)	A113	B107
Acido 3-ciclohexil-5-(2-oxo-pirrolidin-1-il)-benzoico (A108)	A113	B108
Acido 3-etinil-5-(2-oxo-pirrolidin-1-il)-benzoico (A109)	A114	B109
Acido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-etinil-benzoico (A111)	A114	B111
Acido 3-(1,1-Dioxo-1λ^6-[1,2]tiazinan-2-il)-5-propil-benzoico (A112)	A114	B112

Acido 113

Acido 3-(2-oxo-pirrolidin-1-il)-5-pirrolidin-1-il-benzoico (A113)

A una solución de éster metílico del ácido 3-(2-oxo-pirrolidin-1-il)-5-pirrolidin-1-il-benzoico (B113) (85 mg, 0.29 mmol, 1 eq.) en THF (5 ml), se le agregó solución acuosa de NaOH 1 N (0.60 ml, 0.6 mmol, 2 eq.). La mezcla resultante se agitó durante 14 h y después se concentró al vacío. El residuo se diluyó con H_2O y se extrajo con Et_2O. La capa acuosa se acidificó usando una solución acuosa de HCl 2N, y el precipitado blanco formado se extrajo dos veces con AcOEt. La solución orgánica combinada se secó sobre $MgSO_4$ y se concentró al vacío, para dar ácido 3-(2-oxo-pirrolidin-1-il)-5-pirrolidin-1-il-benzoico (A113) (77 mg, 95%), como un sólido blanco. $[M+H]^+$ = 275.0, t.r. = 2.72 min.

Acido 114

Acido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-pirrolidin-1-il-benzoico (A114)

Una solución de éster *ter*-butílico del ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-pirrolidin-1-il-benzoico (B114) (106 mg, 0.29 mmol, 1 eq.) en DCM/TFA (1/1, 4 ml), se agitó a temperatura ambiente durante 2 h y después se concentró al vacío. Se removieron trazas del solvente por destilación azeotrópica con tolueno. El residuo se trituró con Et_2O para dar ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-pirrolidin-1-il-benzoico (A114) (86 mg, 96%), como un sólido pardo claro. $[M+H]^+$ = 311.1, t.r. = 2.75 min.

Acido 115

Acido 3-(4-metil-piperazin-1-il)-5-(2-oxo-pirrolidin-1-il)-benzoico (A115)

A una solución de éster metílico del ácido 3-(4-metil-piperazin-1-il)-5-(2-oxo-pirrolidin-1-il)-benzoico (B115) (296 mg, 0.93 mmol, 1 eq.) en THF (10 ml), se le agregó una solución acuosa de NaOH 1N (1.8 ml, 1.8 mmol, 2 eq.). La mezcla resultante se agitó durante 14 h y después se concentró al vacío. El sólido residual se extrajo exhaustivamente con MeOH y el extracto se concentró al vacío para dar ácido 3-(4-metil-piperazin-1-il)-5-(2-oxo-pirrolidin-1-il)-benzoico (A115) (390 mg, 138%) como un sólido blanquecino. $[M+H]^+$ = 304.0, t.r. = 1.64 min.

Acido 116

Acido 3-(2-oxo-piperidin-1-il)-5-propil-benzoico (A116)

El ácido 116 se preparó del éster 116 de manera análoga al procedimiento descrito para el ácido 114.

A117-A136, A138-A154 y A156-A176 se prepararon de los ésteres B117-B136, B138-B154 y B156-B176, respectivamente, usando un procedimiento análogo al de A113 o A114 (indicado en el cuadro siguiente).

Acido	Procedimiento	$[M+H]^+$	t.r.(min)
Acido 3-(1,1-dioxido-6,7-dihidro-1,2-tiazepin-2(3*H*)-il)-5-propilbenzoico (A117)	A113	308.0 ($[M-H]^-$	2.66
Acido 5-(etilamino)-2-fluoro-3-(2-oxo-1-pirrolidinil)benzoico (A118)	A113	267.2	1.62
Acido 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5 (etilamino)-2-fluorobenzoico (A119)	A113	317.2	2.23
Acido 2-fluoro-3-(2-oxo-1-pirrolidinil)-5-propilbenzoico (A120)	A113	266.2	2.71
Acido 3-(2-oxo-5-fenil-1-piperidinil)-5-propilbenzoico (A121)	A114	338.2	3.37
Acido 3-(1,1-dioxido-2-isotiazolidinil)-5-(etilamino)-2-fluorobenzoico (A122)	A113	303.1	1.98
Acido 3-(1,1-dioxido-4-feniltetrahidro-2*H*-1,2-tiazin-2-il)-5-nitrobenzoico (A123)	A113	394.1	3.47
Acido 3-amino-5-(1,1-dioxido-4-feniltetrahidro-2*H*-1,2-tiazin-2-il)benzoico (A124)	A113	347.2	2.83
Acido 3-(1,1-dioxido-4-feniltetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)benzoico (A125)	A113	375.2	3.17
Acido 3-ciclopentil-5-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)benzoico (A126)	A113	324.0	0.88
Acido 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-[(1-metiletil)amino]benzoico (A127)	A113	313.2	2.38
Acido 3-[etil(metil)amino]-5-(2-oxo-1-pirrolidinil)benzoico (A128)	A114	283.3	2.15
Acido 3-(etilamino)-4-metil-5-(2-oxo-1-pirrolidinil)benzoico (A129)	A113	263.1	2.30
Acido 3-(1,1-dioxido-2-isotiazolidinil)-5-(etilamino)-4-metilbenzoico (A130)	A113	299.0	2.44

Acido	Procedimiento	$[M+H]^+$	t.r.(min)
Acido 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-4-metilbenzoico (A131)	A113	313.1	2.59
Acido 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-4-(metiloxi)benzoico (Al32)	A113	329.1	2.57
Acido 3-(etilamino)-4-(metiloxi)-5-(2-oxo-1-pirrolidinil)benzoico (A133)	A113	279.1	2.34
Acido 3-(1,1-dioxido-2-isotiazolidinil)-5-(etilamino)-4-(metiloxi)benzoico (A134)	A113	315.1	2.45
Acido 3-(dietilamino)-5-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-4-metilbenzoico (A135)	A113	341.1	2.05
Acido 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-4-(metiloxi)-5-[(1*E/Z*)-1-propen-1-il]-benzoico (A136)	A113	326.0	2.87
Acido 3-(1,1-dioxido-2-isotiazolidinil)-5-(2-oxo-1-pirrolidinil)benzoico (A138)	A113	325.3	2.10
Acido 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-etilamino)-2-(metiloxi)benzoico (A139)	A113	329.2	2.02
Acido 1-etil-4-(2-oxo-1-pirrolidinil)-1*H*-indol-6-carboxílico (A140)	A113	273.0	2.53
Acido 3-etil-7-(2-oxo-1-pirrolidinil)-1*H*-indol-5-carboxílico (A141)	A113	273.1	2.68
Acido 3-etil-1-metil-7-(2-oxo-1-pirrolidinil)-1*H*-indol-5-carboxílico (A142)	A113	287.4	2.43
Acido 4-(1,1-dioxido-2-isotiazolidinil)-1-etil-1*H*-indol-6-carboxílico (A143)	A113	309. 3	2.40
Acido 7-(1,1-dioxido-2-isotiazolidinil)-3-etil-1*H*-indol-5-carboxílico (A144)	A113	309.0	2.79
Acido 4-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-1-etil-2,3-dihidro-1*H*-indol-6-carboxílico (A145)	A113	325.3	2.69
Acido 7-(1,1-dioxido-2-isotiazolidinil)-3-etil-1-metil-1*H*-indol-5-carboxílico (A146)	A113		
Acido 4-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-1-etil-1*H*-indol-6-carboxílico (A147)	A113		
Acido 7-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-3-etil-1*H*-indol-5-carboxílico (A148)	A113	340.4	2.68
Acido 1-etil-4-(2-oxo-1-pirrolidinil)-1*H*-benzoimidazol-6-carboxílico (A149)	A113	274.4	1.55
Acido 4-(1,1-dioxido-2-isotiazolidinil)-1-etil-1*H*-benzoimidazol-6-carboxílico (A150)	A113	310.2	1.98

Acido	Procedimiento	$[M+H]^+$	t.r.(min)
Acido 4-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-1-etil-1*H*-benzoimidazol-6-carboxílico (A151)	A113	340.4	2.68
Acido 1-etil-4-(2-oxo-1-pirrolidinil)-1*H*-indazol-6carboxílico (A152)	A113	274.2	2.10
Acido 4-(1,1-dioxido-2-isotiazolidinil)-1-etil-1*H*-indazol-6-carboxílico (A153)	A113	310.3	2.15
Acido 4-(2-oxo-1-pirrolidinil)-1*H*-indol-6-carboxílico (A154)	A113		
Acido 1-metil-4-(2-oxo-1-pirrolidinil)-1*H*-indol-6-carboxílico (A156)	A113	259.4	2.20
Acido 1-butil-4-(2-oxo-1-pirrolidinil)-1*H*-indol-6-carboxílico (A157)	A113	301.0	2.88
Acido 4-(2-oxo-1-pirrolidinil)-1-pentil-1*H*-indol-6-carboxílico (A158)	A113	315.1	3.06
Acido 3-metil-7-(2-oxo-1-pirrolidinil)-1-benzofuran-5-carboxílico (A159)	A113	260.0	2.59
Acido 3-metil-7-(2-oxo-1-pirrolidinil)-1*H*-indol-5-carboxílico (A160)	A113	259.1	2.48
Acido 3-(1-metiletil)-7-(2-oxo-1-pirrolidinil)-1*H*-indol-5-carboxílico (A161)	A113	287.1	2.82
Acido 1-metil-3-(1-metiletil)-7-(2-oxo-1-pirrolidinil)-1*H*-indol-5-carboxílico (A162)	A113	301.2	2.84
Acido 3-etil-7-(2-oxo-1-pirrolidinil)-1-benzofuran-5-carboxílico (A163)	A113	274.1	2.81
Acido 4-metil-8-(2-oxo-1-pirrolidinil)-3,4-dihidro-2*H*-cromeno-6-carboxílico (A164)	A113		
Acido 3-etil-7-(2-oxo-1-piperidinil)-1*H*-indol-5-carboxílico (A165)	A113	287.4	2.56
Acido 3-etil-7-(2-oxo-4-fenil-1-pirrolidinil)-1*H*-indol-5-carboxílico (A166)	A113	349.2	3.21
Acido 1-etil-4-(2-oxo-1-pirrolidinil)-1*H*-1,2,3-benzotriazol-6-carboxílico (A167)	A113	275.2	2.38
Acido 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-[(1-metiletil)oxi]benzoico (A168)	A113	314.15	0.77
Acido 3-ciclopentil-5-(1,1-dioxido-2-isotiazolidinil)benzoico (A169)	A113	310.0	0.83
Acido 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etiloxi)benzoico (A170)	A113	300.12	0.73
Acido 4-etil-8-(2-oxo-1-pirrolidinil)-1,2,3,4-tetrahidro-6-quinoxalincarboxílico (A171)	A113	290.5	2.00
Acido 8-(1,1-dioxido-2-isotiazolidinil)-4-etil-1,2,3,4-tetrahidro-6-quinoxalincarboxílico (A172)	A113	326.2	2.00

Acido	Procedimiento	$[M+H]^+$	t.r.(min)
Acido 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-2-fluoro-5-propilbenzoico (A173)	A113	316.1	2.49
Acido 3-(1,1-dioxido-2-isotiazolidinil)-2-fluoro-5-propilbenzoico (A174)	A113	302.1	2.48
Acido 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-2-fluoro-5-[(1-metiletil)amino]benzoico (A175)	A113	316.2	2.30
Acido 5-ciclopentil-3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-2-fluorobenzoico (A176)	A113	342.2	2.89

Acido 137

Acido 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-4-(metiloxi)-5-propilbenzoico (A137)

El ácido 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-4-(metiloxi)-5-propilbenzoico (A137) se preparó de ácido 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-4-(metiloxi)-5-[(1*E*)-1-propen-1-il]benzoico (A136), de manera análoga al procedimiento descrito para el éster *ter*-butílico del ácido 3-(2-oxo-piperidin-1-il)-5-propil-benzoico (B116).

Acido 155

Acido 4-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-1*H*-indol-6-carboxílico (A155)

A una solución de 4-amino-1*H*-indol-6-carboxilato de metilo (D201) (1.0 g, 5.3 mmol, 1 eq.) en CH_2Cl_2 (50 ml), se le agregó piridina (0.55 g, 6.5 mmol, 1.2 eq.), cloruro de 4-cloro-1-butanosulfonilo (1.14 g, 6 mmol, 1.1 eq.) y DMAP (300 mg, 2.45 mmol, 0.5 eq.), y la mezcla resultante se agitó a

temperatura ambiente durante 5h. Se le agregó NEt_3 (1 ml, 7.2 mmol, 1.3 eq.) y la solución resultante se agitó 2 h y entonces se diluyó con AcOEt, se lavó con una solución acuosa 2N, una solución acuosa saturada de $NaHCO_3$; se secó sobre $MgSO_4$ y se concentró al vacío. El residuo se disolvió en MeOH (20 ml) y se trató con una solución acuosa de NaOH 2N (10 ml, 20 mmol, exceso). La solución resultante se agitó a temperatura ambiente durante 15 h y después se removió al vacío la mayor parte del MeOH. El residuo se dividió entre AcOEt y una solución acuosa de HCl 2N. Las dos capas se separaron y la fase orgánica se secó sobre $MgSO_4$ y se concentró al vacío. La purificación del residuo por cromatografía de vaporización instantánea sobre gel de sílice (CH_2Cl_2/MeOH: 9/1), dio ácido 4-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-1*H*-indol-6-carboxílico (A155) (320 mg, 20%) como un sólido rosa claro. $[M+H]^+$ = 295.0, t.r. = 1.90 min.

Preparación de Aminas

Amina 1 (C1)

Diclorhidrato de (2R,3S)-3-amino-1-ciclohexilamino-4-fenil-butan-2-ol (C1)

El éster *ter*-butílico del ácido ((1S,2R)-1-bencil-3-ciclohexilamino-2-hidroxi-propil)-carbámico (amina BOC-protegida 1 (H1)) (9 g, 25 mmol, 1 eq.), se disolvió en MeOH (70 ml) y después se le agregó una solución 4M de HCl en dioxano (60 ml, exceso). La mezcla resultante se agitó durante 3 h a temperatura ambiente y después los solventes se removieron por evaporación

al vacío. El residuo resultante se lavó con AcOEt y después con Et_2O, antes de secar al vacío para dar el compuesto del título (C1) como un sólido blanco (7.4g, 88%). $[M+H]^+$ 335.31.

Las aminas C2-C20, C24-C33 y C36 se prepararon de sus aminas BOC-protegidas correspondientes (H2-H20, H24-H33 y H36, respectivamente), de manera análoga a la que se describe en C1.

Para las aminas C8-C19, C25-C26 y C29-C32, el HCl 4M en dioxano se reemplazó con 3 equivalentes de ácido p-toluenosulfónico para producir las sales de ácido tosílico.

Amina	$[M+H]^+$	t.r.(min)
Diclorhidrato de (2R,3S)-3-amino-1-ciclobutilamino-4-fenil-butan-2-ol (C2)	235.1	0.32
Diclorhidrato de (2R,3S)-3-amino-1-isobutilamino-4-fenil-butan-2-ol (C3)	237.1	0.86
Diclorhidrato de (2R,3S)-3-amino-4-fenil-1-propilamino-butan-2-ol (C4)	223.1	0.43
Diclorhidrato de (2R,3S)-3-amino-4-fenil-1-(1,1,5-trimetil-hexilamino)-butan-2-ol (C5)	307.2	2.22
Diclorhidrato de (S)-2-((2R,3S)-3-amino-2-hidroxi-4-fenil-butilamino)-*N*-ciclohexil-propionamida (C6)	F899	
Diclorhidrato de (2R,3S)-3-amino-1-[(R)-1-(3-metoxi-fenil)-etilamino]-4-fenil-butanol (C7)	-	-
Ditosilato de (2R,3S)-3-amino-1-(1-metil-1-fenil-etilamino)-4-fenil-butan-2-ol (C8)	-	-
Ditosilato de (2R,3S)-3-amino-1-(3-metil-butilamino)-4-fenil-butan-2-ol (C9)	-	-
Ditosilato de (2R,3S)-3-amino-1-*ter*-butilamino-4-fenil-butan-2-ol (C10)	-	-
Ditosilato de (2R,3S)-3-amino-4-fenil-1-(3-trifluorometoxi-bencilamino)-butan-2-ol (C11)	-	-
Ditosilato de (2R,3S)-3-amino-1-(2,2,3,3,3-pentafluoro-propilamino)-4-fenil-butanol (C12)	-	-
Ditosilato de (2R,3S)-3-amino-1-(2,2,3,3,4,4,4-heptafluoro-butilamino)-4-fenil-butan-2-ol (C13)	362	2.9

Amina	$[M+H]^+$	t.r.(min)
Ditosilato de (2R,3S)-3-amino-1-(3-metoxi-bencilamino)-4-fenil-butan-2-ol (C14)	-	-
Ditosilato de (2R,3S)-3-amino-1-[1-(3-metoxi-fenil)-1-metil-etilamino]-4-fenil-butan-2-ol (C15)	329.1	2.05
Ditosilato de (2R,3S)-3-amino-4-fenil-1-[3-(2,2,2-trifluoro-etil)-bencilamino]-butan-2-ol (C16)	-	-
Ditosilato de (2R,3S)-3-amino-1-[(S)-1-(3-metoxi-fenil)-etilamino]-4-fenil-butan-2-ol (C17)	-	-
Ditosilato de (2R,3S)-3-amino-1-[(S)-1-(3-metoxi-fenil)-etilamino]-4-fenil-butan-2-ol (C18)	-	-
Ditosilato de (2R,3S)-3-amino-1-(5-metil-hexilamino)-4-fenil-butan-2-ol (C19)	-	-
Diclorhidrato de (2R,3S)-3-amino-1-(1,5-dimetil-hexilamino)-4-fenil-butan-2-ol (C20)	293.1	2.04
Diclorhidrato de (2R,3S)-3-amino-1-etilamino-4-fenil-butan-2-ol (C24)	-	-
Ditosilato de (2R,3S)-3-amino-1-(bis-trifluorometil-bencilamino)-4-fenil-butan-2-ol (C25)	-	-
Ditosilato de (2R,3S)-3-amino-1-ciclopropilamino-4-fenil-butan-2-ol (C26)	-	-
Diclorhidrato de (2R,3S)-3-amino-1-(4-metoxi-bencilamino)-4-fenil-butan-2-ol (C27)	-	-
Diclorhidrato de (2R,3S)-3-amino-1-isopropilamino-4-fenil-butan-2-ol (C28)	-	-
Ditosilato de (2R,3S)-3-amino-1-(2-metoxi-bencilamino)-4-fenil-butan-2-ol (C29)	301.1	1.7
Ditosilato de (2R,3S)-3-amino-4-fenil-1-((S)-1-fenil-etilamino)-butan-2-ol (C30)	-	-
Ditosilato de (2R,3S)-3-amino-4-fenil-1-(RR)-1-fenil-etilamino)-butan-2-ol (C31)	-	-
Ditosilato de (2R,3S)-3-amino-1-(4-metil-pentilamino)-4-fenil-butan-2-ol (C32)	-	-
Diclorhidrato de isobutilamida del ácido (R)-2-((2R,3S)-3-amino-2-hidroxi-4-fenil-butilamino)-3-hidroxi-hexanoico (C33)	-	-
Diclorhidrato de isobutilamida del ácido (S)-2-((2R,3S)-3-amino-2-hidroxi-4-fenil-butilamino)-hexanoico (C36)	-	-

Las aminas C40-C114 se prepararon de sus aminas BOC-protegidas correspondientes H40-H114, respectivamente, de manera análoga a la descrita en C1.

Amina	$[M+H]^+$	t.r.(min)
Ditosilato de (2R,3S)-3-amino-1-({1-metil-1-[3-(trifluorometil)fenil]etil}amino)-4-fenil-2-butanol (C40)	367.2	2.44
Diclorhidrato de (2R,3S)-3-amino-1-({1-[3-(metiloxi)fenil]ciclohexil}amino)-4-fenil-2-butanol (C41)		
Ditosilato de (2R,3S)-3-amino-1-{[(1-metil-1*H*-pirazol-4-il)metil]amino}-4-fenil-2-butanol (C42)		
Ditosilato de (2R,3S)-3-amino-4-fenil-1-(tetrahidro-2*H*-piran-4-ilamino)-2-butanol (C43)		
Ditosilato de (2R,3S)-3-amino-1-[(3,3-dimetilbutil)amino]-4-fenil-2-butanol (C44)	265.3	1.52
Ditosilato de (2R,3S)-3-amino-4-fenil-1-[(1,1,3,3-tetrametilbutil)amino]-2-butanol (C45)	293.3	1.76
Ditosilato de (2R,3S)-3-amino-1-[(1,3-dimetilbutil)amino]-4-fenil-2-butanol (C46)	265.3	1.53
Ditosilato de (2R,3S)-3-amino-1-({[4-fluoro-3-(trifluorometil)fenil]metil}amino)-4-fenil-2-butanol (C47)	357.3	1.79
Ditosilato de (2R;3S)-3-amino-1-[(1,1-dimetilhexil)amino]-4-fenil-2-butanol (C48)	293.2	2.06
Ditosilato de (2R,3S)-3-amino-1-({[2-metil-5-(trifluorometil)fenil]metil}amino)-4-fenil-2-butanol (C49)	353.1	2.09
Ditosilato de (2R,3S)-3-amino-1-[(1S)-2,3-dihidro-1*H*-inden-1-ilamino]-4-fenil-2-butanol (C50)		
Ditosilato de (1S,2R)-1-{[(2R,3S)-3-amino-2-hidroxi-4-fenilbutil]amino}-2,3-dihidro-1*H*-inden-2-ol (C51)	313.1	1.83
Ditosilato de (2R,3S)-3-amino-1-{[6-(metiloxi)-2,3-dihidro-1*H*-inden-1-il]amino}-4-fenil-2-butanol (C52)	327. 5	1.82
Ditosilato de (1R,2S)-1-{[(2R,3S)-3-amino-2-hidroxi-4-fenilbutil]amino}-2,3-dihidro-1*H*-inden-2-ol (C53)	313.4	1.56
Ditosilato de (2R,3S)-3-amino-1-({1,1-dimetil-2-[(2-metilpropil)tio]etil}amino)-4-fenil-2-butanol (C54)		
Ditosilato de (2R,3S)-3-amino-1-[[1,1-dimetil-2-(feniloxi) etil]amino}-4-fenil-2-butanol (C55)		
Ditosilato de (2R,3S)-3-amino-1-({1,1-dimetil-2-[(fenilmetil)oxi]etil}amino)-4-fenil-2-butanol (C56)	343.5	1.92
Ditosilato de (2R,3S)-3-amino-1-{[3-(metiloxi)fenil]-amino}-4-fenil-2-butanol (C57)	287.4	2.11
Ditosilato de (2R,3S)-3-amino-4-fenil-1-({2-[3-(trifluorometil)fenil]etil}amino)-2-butanol (C58)	353.4	2.00
Ditosilato de (2R,3S)-3-amino-1-[(1,1-dimetil-2-feniletil)amino]-4-fenil-2-butanol (C59)	313.5	1.98
Ditosilato de (2R,3S)-3-amino-1-{[2-(1-naftalenil)-etil]amino}-4-fenil-2-butanol (C60)	335.4	2.04

Amina	$[M+H]^+$	t.r.(min)
Ditosilato de (2R,3S)-3-amino-1-({1,1-dimetil-2-[3-metiloxi)fenil]etil}amino)-4-fenil-2-butanol (C61)	343.3	1.93
Ditosilato de (2R,3S)-3-amino-4-fenil-1-(fenilamino)-2-butanol (C62)	257.4	2.06
Ditosilato de (2R,3S)-3-amino-1-({1-[3-(metiloxi)fenil] ciclopropil}amino)-4-fenil-2-butanol (C63)	327.5	1.90
Ditosilato de (2R,3S)-3-amino-1-[(ciclohexilmetil)amino]-4-fenil-2-butanol (C64)		
Ditosilato de (2R,3S)-3-amino-4-fenil-1-[(tetrahidro-2*H*-piran-4-ilmetil)amino]-2-butanol (C65)		
(2R,3S)-3-Amino-4-fenil-1-(tetrahidro-2*H*-tiopiran-4-ilamino)-2-butanol (C66)		
Ditosilato de (2R,3S)-3-amino-1-[(1-metilpropil)amino]-4-fenil-2-butanol (C67)	-	
Ditosilato de (2R,3S)-3-amino-1-[[4-(1,1-dimetiletil)-ciclohexil]amino)-4-fenil-2-butanol (C68)	-	
Diclorhidrato de (2R,3S)-3-amino-1-[(1-etilciclobutil)amino]-4-fenil-2-butanol (C69)	-	
Ditosilato de (2R,3S)-3-amino-1-({1,1-dimetil-2-[(2-metilpropil)oxi]etil}amino)-4-fenil-2-butanol (C70)	-	
Ditosilato de (2R,3S)-3-amino-1-({1,1-dimetil-2-[(2-metil-2-propen-1-il)oxi]etil}amino)-4-fenil-2-butanol (C71)		
Ditosilato de (2R,3S)-3-amino-1-[(1R)-2,3-dihidro-1*H*-inden-1-ilamino]-4-fenil-2-butanol (C72)	577.2	2.67
Diclorhidrato de (2R,3S)-3-amino-1-[[1-(4-metilpentil)ciclopropil]amino}-4-fenil-2-butanol (C73)		
Diclorhidrato de (2R,3S)-3-amino-1-[(1-etilciclopropil) amino]-4-fenil-2-butanol (C74)		
Diclorhidrato de (2R,3S)-3-amino-1-[(1-etilciclopropil) amino]-4-fenil-2-butanol (C75)		
Diclorhidrato de (2R,3S)-3-amino-1-(butilamino)-4-fenil-2-butanol (C76)		
Diclorhidrato de (2R,3S)-3-amino-4-fenil-1-[(1-propilciclopropil)amino]-2-butanol (C77)		
Diclorhidrato de (2R,3S)-3-amino-1-[[1-(3-metilbutil)ciclopropil]amino}-4-fenil-2-butanol (C78)		
Diclorhidrato de (2R,3S)-3-amino-1-[[1-(2-metilpropil)ciclopropil]amino}-4-fenil-2-butanol (C79)		
Diclorhidrato de (2R,3S)-3-amino-1-({1-[3-clorofenil)metil]ciclopropil}amino)-4-fenil-2-butanol (C80)		

467
460

Amina	$[M+H]^+$	t.r.(min)
Diclorhidrato de (2R,3S)-3-amino-1-[(4,4-dimetilciclohexil)amino]-4-fenil-2-butanol (C83)		
Diclorhidrato de (2R,3S)-3-amino-4-fenil-1-{[(1R)-1,2,2-trimetilpropil]amino}-2-butanol (C84)		
Diclorhidrato de (2R,3S)-3-amino-4-fenil-1-{[(1S)-1,2,2-trimetilpropil]amino}-2-butanol (C85)		
Diclorhidrato de (2R,3S)-3-amino-1-[(2,2-dimetilciclohexil)amino]-4-fenil-2-butanol (C86)		
(2R,3S)-3-Amino-1-(pentilamino)-4-fenil-2-butanol (C87)		
Diclorhidrato de (2R,3S)-3-amino-1-(hexilamino)-4-fenil-2-butanol (C88)		
Diclorhidrato de (2R,3S)-3-amino-1-[(3,3-dimetilbutil)amino]-4-fenil-2-butanol (C89)		
Diclorhidrato de (2R,3S)-3-amino-1-[(1,1-dimetilpropil)amino]-4-fenil-2-butanol (C90)		
Clorhidrato de (2R,3S)-3-amino-1-[(ciclopropilmetil)amino]-4-fenil-2-butanol (C91)		
Diclorhidrato de (2R,3S)-3-amino-1-[(3,3-dimetilciclopentil)amino]-4-fenil-2-butanol (C92)		
Diclorhidrato de (2R,3S)-3-amino-1-(metilamino)-4-fenil-2-butanol (C93)		
Diclorhidrato de (2R,3S)-3-amino-4-fenil-1-(triciclo[3.3.1.$1^{3,7}$]-dec-1-ilamino)-2-butanol (C94)		
Diclorhidrato de (2R,3S)-3-amino-4-fenil-1-(1,2,3,4-tetrahidro-1-naftalenilamino)-2-butanol (C95)		
Diclorhidrato de (2R,3S)-3-amino-1-({2-[3-(metiloxi)fenil]etilamino)-4-fenil-2-butanol (C96)		
Diclorhidrato de (2R,3S)-3-amino-1-({2-[4-(metiloxi)feniletil]-amino)-4-fenil-2-butanol (C97)		
Diclorhidrato de (2R,3S)-amino-1-({2-[2-(metiloxi)fenil]etil}amino)-4-fenil-2-butanol (C98)		
Diclorhidrato de (2R,3S)-amino-1-{[2-(2-clorofenil)etil]amino}-4-fenil-2-butanol (C99)		
Diclorhidrato de (2R,3S)-3-amino-1-{[2-(3-clorofenil) etil]amino}-4-fenil-2-butanol (C100)		
Diclorhidrato de (2R,3S)-3-amino-1-{[2-(4-clorofenil)etil]amino}-4-fenil-2-butanol (C101)		
Diclorhidrato de (2R,3S)-3-amino-1-{[2-(4-metilfenil)etil]amino}-4-fenil-2-butanol (C102)		
Diclorhidrato de (2R,3S)-3-amino-1-{[2-(2-metilfenil)etil]amino}-4-fenil-2-butanol (C103)		

Amina	$[M+H]^+$	t.r.(min)
Diclorhidrato de (2R,3S)-3-amino-1-{[2-(3,4-diclorofenil)etil]amino}-4-fenil-2-butanol (C104)		
Diclorhidrato de (2R,3S)-3-amino-1-{[2-(2,4-diclorofenil)etil]amino}-4-fenil-2-butanol (C105)		
Diclorhidrato de (2R,3S)-3-amino-1-({2-[3,5-bis-(metiloxi)fenil]etil}amino)-4-fenil-2-butanol (C106)		
Diclorhidrato de (2R,3S)-3-amino-1-({2-[2,3-bis-(metiloxi)fenil]etil}amino)-4-fenil-2-butanol (C107)		
Diclorhidrato de (2R,3S)-3-amino-4-fenil-1-[(fenilmetil)amino]-2-butanol (C108)		
Diclorhidrato de (2R,3S)-3-amino-4-fenil-1-[(2-feniletil)amino]-2-butanol (C109)		
Diclorhidrato de (2R,3S)-3-amino-1-[(1-etilciclohexil)amino]-4-fenil-2-butanol (C110)		
Diclorhidrato de (2R,3S)-3-amino-1-[(1-metilciclopentil)-amino]-4-fenil-2-butanol (C111)		
Diclorhidrato de (2R,3S)-3-amino-4-fenil-1-[(1-propilciclopentil)amino]-2-butanol (C112)		
Diclorhidrato de (2R,3S)-3-amino-4-fenil-1-[(1-propilciclohexil)amino]-2-butanol (Cl 13)		
Diclorhidrato de (2R,3S)-3-amino-1-{[2-(3-clorofenil)-1,1-dimetiletil]amino}-4-fenil-2-butanol (C114)		

Las aminas C115-C147 se prepararon de sus aminas BOC-protegidas correspondientes H115-H147, respectivamente, de manera análoga a la descrita en C1.

Amina	$[M+H]^+$	t.r.(min)
Triclorhidrato de (2R,3S)-3-amino-1-({[3-(metiloxi)fenil]metil}amino)-4-(3-piridinil)-2-butanol (C115)		
Diclorhidrato de (2R,3S)-3-amino-1-({[3-(metiloxi)fenil]metil}-amino)-4-(1,3-tiazol-2-il)-2-butanol (C116)		
Diclorhidrato de (2R,3S)-3-amino-1-(ciclohexilamino)-4-(1,3-tiazol-2-il)-2-butanol (C117)		
Diclorhidrato de (2R,3S)-3-amino-1-[(1,5-dimetilhexil)amino]-4-(1,3-tiazol-2-il)-2-butanol (C118)		
Diclorhidrato de (2R,3S)-3-amino-4-(2-furanil)-1-({[3-(metiloxi)fenil] metil}amino)-2-butanol (C119)		

Amina	$[M+H]^+$	t.r.(min)
Diclorhidrato de (2R,3S)-3-amino-1-(ciclohexilamino)-4-(2-furanil)-2-butanol (C120)		
Diclorhidrato de (2R,3S)-3-amino-1-[(1,5-dimetilhexil)-amino]-4-(2-furanil)-2-butanol (C121)		
Diclorhidrato de (2R,3S)-3-amino-4-(2-furanil)-1-[(1,1,5-trimetilhexil)amino]-2-butanol (C122)		
Triclorhidrato de (2R,3S)-3-amino-1-({[3-(metiloxi)fenil]metil}amino)-4-(2-piridinil)-2-butanol (C123)		
Diclorhidrato de (2R,3S)-3-amino-4-(4-clorofenil)-1-(ciclohexilamino)-2-butanol (C124)		
Diclorhidrato de (2R,3S)-3-amino-4-(4-clorofenil)-1-({[3-(metiloxi)fenil]metil}amino)-2-butanol (C125)		
Diclorhidrato de (2R,3S)-3-amino-4-(3,5-difluorofenil)-1-({[3-(trifluorometil)fenil]metil}amino)-2-butanol (C126)		
Diclorhidrato de (2R,3S)-3-amino-4-(3,5-difluorofenil)-1-({[3-(metiloxi)fenil]metil}amino)-2-butanol (C127)		
Diclorhidrato de (2R,3S)-3-amino-4-(3,5-difluorofenil)-1-[(1,5-dimetilhexil)amino]-2-butanol (C128)		
Diclorhidrato de (2R,3S)-3-amino-1-(ciclohexilamino)-4-(3,5-difluorofenil)-2-butanol (C129)		
Diclorhidrato de (2R,3S)-3-amino-4-(3,5-difluorofenil)-1-[(1,1,5- trimetilhexil)amino]-2-butanol (C130)		
Diclorhidrato de (2R,3S)-3-amino-4-(3,4-difluorofenil)-1-({[3-(metiloxi)fenil]metil}amino)-2-butanol (C131)		
Diclorhidrato de (2R,3S)-3-amino-1-(ciclohexilamino)-4-(3,4-difluorofenil)-2-butanol (C132)		
Diclorhidrato de (2R,3S)-3-amino-4-(3,4-difluorofenil)-1-[(1,1,5-trimetilhexil)amino]-2-butanol (C133)		
Diclorhidrato de (2R,3S)-3-amino-4-(3-clorofenil)-1-({[3-(metiloxi)fenil]metil}amino)-2-butanol (C134)		
Diclorhidrato de (2R,3S)-3-amino-4-(3-clorofenil)-1-(ciclohexilamino)-2-butanol (C135)		
Diclorhidrato de (2R,3S)-3-amino-4-(2-clorofenil)-1-({[3-(metiloxi)fenil]metil}amino)-2-butanol (C136)		
Diclorhidrato de (2R,3S)-3-amino-4-(2-clorofenil)-1-(ciclohexilamino)-2-butanol (C137)		
Diclorhidrato de (2R,3S)-3-amino-4-(2-clorofenil)-1-[(1,5-dimetilhexil)amino]-2-butanol (C138)		
Diclorhidrato de (2R,3S)-3-amino-4-(3-clorofenil)-1-[(1,5-dimetilhexil)amino]-2-butanol (C139)		

Amina	$[M+H]^+$	t.r.(min)
Diclorhidrato de (2R,3S)-3-amino-4-(3-fluorofenil)-1-({[3-(metiloxi)fenil]metil}amino)-2-butanol (C140)		
Diclorhidrato de (2R,3S)-3-amino-1-[(1,5-dimetilhexil)-amino]-4-(3-fluorofenil)-2-butanol (C141)		
Diclorhidrato de (2R,3S)-3-amino-1-({[3-(metiloxi)fenil]metil}amino)-4-(2-tienil)-2-butanol (C142)		
Diclorhidrato de (2R,3S)-3-amino-1-[(1,5-dimetilhexil)-amino]-4-(2-tienil)-2-butanol (C143)		
Diclorhidrato de (2R,3S)-3-amino-1-({[3-(metiloxi)-fenil]metil}amino)-4-(1*H*-pirazol-1-il)-2-butanol (C144)		
Diclorhidrato de (2R,3S)-3-amino-1-[(1,5-dimetilhexil)amino]-4-(1H-pirazol-1-il)-2-butanol (C145)		
Diclorhidrato de (2R,3S)-3-amino-1-({(3-(metiloxi)fenil]-metil}amino)-4-(3-tienil)-2-butanol (C146)		
Diclorhidrato de (2R,3S)-3-amino-1-[(1,5-dimetilhexil)-amino]-4-(3-tienil)-2-butanol (C147)		

Las aminas C148-C156 se prepararon de sus aminas BOC-protegidas correspondientes H148-H156, respectivamente, de manera análoga a la descrita en C1.

Amina	$[M+H]^+$	t.r.(min)
Diclorhidrato de (2R,3S)-3-amino-4-fenil-1-[(1-propilciclobutil)amino]-2-butanol (C148)		
Diclorhidrato de (2R,3S)-3-amino-1-{[1-(1-metiletil)-ciclobutil]amino}-4-fenil-2-butanol (C149)		
Diclorhidrato de (2R,3S)-3-amino-1-({1-[(3-clorofenil)-metil]ciclobutil}amino)-4-fenil-2-butanol (C150)		
Diclorhidrato de (2R,3S)-3-amino-4-fenil-1-(triciclo-[3.3.1.1^{3,7}]dec-2-ilamino)-2-butanol (C151)		
Diclorhidrato de (2R,3S)-3-amino-1-[(1*r*,4*R*)-biciclo [2.2.1]-hept-1-ilamino]-4-fenil-2-butanol (C152)		
Diclorhidrato de (2R,3S)-3-amino-1-(biciclo[2.2.2]oct-1-ilamino)-4-fenil-2-butanol (C153)		
Diclorhidrato de (2R,3S)-3-amino-1-{[(1-etil-1*H*-pirazol-4-il)metil]amino}-4-fenil-2-butanol (C154)	289.5	1.13
Diclorhidrato de (2R,3S)-3-amino-1-[(4,4-difluorociclohexil)-amino]-4-fenil-2-butanol (C155)	299. 3	1.65
Ditosilato de (2R,3S)-3-amino-1-({[3,4-bis(metiloxi)fenil]-metil}amino)-4-fenil-2-butanol (C156)		

Amina 157

Diclorhidrato de (2R,3S)-3-amino-1-{[(3-etil-5-isoxazolil)metil]-amino}-4-fenil-2-butanol (C157)

El diclorhidrato de (2R,3S)-3-amino-1-{[(3-etil-5-isoxazolil)-metil]amino}-4-fenil-2-butanol (C157) se obtuvo de la amina BOC-protegida H157, de manera análoga al procedimiento descrito para la amina C1.

Ejemplos

Ejemplo 1

N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-5-(2-oxopirrolidin-1-il)-N',N'-dipropilisoftalamida (E1)

A una solución de ácido 5-(2-oxo-pirrolidin-1-il)-*N,N*-dipropil-isoftalámico (A80) (66 mg, 0.2 mmol, 1 eq.) en DMF (5 ml), a temperatura ambiente, se le agregó EDAC.HCl (46 mg, 0.24 mmol, 1.2 eq.), HOBT (37 mg, 0.24 mmol, 1.2 eq.), 4-etilmorfolina (153 µl, 1.2 mmol, 6 eq.) y diclorhidrato de (S)-2-((2R,3S)-3-amino-2-hidroxi-4-fenil-butilamino)-*N*-ciclohexil-propionamida (C6) (82 mg, 0.2 mmol, 1 eq.). La mezcla resultante se agitó durante 3 h y después se concentró al vacío. El residuo se diluyó en CH_2Cl_2 y la fase orgánica se lavó con una solución acuosa saturada de $NaHCO_3$, se secó sobre $MgSO_4$ y se concentró al vacío. La purificación del residuo por LC preparativa / MS, dio la N-[(1S,2R)-1-bencil-3-((S)-1-ciclohexilcarbamoil-

etilamino)-2-hidroxipropil]-5-(2-oxopirrolidin-1-il)-N',N'-dipropilisoftalamida (E1) (78 mg, 60%), como una espuma blanca. $[M+H]^+$ = 648.3, t.r. = 2.70.

Ejemplos 2-62

Los compuestos de los ejemplos 2-62 se prepararon de manera análoga al ejemplo 1, a partir del ácido y las aminas apropiadas indicadas en el siguiente cuadro:

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-5-(2-oxopirrolidin-1-il)-N',N'-dipropilisoftalamida (E2)	A80	C6	648.3	2.7
Ester metílico del ácido N-[(1S,2R)-1-bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-5-(2-oxopirrolidin-1-il)-isoftalámico (E3)	A75	C6	579.2	2.47
Ester ter-butílico del ácido N-[(1S,2R)-1-bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-5-(2-oxopirrolidin-1-il)-isoftalámico (E4)	A74	C6	621.2	2.74
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-5-(2-oxopirrolidin-1-il)-N'-propilisoftalamida (E5)	A77	C6	606.2	2.45
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-N',N'-dimetil-5-(2-oxopirrolidin-1-il)-isoftalamida (E6)	A78	C6	592.2	2.31
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-N'-metil-5-(2-oxopirrolidin-1-il)-isoftalamida (E7)	A79	C6	578.2	2.29

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-3-hidroximetil-5-(2-oxopirrolidin-1-il)-benzamida (E8)	A76	C6	551.2	2.28
N-[(1S,2R)-1-Bencil-2-hidroxi-3-(3-metoxibencilamino)-propil]-3-(2-oxopirrolidin-1-il)-5-((E)-estiril)benzamida (E9)	A102	C14	590.2	2.83
N-[(1S,2R)-1-Bencil-2-hidroxi-3-(3-metoxibencilamino)-propil]-3-(2-oxopirrolidin-1-il)-5-fenetilbenzamida (E10)	A103	C14	592.2	2.80
N-[(1S,2R)-1-Bencil-2-hidroxi-3-(3-metoxibencilamino)-propil]-3-ciclopentil-5-(2-oxopirrolidin-1-il)benzamida (E11)	A107	C14	556.3	2.75
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-3-ciclopentil-5-(2-oxopirrolidin-1-il)benzamida (E12)	A107	C6	589.3	2.78
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-3-ciclohexil-5-(2-oxopirrolidin-1-il)benzamida (E13)	A108	C6	603.3	2.86
N-[(1S,2R)-1-Bencil-2-hidroxi-3-(3-metoxibencilamino)-propil]-3-ciclohexil-5-(2-oxopirrolidin-1-il)benzamida (E14)	A108	C14	570.3	2.84
N-[(1S,2R)-1-Bencil-2-hidroxi-3-(3-metoxibencilamino)propil]-3-(2-oxopirrolidin-1-il)-5-propil-benzamida (E15)	A108	C14	530.2	2.64
N-(1-Bencil-3-ciclohexilamino-2-hidroxipropil)-3-(2-oxopirrolidin-1-il)-5-propilbenzamida (E16)	A106	C1	492.2	2.61
N-[1-Bencil-2-hidroxi-3-(3-metoxi-bencilamino)propil]-3-(2-metil-propenil)-5-(2-oxopirrolidin-1-il)benzamida (E17)	A101	C14	542.3	2.69
N-[1-Bencil-2-hidroxi-3-(3-metoxibencilamino) propil]-3-isobutil-5-(2-oxopirrolidin-1-il)-benzamida (E18)	A105	C14	544.3	2.73
N-(1-Bencil-3-ciclohexilamino-2-hidroxipropil)-3-isopropil-5-(2-oxopirrolidin-1-il)benzamida (E19)	A104	C1	492.3	2.60
N-(1-Bencil-3-ciclohexilamino-2-hidroxipropil)-3-isobutil-5-(2-oxopirrolidin-1-il)benzamida (E20)	A105	C1	506.3	2.71

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
N-(1-Bencil-3-ciclohexilamino-2-hidroxipropil)-3-ciclopentil-5-(2-oxopirrolidin-1-il)benzamida (E21)	A107	C16	518.4	2.77
N-[1-Bencil-2-hidroxi-3-(3-trifluorometilbencilamino)propil]-3-ciclopentil-5-(2-oxopirrolidin-1-il)benzamida (E22)	A107	C16	594.4	2.97
N-[1-Bencil-2-hidroxi-3-(3-trifluorometil-bencilamino)propil]-3-(2-oxopirrolidin-1-il)-5-propilbenzamida (E23)	A106	C16	568.3	2.69
N-[1-Bencil-3-(1,5-dimetilhexilamino)-2-hidroxipropil]-3-(2-oxopirrolidin-1-il)-5-propilbenzamida, sal formiato (E24)	A106	C20	522.4	2.67
N-[1-Bencil-2-hidroxi-3-(3-trifluorometil-bencilamino)propil]-3-etinil-5-(2-oxopirrolidin-1-il)benzamida (E25)	A109	C16	550.3	2. 47
N-[1-Bencil-3-(1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-3-(2-oxopirrolidin-1-il)-5-propilbenzamida (E26)	A106	C6	563.4	2.70
N-[1-Bencil-2-hidroxi-3-(3-trifluorometilbencilamino)propil]-2-fluoro-3-(2-oxopirrolidin-1-il)-5-trifluorometil-benzamida, sal formiato (E27)	A100	C16	612.0	2.76
ácido fórmico - 5-ciclopentil-3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-2-fluoro-*N*-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-({[3-trifluorometil)fenil]metil}amino)propil]-benzamida (1:1) (E28)	A176	C16	662.5	3.00
ácido fórmico - 5-ciclopentil-3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-2-fluoro-*N*-[(1S,2R)-2-hidroxi-3-({1-metil-1-[3-(metoxi)fenil]etil}amino)-1-(fenilmetil)propil]-benzamida (1:1) (E29)	A176	C15	652.5	2.92
ácido fórmico - 5-ciclopentil-3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-*N*-[(1S,2R)-3-{[(1-etil-1*H*-pirazol-4-il)-metil]amino}-2-hidroxi-1-(fenilmetil)propil]-2-fluorobenzamida (1:1) (E30)	A176	C154	612.5	2.62
ácido fórmico - 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-2-fluoro-*N*-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-({[3-(trifluorometil)fenil]metil}-amino)propil]-5-[(1-metiletil)amino]-benzamida (1:1) (E31)	A175	C16	651.5	2.78

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
ácido fórmico - 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-2-fluoro-*N*-[(1S,2R)-2-hidroxi-3-({1-metil-1-[3-(metiloxi)fenil]etil}amino)-1-(fenilmetil)propil]-5-[(1-metiletil)amino]-benzamida (1:1) (E32)	A175	C15	641.5	2.65
ácido fórmico - 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-*N*-[(1S,2R)-3-{[(1-etil-1*H*-pirazol-4-il)metil]amino}-2-hidroxi-1-(fenilmetil)propil]-2-fluoro-5-[(1-metiletil)-amino]-benzamida (1:1) (E33)	A175	C154	601.5	2.34
ácido fórmico - 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-2-fluoro-*N*-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-[(1,1,5-trimetilhexil)amino]-propil]-5-[(1-metiletil)amino]-benzamida (1:1) (E34)	A175	C5	619.6	2.94
ácido fórmico - 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-2-fluoro-*N*-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-(tetrahidro-2*H*-piran-4-ilamino) propil]-5-[(1-metiletil)amino]-benzamida (1:1) (E35)	A175	C43	577.5	2.27
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-3,5-bis-(2-oxopirrolidin-1-il)benzamida (E36)	A24	C6	604.2	2.02
3-Acetilamino-N-[(1S,2R)-1-bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-5-(2-oxopirrolidin-1-il)-benzamida (E37)	A50	C6	578.1	2.38
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-3-metanosulfonilamino-5-(2-oxopirrolidin-1-il)-benzamida (E38)	A53	C6	614.1	2.42
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-3-isopropilamino-5-(2-oxopirrolidin-1-il)-benzamida (E39)	A44	C6	578.2	2.59
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-3-(2-oxopirrolidin-1-il)-5-propilaminobenzamida (E40)	A35	C6	578.3	2.62
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-3-ciclopentilamino-5-(2-oxopirrolidin-1-il)-benzamida (E41)	A45	C6	604.2	2.69

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-3-dietilamino-5-(2-oxopirrolidin-1-il)-benzamida (E42)	A33	C6	592.2	2.69
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-3-morfolin-4-il-5-(2-oxopirrolidin-1-il)-benzamida (E43)	A29	C6	606.2	2.43
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-3-(4-metilpiperazin-1-il)-5-(2-oxopirrolidin-1-il)benzamida (E44)	A115	C6	619.2	2.05
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-3-(2-oxopirrolidin-1-il)-5-piperidin-1-il-benzamida (E45)	A28	C6	604.2	2.64
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-3-(2-oxopirrolidin-1-il)-5-pirrolidin-1-il-benzamida (E46)	A113	C6	590.2	2.65
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-3-(2-oxopirrolidin-1-il)-5-fenilaminobenzamida (E47)	A30	C6	612.2	2.70
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-4-metoxi-3,5-bis-(2-oxopirrolidin-1-il)-benzamida (E48)	A26	C6	634.2	2.36
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-4-cloro-3,5-bis-(2-oxopirrolidin-1-il)-benzamida (E49)	A25	C6	638.1	2.41
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-3-etilamino-5-(2-oxopirrolidin-1-il)-benzamida (E50)	A31	C6	564.2	2.48
3-Bencilamino-N-[(1S,2R)-1-bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-5-(2-oxopirrolidin-1-il)benzamida (E51)	A37	C6	626.2	2.70

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-3-(3-metilbutilamino)-5-(2-oxopirrolidin-1-il)-benzamida (E52)	A38	C6	606.2	2.79
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-3-ciclohexilamino-5-(2-oxopirrolidin-1-il)-benzamida (E53)	A46	C6	618.2	2.77
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-3-(2-oxopirrolidin-1-il)-5-pentilaminobenzamida (E54)	A39	C6	606.2	2.77
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-3-(1-etilpropilamino)-5-(2-oxopirrolidin-1-il)-benzamida (E55)	A43	C6	606.2	2.77
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-3-butilamino-5-(2-oxopirrolidin-1-il)-benzamida (E56)	A40	C6	592.2	2.7
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-3-(2,2-dimetilpropilamino)-5-(2-oxopirrolidin-1-il)-benzamida (E57)	A41	C6	604.2	2.78
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-3-(ciclopropilmetilamino)-5-(2-oxopirrolidin-1-il)-benzamida (E58)	A42	C6	590.2	2.60
3-(Acetilpropilamino)-N-[(1S,2R)-1-bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-5-(2-oxopirrolidin-1-il)-benzamida (E59)	A48	C6	620.2	2.47
N-[(1S,2R)-1-Bencil-3-(1,5-dimetilhexilamino)-2-hidroxipropil]-3-isopropilamino-5-(2-oxopirrolidin-1-il)-benzamida (E60)	A44	C20	537.3	2.69
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-3-nitro-5-(2-oxopirrolidin-1-il)-benzamida, sal formiato (E61)	A27	C6	566.1	2.56
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-3-nitro-5-(2-oxopirrolidin-1-il)-benzamida (E62)	A27	C6	566.1	2.56

Ejemplo 63

3-Amino-N-[(1S,2R)-1-bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-5-(2-oxopirrolidin-1-il)benzamida (E63)

Una mezcla de *N*-[(1S,2R)-1-bencil-3-((S)-1-ciclohexilcarbamoil-etilamino)-2-hidroxi- propil]-3-nitro-5-(2-oxo-pirrolidin-1-il)-benzamida (E62) (40 mg, 0.07 mmol, 1 eq.), Pd 10% sobre carbón (50% en húmedo, 10 mg, 12.5% p/p), NH_4COOH (55 mg, 0.90 mmol, 13 eq.), EtOH (5 ml) y H_2O (2.5 ml), se agitó a 50°C durante 2 h, y después se enfrió a temperatura ambiente; el catalizador se separó por filtración a través de una almohadilla de celite. La mayor parte del EtOH se removió al vacío y el residuo se dividió entre AcOEt y solución acuosa saturada de $NaHCO_3$. La fase acuosa se extrajo con AcOEt. La fase orgánica combinada se secó sobre $MgSO_4$ y se concentró al vacío. El residuo se trituró con Et_2O para dar 3-amino-*N*-[(1S,2R)-1-bencil-3-((S)-1-ciclohexilcarbamoil-etilamino)-2-hidroxipropil]-5-(2-oxo-pirrolidin-1-il)-benzamida (E63) (15mg, 38%), como un sólido amarillo claro. $[M+H]^+$ = 536.1, t.r. = 2.27 min.

Ejemplos 64-65

Los ejemplos 64-65 se prepararon de manera análoga al ejemplo 1 a partir del ácido y las aminas apropiadas indicadas en el siguiente cuadro:

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
3-(Acetilisopropilamino)-N-[(1S,2R)-1-bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-5-(2-oxo-pirrolidin-1-il)-benzamida (E64)	A49	C6	620.2	2.44
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-3-(metanosulfonilpropilamino)-5-(2-oxopirrolidin-1-il)-benzamida (E65)	A52	C6	656.2	2.56

Ejemplo 66

N-((1S,2R)-3-Amino-1-bencil-2-hidroxipropil)-3-etilamino-5-(2-oxopirrolidin-1-il)benzamida (E66)

El compuesto del ejemplo 66 (E66) se preparó de manera análoga al ejemplo 182, a partir de éster bencílico del ácido [(2R,3S)-3-({1-[3-etilamino-5-(2-oxo-pirrolidin-1-il)-fenil]-metanoil}-amino)-2-hidroxi-4-fenil-butil]-carbámico (D106).

Ejemplos 67-87

Los ejemplos 67-87 se prepararon de manera análoga al ejemplo 1, a partir del ácido y las aminas apropiadas indicadas en el siguiente cuadro:

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
N-((1S,2R)-1-Bencil-3-ciclopropilamino-2-hidroxipropil)-3-etilamino-5-(2-oxopirrolidin-1-il)benzamida (E67)	A31	C26	451.2	2.23
N-[(1S,2R)-1-Bencil-2-hidroxi-3-(3-metoxi-bencilamino)-propil]-3-etilamino-5-(2-oxopirrolidin-1-il)benzamida, sal formiato (E68)	A31	C14	531.2	2.41
N-[(1S,2R)-1-Bencil-3-ciclohexilamino-2-hidroxipropil)-3-etilamino-5-(2-oxopirrolidin-1-il)benzamida, sal formiato (E69)	A31	C24	493.2	2.39
N-((1S,2R)-1-Bencil-3-etilamino-2-hidroxipropil)-3-etilamino-5-(2-oxopirrolidin-1-il)benzamida, sal formiato (E70)	A31	C24	439.2	2.20
N-[(1S,2R)-1-Bencil-2-hidroxi-3-(4-metoxibencilamino)-propil]-3-etilamino-5-(2-oxopirrolidin-1-il)benzamida (E71)	A31	C27	531.2	2.41
N-[(1S,2R)-1-Bencil-2-hidroxi-3-isopropilaminopropil)-3-etilamino-5-(2-oxopirrolidin-1-il)benzamida(E72)	A31	C28	453.2	2.20
N-[(1S,2R)-1-Bencil-2-hidroxi-3-(3-trifluorometilbencilamino)-propil]-3-etilamino-5-(2-oxopirrolidin-1-il)benzamida (E73)	A31	C16	569.2	2.54
N-[(1S,2R)-1-Bencil-2-hidroxi-3-(2,2,3,3,3-pentafluoro-propilamino)-propil]-3-etilamino-5-(2-oxopirrolidin-1-il)benzamida (E74)	A31	C12	543.1	2.92
N-[(1S,2R)-1-Bencil-3-(2,2,3,3,4,4,4-heptafluorobutilamino)-2-hidroxipropil]-3-etilamino-5-(2-oxopirrolidin-1-il)benzamida (E75)	A31	C13	593.1	3.13
N-[(1S,2R)-1-Bencil-2-hidroxi-3-(R)-1-feniletilamino)propil]-3-etilamino-5-(2-oxopirrolidin-1-il)benzamida (E76)	A31	C31	515.2	2.38
N-[(1S,2R)-1-Bencil-2-hidroxi-3-((S)-1-feniletilamino)propil]-3-etilamino-5-(2-oxopirrolidin-1-il)benzamida (E77)	A31	C30	515.2	2.38
N-[(1S,2R)-1-Bencil-2-hidroxi-3-(2-metoxibencilamino)-propil]-3-etilamino-5-(2-oxopirrolidin-1-il)benzamida (E78)	A31	C29	531.2	2.37
N-[(1S,2R)-1-Bencil-3-(3,5-bis-trifluorometilbencilamino)-2-hidroxipropil]-3-etilamino-5-(2-oxopirrolidin-1-il)benzamida (E79)	A31	C25	637.1	2.74

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
N-{(1S,2R)-1-Bencil-2-hidroxi-3-[(R)-1-(3-metoxifenil)-etilamino]-propil}-3-etilamino-5-(2-oxopirrolidin-1-il)benzamida (E80)	A31	C7	545.2	2.41
N-{(1S,2R)-1-Bencil-2-hidroxi-3-[(S)-1-(3-metoxifenil)-etilamino]-propil}-3-etilamino-5-(2-oxopirrolidin-1-il)benzamida (E81)	A31	C17	545.2	2.43
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexil-carbamoiletilamino)-2-hidroxipropil]-3-isobutilamino-5-(2-oxopirrolidin-1-il)-benzamida (E82)	A36	C6	592.2	2.66
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexil-carbamoiletilamino)-2-hidroxipropil]-3-dimetilamino-5-(2-oxopirrolidin-1-il)-benzamida (E83)	A34	C6	564.2	2.47
N-[(1S,2R)-1-Bencil-2-hidroxi-3-(1-metil-1-feniletilamino)-propil]-3-etilamino-5-(2-oxopirrolidin-1-il)benzamida (E84)	A31	C8	529.3	2.44
N-((1S,2R)-1-Bencil-3-ter-butilamino-2-hidroxipropil)-3-etilamino-5-(2-oxopirrolidin-1-il)benzamida (E85)	A31	C10	467.3	2.25
N-[(1S,2R)-1-Bencil-2-hidroxi-3-(3-trifluorometoxibencilamino)-propil]-3-etilamino-5-(2-oxopirrolidin-1-il)benzamida (E86)	A31	C11	585.3	2.61
N-((1S,2R)-1-Bencil-2-hidroxi-3-(3-metilbutilamino)-propil]-3-etilamino-5-(2-oxopirrolidin-1-il)benzamida (E87)	A31	C9	481.3	2.38

Ejemplo 88

N-((1S,2R)-3-Amino-1-bencil-2-hidroxipropil)-3-isopropilamino-5-(2-oxopirrolidin-1-il)benzamida (E88)

El compuesto del ejemplo 88 se preparó de manera análoga al ejemplo 182, a partir del éster bencílico del ácido [(2R,3S)-3-((1-[3-

isopropilamino-5-(2-oxo-pirrolidin-1-il)-fenil]-metanoil}-amino)-2-hidroxi-4-fenil-butil]-carbámico (D107). $[M+H]^+$ = 425.2, t.r. = 2.20 min.

Ejemplos 89-102

Los compuestos de los ejemplos 89-102 se prepararon de manera análoga al ejemplo 1, a partir del ácido y las aminas apropiadas indicadas en el siguiente cuadro:

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-3-metilamino-5-(2-oxopirrolidin-1-il)-benzamida (E89)	A32	C6	550.3	2.37
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-3-(metanosulfonilmetilamino)-5-(2-oxopirrolidin-1-il)-benzamida (E90)	A51	C6	628.2	2.41
3-(Acetilmetilamino)-N-[(1S,2R)-1-bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-5-(2-oxopirrolidin-1-il)-benzamida (E91)	A47	C6	592.2	2.31
N-((1S,2R)-1-Bencil-3-ciclopentilamino-2-hidroxipropil)-3-etilamino-5-(2-oxopirrolidin-1-il)benzamida (E92)	A31	C18	479.2	2.31
N-[(1S,2R)-1-Bencil-2-hidroxi-3-(4-metilpentilamino)-propil]-3-etilamino-5-(2-oxopirrolidin-1-il)benzamida (E93)	A31	C32	495.3	2.51
N-[(1S,2R)-1-Bencil-2-hidroxi-3-(5-metilhexilamino)-propil]-3-etilamino-5-(2-oxopirrolidin-1-il)benzamida (E94)	A31	C19	509.3	2.62
N-[(1S,2R)-1-Bencil-3-(1,5-dimetil-hexilamino)-2-hidroxipropil]-3-etilamino-5-(2-oxopirrolidin-1-il)benzamida, sal formiato (E95)	A31	C20	523.3	2.68

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
N-((1S,2R)-1-Bencil-3-ciclohexilamino-2-hidroxipropil)-3-etilamino-5-(2-oxopirrolidin-1-il)benzamida (E96)	A31	C7	493.2	2.38
N-(1-Bencil-3-ciclobutilamino-2-hidroxipropil)-3-etilamino-5-(2-oxopirrolidin-1-il)benzamida (E97)	A31	C2	465.4	2.29
N-(1-Bencil-3-cicloheptilamino-2-hidroxipropil)-3-etilamino-5-(2-oxopirrolidin-1-il)benzamida (E98)	A31	C33	507.3	2.52
N-(1-Bencil-2-hidroxi-3-isobutilaminopropil)-3-etilamino-5-(2-oxopirrolidin-1-il)benzamida (E99)	A31	C3	424.2	2.35
N-[1-Bencil-2-hidroxi-3-(1,1,5-trimetil-hexilamino)propil]-3-etilamino-5-(2-oxopirrolidin-1-il)benzamida (E100)	A31	C5	537.3	2.80
N-(1-Bencil-2-hidroxi-3-propilaminopropil)-3-etilamino-5-(2-oxopirrolidin-1-il)benzamida (E101)	A31	C4	453.2	2.29
N-{1-Bencil-2-hidroxi-3-[1-(3-metoxifenil)-1-metiletilamino]propil}-3-etilamino-5-(2-oxopirrolidin-1-il)benzamida, sal formiato (E102)	A31	C15	559.2	2.59

Ejemplos 103-170

Los ejemplos 103-170 se prepararon por medio de aminación reductiva, usando N-((1S,2R)-3-amino-1-bencil-2-hidroxipropil)-3-etilamino-5-(2-oxopirrolidin-1-il)benzamida (E66), en un procedimiento análogo al descrito para E183.

Ejemplo	$[M+H]^+$	t.r. (min)
N-[(1S,2R)-1-Bencil-3-(3,4-dicloro-bencilamino)-2-hidroxi-propil]-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E103)		
N-((1S,2R)-1-Bencil-3-bencilamino-2-hidroxi-propil)-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E104)		
N-[(1S,2R)-1-Bencil-3-(4-fluoro-bencilamino)-2-hidroxi-propil]-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E105)		
N-[(1S,2R)-1-Bencil-2-hidroxi-3-(4-trifluorometil-bencilamino)-propil]-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E106)		
N-[(1S,2R)-1-Bencil-3-[(furan-2-ilmetil)-amino]-2-hidroxi-propil]-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E107)		
N-[(1S,2R)-1-Bencil-2-hidroxi-3-[(quinolin-4-ilmetil)-amino]-propil]-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E108)		
N-[(1S,2R)-1-Bencil-2-hidroxi-3-(3-hidroxi-bencilamino)-propil]-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E109)		
N-[(1S,2R)-1-Bencil-2-hidroxi-3-[(tiofen-2-ilmetil)-amino]-propil]-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E110)		
N-[(1S,2R)-1-Bencil-2-hidroxi-3-[(tiofen-3-ilmetil)-amino]-propil]-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E111)		
N-[(1S,2R)-1-Bencil-3-(3-cloro-4-metoxi-bencilamino)-2-hidroxi-propil]-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E112)		
N-[(1S,2R)-1-Bencil-3-(2,3-dicloro-bencilamino)-2-hidroxi-propil]-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E113)		
N-[(1S,2R)-3-(4-Acetilamino-bencilamino)-1-bencil-2-hidroxi-propil]-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E 114)		
N-[(1S,2R)-1-Bencil-3-(4-ciano-bencilamino)-2-hidroxi-propil]-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E115)		
N-((1S,2R)-1-Bencil-2-hidroxi-3-fenetilamino-propil)-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E116)		
N-[(1S,2R)-1-Bencil-2-hidroxi-3-[(1*H*-indol-3-ilmetil)-amino]-propil]-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E117)		
N-[(1S,2R)-1-Bencil-2-hidroxi-3-(3-fenil-butilamino)-propil]-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E118)		
N-[(1S,2R)-3-[(1*H*-Benzoimidazol-5-ilmetil)-amino]-1-bencil-2-hidroxi-propil]-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E119)		

Ejemplo	$[M+H]^+$	t.r. (min)
N-{(1S,2R)-1-Bencil-3-[(E)-3-(4-fluoro-fenil)-alilamino]-2-hidroxi-propil}-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E120)		
N-[(1S,2R)-1-Bencil-2-hidroxi-3-(4-isopropoxi-bencilamino)-propil]-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E121)		
N-[(1S,2R)-1-Bencil-2-hidroxi-3-((E)-3-*p*-tolil-alilamino)-propil]-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E122)		
N-{(1S,2R)-1-Bencil-3-[(2-etil-5-metil-3*H*-imidazol-4-ilmetil)-amino]-2-hidroxi-propil}-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E123)		
N-[(1S,2R)-1-Bencil-2-hidroxi-3-(2-metil-3-fenil-propilamino)-propil]-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E124)		
N-[(1S,2R)-1-Bencil-2-hidroxi-3-(3-metoxi-4-nitro-bencilamino)-propil]-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E125)		
N-[(1S,2R)-1-Bencil-3-(5-ciano-2-metoxi-bencilamino)-2-hidroxi-propil]-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E126)		
N-{(1S,2R)-1-Bencil-3-[(ciclohex-3-enilmetil)-amino]-2-hidroxi-propil}-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E127)		
N-[(1S,2R)-1-Bencil-2-hidroxi-3-(2-fenil-propilamino)-propil]-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E128)		
N-[(1S,2R)-1-Bencil-2-hidroxi-3-(3-metilsulfanil-propilamino)-propil]-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E129)		
N-[(1S,2R)-1-Bencil-3-(3-ciano-bencilamino)-2-hidroxi-propil]-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E130)		
N-{(1S,2R)-1-Bencil-2-hidroxi-3-[(5-metil-tiofen-2-ilmetil)-amino]-propil}-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E131)		
N-[(1S,2R)-1-Bencil-2-hidroxi-3-(2-metoxi-5-metil-bencilamino)-propil]-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E132)		
N-{(1S,2R)-3-[(Benzofuran-2-ilmetil)-amino]-1-bencil-2-hidroxi-propil}-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E133)		
N-[(1S,2R)-1-Bencil-3-(3-fluoro-bencilamino)-2-hidroxi-propil]-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E134)		
N-[(1S,2R)-1-Bencil-2-hidroxi-3-(2-p-tolil-etilamino)-propil]-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E135)		

Ejemplo	$[M+H]^+$	t.r. (min)
N-[(1S,2R)-1-Bencil-3-(dimetilamino-dimetil-propilamino)-2-hidroxi-propil]-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E136)		
N-{(1S,2R)-1-Bencil-2-hidroxi-3-[(1*H*-indol-5-ilmetil)-amino]-propil}-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E137)		
N-{(1S,2R)-1-Bencil-2-hidroxi-3-[(2-metil-tiazol-4-ilmetil)-amino]-propil}-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E138)		
N-[(1S,2R)-1-Bencil-3-(2-benciloxi-etilamino)-2-hidroxi-propil]-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E139)		
N-[(1S,2R)-1-Bencil-3-(3,4-dimetoxi-bencilamino)-2-hidroxi-propil]-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E140)		
N-[(1S,2R)-1-Bencil-2-hidroxi-3-(3-nitro-bencilamino)-propil]-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E141)		
N-[(1S,2R)-1-Bencil-3-(3-cloro-bencilamino)-2-hidroxi-propil]-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E142)		
N-[(1S,2R)-1-Bencil-3-(3-etoxi-bencilamino)-2-hidroxi-propil]-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E143)		
N-{(1S,2R)-1-Bencil-3-[(5-cloro-tiofen-2-ilmetil)-amino]-2-hidroxi-propil}-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E144)		
N-{(1S,2R)-1-Bencil-2-hidroxi-2-[(tiazol-2-ilmetil)-amino]-propil}-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E145)		
N-{(1S,2R)-1-Bencil-2-hidroxi-3-[(piridin-3-ilmetil)-amino]-propil}-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E146)		
N-[(1S,2R)-1-Bencil-2-hidroxi-3-(4-hidroxi-3-metoxi-bencilamino)-propil]-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E147)		
N-[(1S,2R)-1-Bencil-2-hidroxi-3-(3-hidroximetil-bencilamino)-propil]-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E148)		
N-{(1S,2R)-1-Bencil-2-hidroxi-3-[3-(4-metoxi-fenil)-propilamino]-propil}-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E149)		
N-[(1S,2R)-1-Bencil-3-(4-dimetilaminometil-bencilamino)-2-hidroxi-propil]-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E150)		

Ejemplo	$[M+H]^+$	t.r. (min)
N-[(1S,2R)-1-Bencil-3-(3,4-difluoro-bencilamino)-2-hidroxi-propil]-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E151)		
N-{(1S,2R)-1-Bencil-2-hidroxi-3-[(5-metoximetil-furan-2-ilmetil)-amino]-propil}-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E152)		
N-[(1S,2R)-1-Bencil-2-hidroxi-3-(3-propoxi-bencilamino)-propil]-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E153)		
N-[(1S,2R)-1-Bencil-3-(4-ciano-3-metoxi-bencilamino)-2-hidroxi-propil]-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E154)		
N-[(1S,2R)-1-Bencil-2-hidroxi-3-(3-imidazol-1-il-bencilamino)-propil]-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E155)		
N-[(1S,2R)-1-Bencil-2-hidroxi-3-(3-pirimidin-5-il-bencilamino)-propil]-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E156)		
N-{(1S,2R)-1-Bencil-2-hidroxi-3-[(6-metoxi-piridin-3-ilmetil)-amino]-propil}-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E157)		
N-{(1S,2R)-1-Bencil-2-hidroxi-3-[(6-metoxi-piridin-2-ilmetil)-amino]-propil}-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E158)		
N-[(1S,2R)-1-Bencil-3-(3-ter-butoximetil-bencilamino)-2-hidroxi-propil]-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E159)		
N-[(1S,2R)-1-Bencil-2-hidroxi-3-(3-prop-2-iniloxi-bencilamino)-propil]-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E160)		
N-[(1S,2R)-3-(3-Acetilamino-bencilamino)-1-bencil-2-hidroxi-propil]-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E161)		
N-{(1S,2R)-1-Bencil-2-hidroxi-3-[3-(3-metoxi-fenil)-propilamino]-propil}-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E162)		
N-{(1S,2R)-1-Bencil-3-[3-(4-cloro-fenil)-propilamino]-2-hidroxi-propil}-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E163)		
N-[(1S,2R)-1-Bencil-2-hidroxi-3-(3-#p-tolil-propilamino)-propil]-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E164)		
N-{(1S,2R)-1-Bencil-2-hidroxi-3-[3-(2*H*-tetrazol-5-il)-bencilamino]-propil}-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E165)		

Ejemplo	$[M+H]^+$	t.r. (min)
N-{(1S,2R)-1-Bencil-2-hidroxi-3-[3-(1*H*-pirazol-3-il)-bencilamino]-propil}-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E166)		
N-{(1S,2R)-1-Bencil-2-hidroxi-3-[3-(1*H*-imidazol-2-il)-bencilamino]-propil}-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E167)		
N-[(1S,2R)-1-Bencil-3-(4-fluoro-3-metoxi-bencilamino)-2-hidroxi-propil]-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E168)		
N-{(1S,2R)-1-Bencil-3-[2,2-dimetil-3-(2-oxo-pirrolidin-1-il)-propilamino]-2-hidroxi-propil}-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E169)		
N-{(1S,2R)-3-[(Benzotiazol-6-ilmetil)-amino]-1-bencil-2-hidroxi-propil}-3-etilamino-5-(2-oxo-pirrolidin-1-il)-benzamida (E170)		

Ejemplos 171-181

Los compuestos de los ejemplos 171-181 se prepararon de manera análoga al ejemplo 1, a partir del ácido y las aminas apropiadas indicadas en el siguiente cuadro:

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-3-(2-oxopirrolidin-1-il)-5-propoxibenzamida, sal formiato (E171)	A10	C6	579.4	2.34
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexil-carbamoiletilamino)-2-hidroxipropil]-3-metoxi-5-(2-oxopirrolidin-1-il)benzamida (E172)	A9	C6	551.2	2.09
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-3-isopropoxi-5-(2-oxopirrolidin-1-il)benzamida (E173)	A12	C6	579.2	2.68

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-3-(3-hidroxipropoxi)-5-(2-oxopirrolidin-1-il)-benzamida (E174)	A15	C6	595.2	2.40
N-[(1S,2R)-1-Bencil)-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-3-(3-metoxipropoxi)-5-(2-oxopirrolidin-1-il)-benzamida (E175)	A17	C6	609.2	2.59
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-3-(2-hidroxietoxi)-5-(2-oxopirrolidin-1-il)-benzamida (E176)	A16	C6	581.1	2.36
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-3-(2-metoxietoxi)-5-(2-oxopirrolidin-1-il)-benzamida (E177)	A14	C6	595.2	2.50
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-3-(2-oxopirrolidin-1-il)-5-pentoxibenzamida (E178)	A13	C6	607.2	2.87
N-[(1S,2R)-1-Bencil-2-hidroxi-3-((S)-1-isobutilcarbamoil-pentilamino)-propil]-3-isopropoxi-5-(2-oxopirrolidin-1-il)benzamida (E179)	A12	C36	595.2	2.75
N-[(1S,2R)-1-Bencil-2-hidroxi-3-(3-metoxibencilamino)propil]-3-isopropoxi-5-(2-oxopirrolidin-1-il)benzamida (E180)	A12	C14	546.1	2.59
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-3-etoxi-5-(2-oxopirrolidin-1-il)benzamida (E181)	A11	C6	565.2	2.54

487
483

Ejemplo 182

N-((1S,2R)-3-Amino-1-bencil-2-hidroxipropil)-3-(2-oxopirrolidin-1-il)-5-pentiloxibenzamida (E182)

Una mezcla de éster bencílico de ácido [(2R,3S)-2-hidroxi-3-({1-[3-(2-oxo-pirrolidin-1-il)-5-pentiloxi-fenil]-metanoil}-amino)-4-fenil-butil]-carbámico (D105) (820 mg, 1.4 mmol, 1 eq.), paladio al 10% sobre carbón (50% en húmedo, 100 mg, 6% p/p), NH_4CO_2H (800 mg, 12.7 mmol, 9 eq.), EtOH (25 ml) y H_2O (10 ml), se agitó a 60 °C durante 1 h. Después, la mezcla se enfrió a temperatura ambiente y el catalizador se separó por filtración a través de una almohadilla de celite. La mayor parte del EtOH se removió al vacío y el residuo se dividió entre AcOEt y H_2O. La fase acuosa se extrajo con AcOEt. La fase orgánica combinada se secó sobre $MgSO_4$ y se concentró al vacío, para dar *N*-((1S,2R)-3-amino-1-bencil-2-hidroxi-propil)-3-(2-oxo-pirrolidin-1-il)-5-pentiloxi-benzamida (420 mg, 66%), como un sólido blanco. $[M+H]^+$ = 454.0, t.r. = 2.63 min.

Ejemplo 183

N-[(1S,2R)-1-Bencil-2-hidroxi-3-(1-propilbutilamino)-propil]-3-(2-oxopirrolidin-1-il)-5-pentiloxibenzamida (E183)

A una solución de *N*-((1S,2R)-3-amino-1-bencil-2-hidroxi-propil)-3-(2-oxo-pirrolidin-1-il)-5-pentiloxi-benzamida (E182) (30 mg, 0.066 mmol,

1eq.) en $(CH_2Cl)_2$ (5 ml), se le agregó triacetoxiborohidruro de sodio (20 mg, 0.094 mmol, 1.4 eq.), 4-heptanona (10 µl, 0.070 mmol, 1.1 eq.) y CH_3COOH (4 µl, 0.070 mmol, 1,1 eq.). La mezcla resultante se agitó a temperatura ambiente durante 92 horas, se diluyó con CH_2Cl_2, y se lavó con una solución acuosa saturada de $NaHCO_3$; se secó sobre $MgSO_4$ y se concentró al vacío. La purificación del residuo por cromatografía de vaporización instantánea sobre gel de sílice (isohexano/acetato de etilo: 3/2), dio *N*-[(1S,2R)-1-bencil-2-hidroxi-3-(1-propil-butilamino)-propil]-3-(2-oxo-pirrolidin-1-il)-5-pentiloxi-benzamida (4.2 mg, 11%), como un aceite incoloro. $[M+H]^+$ = 552.2, t.r. = 2.98 min.

Ejemplos 184-192

Los siguientes compuestos se prepararon de manera análoga al ejemplo 183, a partir de ácido 3-pentoxi-5-(2-oxo-pirrolidin-1-il)-benzoico (A13) y el aldehído o cetona apropiada:

Ejemplo	$[M+H]^+$	t.r. (min)
N-[(1S,2R)-1-Bencil-2-hidroxi-3-(3-metoxibencilamino)-propil]-3-(2-oxopirrolidin-1-il)-5-pentiloxibenzamida (E184)	574.2	2.87
N-((1S,2R)-1-Bencil-3-bencilamino-2-hidroxipropil)-3-(2-oxopirrolidin-1-il)-5-pentiloxibenzamida (E185)	544.1	2.83
N-((1S,2R)-1-Bencil-3-etilamino-2-hidroxipropil)-3-(2-oxopirrolidin-1-il)-5-pentiloxi-benzamida (E186)	482.2	2.70
N-((1S,2R)-1-Bencil-2-hidroxi-3-fenetilaminopropil)-3-(2-oxopirrolidin-1-il)-5-pentiloxibenzamida (E187)	558.2	2.91

Ejemplo	$[M+H]^+$	t.r. (min)
N-[(1S,2R)-1-Bencil-2-hidroxi-3-(2-fenilpropilamino)-propil]-3-(2-oxopirrolidin-1-il)-5-pentiloxibenzamida (E188)	572.2	2.95
N-((1S,2R)-1-Bencil-3-ciclohexilamino-2-hidroxipropil)-3-(2-oxopirrolidin-1-il)-5-pentiloxibenzamida (E189)	536.2	2.84
N-((1S,2R)-1-Bencil-2-hidroxi-3-(1-metilpiperidin-4-ilamino)-propil]-3-(2-oxopirrolidin-1-il)-5-pentiloxibenzamida (E190)	551.2	2.43
N-((1S,2R)-1-Bencil-2-hidroxi-3-(3-metilbutilamino)-propil]-3-(2-oxopirrolidin-1-il)-5-pentiloxibenzamida (E191)	524.2	2.87
N-[(1S,2R)-1-Bencil-3-(1-etilpropilamino)-2-hidroxipropil]-3-(2-oxopirrolidin-1-il)-5-pentiloxibenzamida (E192)	594.3	3.09

Ejemplos 193-204

Los compuestos de los ejemplos 193-204 se prepararon de manera análoga al ejemplo 1, a partir del ácido y las aminas apropiadas indicadas en el cuadro siguiente:

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
N-[(1S,2R)-1-Bencil-3-(1,5-dimetil-hexilamino)-2-hidroxi-propil]-3-isopropoxi-5-(2-oxopirrolidin-1-il)benzamida (E193)	A11	C20	538.3	2.81
N-[1-Bencil-2-hidroxi-3-(3-trifluorometil-bencilamino)propil]-3-etoxi-5-(2-oxopirrolidin-1-il)benzamida (E194)	A11	C16	570.3	2.64
N-[1-Bencil-3-(1,5-dimetilhexilamino)-2-hidroxipropil]-3-etoxi-5-(2-oxopirrolidin-1-il)-benzamida, sal formiato (E195)	A11	C20	524.3	2.74
N-(1-Bencil-3-ciclohexilamino-2-hidroxipropil)-3-etoxi-5-(2-oxopirrolidin-1-il)-benzamida (E196)	A11	C1	494.3	2.45
N-[1-Bencil-2-hidroxi-3-(3-metoxibencilamino)-propil]-3-etoxi-5-(2-oxopirrolidin-1-il)-benzamida (E197)	A11	C14	532.3	2.50

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexil-carbamoiletilamino)-2-hidroxipropil]-3-metanosulfonil-5-(2-oxopirrolidin-1-il)-benzamida (E198)	A5	C6	599.1	2.41
N-[1-Bencil-2-hidroxi-3-(3-trifluorometil-bencilamino)propil]-3-metilsulfanil-5-(2-oxopirrolidin-1-il)-benzamida (E199)	A1	C16	572.2	2.72
N-[1-Bencil-2-hidroxi-3-(3-trifluorometil-bencilamino)propil]-3-etilsulfanil-5-(2-oxopirrolidin-1-il)benzamida (E200)	A2	C16	586.2	2.80
N-[1-Bencil-2-hidroxi-3-(3-trifluorometil-bencilamino)propil]-3-etanosulfonil-5-(2-oxopirrolidin-1-il)-benzamida (E201)	A6	C16	618.2	2.70
N-[1-Bencil-2-hidroxi-3-(3-trifluorometil-bencilamino)propil]-3-metanosulfonil-5-(2-oxopirrolidin-1-il)-benzamida (E202)	A5	C16	604.1	2.57
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-N',N'-dipropilisoftalamida (E203)	A94	C6	684.2	2.67
3-Azidometil-N-[(1S,2R)-1-bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-benzamida (E204)	A85	C6	612.2	2.52

Ejemplo 205

3-Aminometil-N-[1S,2R)-1-bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)benzamida (E205)

Una mezcla de 3-azidometil-*N*-[(1S,2R)-1-bencil-3-((S)-1-ciclohexilcarbamoil-etilamino)-2-hidroxi-propil]-5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-benzamida (E204) (70 mg, 0.12 mmol, 1 eq.), paladio al 10% sobre carbón (50% en húmedo, 20 mg, 15% p/p), NH_4COOH (65 mg, 1 mmol, 9 eq.), EtOH

(5 ml) y H_2O (2.5 ml), se agitó a 50°C durante 2 h; después se enfrió a temperatura ambiente y el catalizador se separó por filtración a través de una almohadilla de celite. La mayor parte del EtOH se removió al vacío y el residuo se dividió entre AcOEt y una solución acuosa saturada de $NaHCO_3$. La fase acuosa se extrajo con AcOEt. La fase orgánica combinada se secó sobre $MgSO_4$ y se concentró al vacío. El residuo se trituró con Et_2O para dar 3-aminometil-*N*-[(1S,2R)-1-bencil-3-((S)-1-ciclohexilcarbamoil-etilamino)-2-hidroxi-propil]-5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-benzamida (20 mg, 30%), como un sólido blanco. $[M+H]^+$ = 586.2, t.r. = 1.98 min.

Ejemplos 206-207

Los compuestos de los ejemplos 206-207 se prepararon de manera análoga al ejemplo 1, a partir del ácido y las aminas apropiadas indicadas en el cuadro siguiente:

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexil-carbamoiletilamino)-2-hidroxipropil]-3-dimetilaminometil-5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-benzamida (E206)	A84	C6	614.2	1.99
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-vinil-benzamida (E207)	A88	C6	583.1	2.53

Ejemplo 208

N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-etil-benzamida (E208) }

El compuesto del ejemplo 208 se preparó del compuesto del ejemplo 214 de manera análoga al ejemplo 213. [M+H]+ = 585.2, t.r. = 2.56 min.

Ejemplos 209-212

Los compuestos de los ejemplos 209-212 se prepararon de manera análoga al ejemplo 1, a partir del ácido y las aminas apropiadas indicadas en el cuadro siguiente:

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexil-carbamoiletilamino)-2-hidroxipropil]-3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-metoximetilbenzamida (E209)	A86	C6	601.2	2.41
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexil-carbamoiletilamino)-2-hidroxipropil]-3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-etoximetilbenzamida (E210)	A87	C6	615.2	2.50
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexil-carbamoiletilamino)-2-hidroxipropil]-3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-(Z/E)-propenilbenzamida (E211)	A89	C6	597.2	2.61
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexil-carbamoiletilamino)-2-hidroxipropil]-3-(Z/E)-but-1-enil-5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-benzamida (E212)	A90	C6	611.2	2.70

Ejemplo 213

N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-propilbenzamida (E213)

Una mezcla de *N*-[(1S,2R)-1-bencil-3-((S)-1-ciclohexilcarbamoil-etilamino)-2-hidroxi-propil]-3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-propenil-benzamida (E211) (50 mg, 0.083 mmol, 1 eq.), paladio al 10% sobre carbón (50% en húmedo, 15 mg, 15% p/p), NH_4COOH (50 mg, 0.79 mmol, 9 eq.) y EtOH (5 ml), se agitó a 60°C durante 1 h; después se enfrió a temperatura ambiente y el catalizador se separó por filtración a través de una almohadilla de celite. La mayor parte del EtOH se removió al vacío y el residuo se dividió entre AcOEt y una solución acuosa saturada de $NaHCO_3$. La fase acuosa se extrajo con AcOEt. La fase orgánica combinada se secó sobre $MgSO_4$ y se concentró al vacío. El residuo se trituró con Et_2O para dar la *N*-[(1S,2R)-1-bencil-3-((S)-1-ciclohexilcarbamoil-etilamino)-2-hidroxi-propil]-3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-propil-benzamida (45 mg, 90%), como un sólido blanco. $[M+H]^+$ = 599.2, t.r. = 2.63 min.

Ejemplo 214

N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-3-butil-5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)benzamida (E214)

El compuesto del ejemplo 214 se preparó de N-[(1S,2R)-1-

bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-3-(Z/E)-but-1-enil-5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)benzamida (E212), de manera análoga al ejemplo 213. $[M+H]^+$ = 613.2, t.r. = 2.75 min.

Ejemplos 215-216

Los compuestos de los ejemplos 215-216 se prepararon de manera análoga al ejemplo 1, a partir del ácido y las aminas apropiadas indicadas en el cuadro siguiente:

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexil-carbamoiletilamino)-2-hidroxipropil]-3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-(2-metilpropenil)-benzamida (E215)	A91	C6	611.2	2.70
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-fluorometilbenzamida (E216)	A83	C6	589.2	2.44

Ejemplo 217

N-[1-Bencil-3-(1-ciclohexilcarbamoiletilamino)-2-hidroxi-propil]-3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-isobutilbenzamida (E217)

El compuesto del ejemplo 217 se preparó del compuesto del ejemplo 215 de manera análoga al ejemplo 213. $[M+H]^+$ = 613.3, t.r. = 2.72 min.

C788
491

Ejemplos 218-220 y 222

Los compuestos de los ejemplos 218-220 y 222 se prepararon de manera análoga al ejemplo 213, a partir de la amina apropiada indicada en el cuadro siguiente:

Ejemplo	Amina	$[M+H]^+$	t.r. (min)
N-[1-Bencil-2-hidroxi-3-(3-trifluorometilbencilamino)propil]-3- (1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-propilbenzamida (E218)	C16	604.3	2.76
N-[1-Bencil-3-(1, 5-dimetilhexilamino)-2-hidroxipropil]-3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-propilbenzamida, sal formiato (E219)	C26	558.3	2.87
N-(1-Bencil-3-ciclohexilamino-2-hidroxipropil)-3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-propilbenzamida (E220)	C6	528.3	2.61
N-[1-Bencil-2-hidroxi-3-(3-metoxibencilamino)-propil]-3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-propil-benzamida (E222)	C14	566.2	2.64

Ejemplos 221 y 223-226

Los compuestos de los ejemplos 221 y 223-226 se prepararon de manera análoga al ejemplo 1, a partir del ácido y las aminas apropiadas indicadas en el cuadro siguiente:

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
N-[1-Bencil-3-(1-ciclohexil-carbamoiletilamino)-2-hidroxipropil]-5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)isoftalamida (E221)	A92	C6	600.2	2.23
N-[1-Bencil-3-(1-ciclohexilcarbamoil-etilamino)-2-hidroxipropil]-3-ciano-5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-benzamida (E223)	A93	C6	582.2	2.47
N-[1-Bencil-2-hidroxi-3-(3-trifluorometil-bencilamino)propil]-3-ciano-5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)benzamida (E224)	A93	C16	587.2	2.43
N-[1-Bencil-2-hidroxi-3-(3-trifluorometil-bencilamino)propil]-3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-etinil-benzamida, sal formiato (E225)	A111	C16	586.2	2.71
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexil-carbamoiletilamino)-2-hidroxipropil]-3-nitro-5-(2-oxopiperidin-1-il) benzamida (E226)	A82	C6	580.2	2.55

Ejemplo 227

3-Amino-N-[(1S,2R)-1-bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-5-(2-oxopiperidin-1-il)benzamida (E227)

El compuesto del ejemplo 227 se preparó del compuesto del ejemplo 226, de manera análoga al procedimiento descrito para el ejemplo 63. $[M+H]^+$ = 550.1, t.r. = 2.31 min.

Ejemplos 228-251

Los compuestos de los ejemplos 228-251 se prepararon de manera análoga al ejemplo 1, a partir del ácido y las aminas apropiadas

indicadas en el cuadro siguiente:

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoil-etilamino)-2-hidroxipropil]-3-(2-oxopiperidin-1-il)-5-propilaminobenzamida (E228)	A58	C6	592.2	2.59
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoil-etilamino)-2-hidroxipropil]-3-dietilamino-5-(2-oxopiperidin-1-il)benzamida (E229)	A60	C6	606.3	2.62
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoil-etilamino)-2-hidroxipropil]-3-etilamino-5-(2-oxopiperidin-1-il)benzamida (E230)	A59	C6	578.2	2.46
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoil-etilamino)-2-hidroxipropil]-3-metilamino-5-(2-oxopiperidin-1-il)benzamida (E231)	A57	C6	564.3	2.40
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoil-etilamino)-2-hidroxipropil]-3-(2-oxopiperidin-1-il)-5-piperidin-1-ilbenzamida (E232)	A55	C6	618.3	2.65
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoil-etilamino)-2-hidroxipropil]-3-morfolin-4-il-5-(2-oxopiperidin-1-il)benzamida (E233)	A56	C6	620.3	2.43
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoil-etilamino)-2-hidroxipropil]-3-(2-oxopiperidin-1-il)-5-pirrolidin-1-il-benzamida (E234)	A54	C6	604.3	2.64
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoil-etilamino)-2-hidroxipropil]-3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-isopropilaminobenzamida (E235)	A72	C6	614.2	2.58
N-[(1S,2R)-1-Bencil-2-hidroxi-3-((1S,2R)-2-hidroxi-1-isobutilcarbamoil-pentilamino)-propil]-3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-isopropilamino-benzamida (E236)	A72	C33	646.2	2.63
3-Bencilamino-N-[(1S,2R)-1-bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxi-propil]-5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)benzamida (E237)	A64	C6	662.2	2.71
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-3-butilamino-5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-benzamida (E238)	A65	C6	628.2	2.71

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoil-etilamino)-2-hidroxipropil]-3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-(3-metilbutilamino)-benzamida (E239)	A66	C6	642.2	2.79
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoil-etilamino)-2-hidroxipropil]-3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-fenetilamino-benzamida (E240)	A67	C6	676.2	2.80
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoil-etilamino)-2-hidroxipropil]-3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-pentilaminobenzamida (E241)	A68	C6	642.2	2.79
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoil-etilamino)-2-hidroxipropil]-3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-propilaminobenzamida (E242)	A69	C6	614.2	2.57
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoil-etilamino)-2-hidroxipropil]-3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-etilaminobenzamida (E243)	A70	C6	600.2	2.47
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoil-etilamino)-2-hidroxipropil]-3-dietilamino-5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-benzamida (E244)	A63	C6	628.2	2.63
N-[(1S,2R)-1-Bencil-3-(1,5-dimetilhexilamino)-2-hidroxipropil]-3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-etilaminobenzamida (E245)	A70	C20	559.2	2.68
N-[(1S,2R)-1-Bencil-3-(1, 5-dimetilhexilamino)-2-hidroxipropil]-3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-isopropilaminobenzamida (E246)	A72	C20	573.2	2.77
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoil-etilamino)-2-hidroxipropil]-3-(ciclopropil-metilamino)-5-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-benzamida (E247)	A71	C6	626.2	2.59
N-[(1S,2R)-1-Bencil-2-hidroxi-3-(3-metoxibencilamino)propil]-3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-etilamino-benzamida, sal formiato (E248)	A70	C14	567.2	2.44
N-[(1S,2R)-1-Bencil-2-hidroxi-3-(3-trifluorometil-bencilamino)propil]-3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-etilaminobenzamida, sal formiato (E249)	A70	C16	605.1	2.60

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
N-((1S,2R)-1-Bencil-3-ciclohexilamino-2-hidroxipropil)-3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-etilaminobenzamida (E250)	A70	C1	529.3	2.40
N-[1-Bencil-2-hidroxi-3-(3-trifluorometil-bencilamino)propil]-3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-morfolin-4-il-benzamida, sal formiato (E251)	A61	C16	647.3	2.39

Ejemplo 252

N-[(1S,2R)-1-Bencil-2-hidroxi-3-(3-trifluorometil-bencilamino)-propil]-3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-pirrolidin-1-il-benzamida, sal formiato (E252)

A una solución de ácido 3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-pirrolidin-1-il-benzoico (A114) (62 mg, 0.2 mmol, 1 eq.) en DMF (5 ml), a temperatura ambiente, se le agregó (2R,3S)-3-amino-4-fenil-1-(3-trifluorometil-bencilamino)-butan-2-ol (C16) (82 mg, 0.2 mmol, 1 eq.), clorhidrato de 1-(3-dimetilaminopropil)-3-etil-carbodiimida (46 mg, 0.24 mmol, 1.2 eq.), 1-hidroxibenzotriazol hidratado (37 mg, 0.24 mmol, 1.2 eq.) y 4-etilmorfolina (152 µl, 1.2 mmol, 6 eq.). La mezcla resultante se agitó durante 4 h y después se concentró al vacío. El residuo se diluyó con AcOEt y la fase orgánica se lavó con una solución acuosa saturada de $NaHCO_3$, se secó sobre $MgSO_4$ y se concentró al vacío. El residuo se purificó por trituración con Et_2O, para producir la *N*-[(1S,2R)-1-bencil-2-hidroxi-3-(3-trifluorometil-bencilamino)-

propil]-3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-pirrolidin-1-il-benzamida, como un sólido blanco (46 mg, 36%). $[M+H]^+$ = 631.2, t.r. = 2. 65 min.

Ejemplos 253-289

Los compuestos de los ejemplos 253-289 se prepararon de manera análoga al ejemplo 1, a partir del ácido y las aminas apropiadas indicadas en el cuadro siguiente:

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
N-[1-Bencil-2-hidroxi-3-(3-trifluorometil-bencilamino)propil]-3-(1,1-dioxo-1-16-isotiazolidin-2-il)-5-metilaminobenzamida, sal formiato (E253)	A62	C16	591.2	2.58
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexil-carbamoiletilamino)-2-hidroxipropil]-3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-etoxibenzamida (E254)	A18	C6	601.2	2.54
N-[1-Bencil-2-hidroxi-3-(3-trifluorometil-bencilamino)propil]-3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-etoxi-benzamida (E255)	A18	C16	606.2	2.66
N-[1-Bencil-3-(1,5-dimetilhexilamino)-2-hidroxipropil]-3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-etoxibenzamida, sal formiato (E256)	A18	C20	560.3	2.74
N-[1-Bencil-2-hidroxi-3-(3-metoxibencilamino)-propil]-3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-etoxibenzamida (E257)	A18	C14	568.3	2.50
N-(1-Bencil-3-ciclohexilamino-2-hidroxipropil)-3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-etoxibenzamida (E258)	A18	C1	530.2	2.47
N-[1-Bencil-3-(1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5- isopropoxibenzamida (E259)	A19	C6	615.4	2.68

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
N-[1-Bencil-3-(1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-propoxibenzamida (E260)	A21	C6	615.4	2.89
N-[1-Bencil-3-(1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-pentiloxibenzamida (E261)	A22	C6	643.5	2.89
N-[1-Bencil-3-(1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-metoxibenzamida (E262)	A20	C6	587.4	2.49
N-(1-Bencil-3-ciclopropilamino-2-hidroxipropil)-3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-etoxibenzamida (E263)	A18	C26	488.2	2.37
N-[1-Bencil-2-hidroxi-3-(3-trifluorometoxibencilamino)propil]-3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-etoxibenzamida (E264)	A18	C11	622.2	2.91
N-[1-Bencil-2-hidroxi-3-(3-trifluorometil-bencilamino)propil]-3-(1,1-dioxo-1λ^6isotiazolidin-2-il)-5-metilsulfanilbenzamida (E265)	A3	C16	608.2	2.73
N-[1-Bencil-2-hidroxi-3-(3-trifluorometil-bencilamino)propil]-3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-etilsulfanilbenzamida (E266)	A4	C16	622.2	2.82
N-[1-Bencil-2-hidroxi-3-(3-trifluorometil-bencilamino)propil]-3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-etanosulfonilbenzamida (E267)	A8	C16	654.1	2.65
N-[1-Bencil-2-hidroxi-3-(3-trifluorometil-bencilamino)propil]-3-(1,1-dioxo-1λ^6-isotiazolidin-2-il)-5-metanosulfonilbenzamida (E268)	A7	C16	640.2	2.62
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexil-carbamoiletilamino)-2-hidroxipropil]-5-(2-oxopiperidin-1-il)-N',N'-dipropilisoftalamida (E269)	A81	C6	662.3	2.63
ácido fórmico - 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-2-fluoro-N-{(1S,2R)-2-hidroxi-1-(fenilmetil)-3-[({3-[(trifluorometil)oxi]fenil}metil)-amino]propil}-5-[(1-metiletil)amino]benzamida (1:1) (E270)	A175	C11	667.4	2.82
3-(1,1-Dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-N-[(1S,2R)-3-{[(3-etil-5-isoxazolil)-metil]amino}-2-hidroxi-1-(fenilmetil)propil]-2-fluorobenzamida (E271)	A119	C157	588.4	2.30

1695
498

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
4-(1,1-Dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-1-etil-*N*-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-(tetrahidro-2*H*-piran-4-ilamino)propil]-1*H*-benzoimidazol-6-carboxamida (E272)	A151	C43	570.4	1.91
8-(1,1-Dioxido-2-isotiazolidinil)-4-etil-*N*-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-(tetrahidro-2*H*-piran-4- ilamino)propil]-1,2,3,4-tetrahidro-6-quinoxalincarboxamida (E273)	A172	C43	572.4	2.08
8-(1,1-Dioxido-2-isotiazolidinil)-4-etil-*N*-[(1S,2R)-3-{[(1-etil-1*H*-pirazol-4-il)metil]amino}-2-hidroxi-1-(fenilmetil)propil]-1,2,3,4-tetrahidro-6-quinoxalincarboxamida (E274)	A172	C154	596.4	2.15
4-(1,1-Dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-1-etil-*N*-[(1S,2R)-2-hidroxi-3-[(1-metiletil)amino]-1-(fenilmetil)propil]-1*H*-benzoimidazol-6-carboxamida (E275)	A151	C28	528.4	1.92
8-(1,1-Dioxido-2-isotiazolidinil)-4-etil-*N*-[(1S,2R)-2-hidroxi-3-[(1-metiletil)amino]-1-(fenilmetil)propil]-1,2,3,4-tetrahidro-6-quinoxalincarboxamida (E276)	A172	C28	530.4	2.11
N-[(1S,2R)-1-Bencil-3-((S)-1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-5-(1,1-dioxo-1λ^6-[1,2]tiazinan-2-il)-N',N'-dipropilisoftalamida (E277)	A95	C8	698.2	2.68
N-[1-Bencil-2-hidroxi-3-(3-trifluorometilbencilamino)propil]-5-(1,1-dioxo-1λ^6-[1,2]tiazinan-2-il)-N',N'-dipropilisoftalamida (E278)	A95	C16	703.3	2.87
N-(1-Bencil-3-ciclopropilamino-2-hidroxipropil)-5-(1,1-dioxo-1λ^6-[1,2]tiazinan-2-il)-N',N'-dipropilisoftalamida (E279)	A95	C26	585.3	2.55
N-[1-Bencil-2-hidroxi-3-(3-trifluorometilbencilamino)propil]-3-(1,1-dioxo-1λ^6-[1,2]tiazinan-2-il)-5-propilbenzamida (E280)	A112	C16	618.2	3.07
N-[1-Bencil-2-hidroxi-3-(3-metoxibencilamino)-propil]-3-(1,1-dioxo-1λ^6-[1,2]tiazinan-2-il)-5-propilbenzamida, sal formiato (E281)	A112	C14	580.3	2.77
N-[1-Bencil-3-(1,5-dimetilhexilamino)-2-hidroxipropil]-3-(1,1-dioxo-1λ^6-[1,2]tiazinan-2-il)-5-propilbenzamida, sal formiato (E282)	A112	C20	572.3	3.01

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
N-[1-Bencil-3-(1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-3-(1,1-dioxo-1λ^6-[1,2]tiazinan-2-il)-5-propilbenzamida (E283)	A112	C6	613.4	2.80
N-[1-Bencil-2-hidroxi-3-(3-metoxibencilamino)-propil]-5-(1,1-dioxo-1λ^6-[1,2]tiazinan-2-il)-N',N'-dipropil-isoftalamida (E284)	A95	C14	665.3	2.85
N-[1-Bencil-2-hidroxi-3-(3-trifluorometoxi-bencilamino)propil]-5-(1,1-dioxo-1λ^6-[1,2]-tiazinan-2-il)-N',N'-dipropilisoftalamida, sal formiato (E285)	A95	C11	719.2	3.02
N-[1-Bencil-2-hidroxi-3-(3-trifluorometil-bencilamino)propil]-3-(1,1-dioxo-1λ^6-[1,2]-tiazinan-2-il)-5-etilaminobenzamida, sal formiato (E286)	A73	C16	619.2	2.73
N-[1-Bencil-2-hidroxi-3-(3-metoxibencilamino)-propil]-3-(1,1-dioxo-1λ^6-[1,2]tiazinan-2-il)-5-etilaminobenzamida, sal formiato (E287)	A73	C14	581.2	2.72
N-[1-Bencil-3-(1,5-dimetilhexilamino)-2-hidroxipropil]-3-(1,1-dioxo-1λ^6-[1,2]tiazinan-2-il)-5-etilaminobenzamida, sal formiato (E288)	A73	C20	573.3	2.99
N-[1-Bencil-3-(1-ciclohexilcarbamoiletilamino)-2-hidroxipropil]-3-(1,1-dioxo-1λ^6-[1,2]tiazinan-2-il)-5-etilaminobenzamida (E289)	A73	C6	614.3	2.75

Ejemplos 290-427 (E290-E427)

Los siguientes compuestos se prepararon de manera análoga al ejemplo 183, a partir de la amina apropiada y el aldehído o cetona apropiada:

Ejemplo	Precursor	$[M+H]^+$	t.r. (min)
ácido fórmico - N-{(1S,2R)-1-Bencil-3-[(3,5-diclorobencil)amino]-2-hidroxipropil}-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzamida (1:1) (E290)	D120	619.3	2.69
ácido fórmico - N-{(1S,2R)-1-Bencil-3-[(2-fluoro-5-metoxibencil)amino]-2-hidroxipropil}-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzamida (1:1) (E291)	D120	599.4	2.48
ácido fórmico - N-{(1S,2R)-1-Bencil-3-[(4-fluoro-3-metoxibencil)amino]-2-hidroxipropil}-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzamida (1:1) (E292)	D120	599.4	2.52
ácido fórmico - N-{(1S,2R)-1-Bencil-3-[(3,5-dimetilbencil)amino]-2-hidroxipropil}-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzamida (1:1) (E293)	D120	579.3	2.68
N-{(1S,2R)-1-Bencil-3-[(3,5-difluorobencil)amino]-2-hidroxipropil}-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzamida (E294)	D120	587.3	2.61
N-((1S,2R)-1-Bencil-2-hidroxi-3-{[3-nitro-5-(trifluorometil)bencil]amino}propil)-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzamida (E295)	D120	664.2	2.78
N-((1S,2R)-1-Bencil-3-{[(5-cianopiridin-3-il)metil]amino}-2-hidroxipropil)-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzamida (E296)	D120	577.3	2.42
ácido fórmico - N-(1S,2R)-1-Bencil-3-[(3-cloro-5-metoxibencil)amino]-2-hidroxipropil}-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzamida (1:1) (E297)	D120	615.3	2.70
N-{(1S,2R)-1-Bencil-3-[(3-bromo-5-fluorobencil)amino]-2-hidroxipropil}-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzamida (E298)	D120	649.2	2.70
5-{[((2R,3S)-3-{[3-(1,1-Dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzoil]amino}-2-hidroxi-4-fenilbutil)amino]metil}-N-metilnicotinamida (E299)	D120	609.3	2.34
ácido fórmico - N-{(1S,2R)-1-Bencil-3-[(3-bromo-5-metoxibencil)amino]-2-hidroxipropil}-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzamida (1:1) (E300)	D120	661.2	2.71

Ejemplo	Precursor	$[M+H]^+$	t.r. (min)
5-{[((2R,3S)-3-{[3-(1,1-Dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzoil]amino}-2-hidroxi-4-fenilbutil)amino]metil}nicotinato de metilo (E301)	D120	610.3	2.44
N-{(1S,2R)-1-Bencil-3-[(3,5-di-ter-butilbencil)amino]-2-hidroxipropil}-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzamida (E302)	D120	663.4	3.14
N-((1S,2R)-1-Bencil-2-hidroxi-3-{[3-metil-5-(metilsulfonil)bencil]amino}propil)-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzamida (E303)	D120	643.3	2.53
N-{(1S,2R)-1-Bencil-2-hidroxi-3-[(3-metoxi-5-metilbencil)amino]propil}-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzamida (E304)	D120	595.3	2.65
5-{[((2R,3S)-3-{[3-(1,1-Dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzoil]amino}-2-hidroxi-4-fenilbutil)-amino]metil}isoftalato de dimetilo (E305)	D120	667.3	2.63
N-{(1S,2R)-1-Bencil-3-[(3,5-diisopropoxi-bencil)amino]-2-hidroxipropil}-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzamida (E306)	D120	667.4	2.91
N-{(1S,2R)-1-Bencil-3-{[(4-bromo-2-tienil)metil]amino}-2-hidroxipropil)-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzamida (E307)	D120	637.3	2.56
N-{(1S,2R)-1-Bencil-3-[(2,3-dihidro-1-benzofuran-6-ilmetil)amino]-2-hidroxipropil}-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzamida (E308)	D120	593.3	2.42
ácido fórmico - N-((1S,2R)-1-Bencil-3-{[(4-cloro-1-metil-1*H*- pirazol-3-il)metil]amino}-2-hidroxipropil)-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)-benzamida (1:1) (E309)	D 120	589.3	2.26
N-((1S,2R)-1-Bencil-3-{[(2-bromo-1,3-tiazol-5-il)metil]amino}-2-hidroxipropil)-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzamida (E310)	D120	638.2	2.36
N-((1S,2R)-1-Bencil-3-{[(4-bromo-1*H*-pirrol-2-il)metil]amino}-2-hidroxipropil)-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzamida (E311)	D120	618.2	2.54
ácido fórmico - N-((1S,2R)-1-Bencil-3-{[(2-butil-1*H*-imidazol-4-il)metil]amino}-2-hidroxipropil)-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)-benzamida (1:1) (E312)	D120	597. 4	2.11
N-{(1S,2R)-1-Bencil-3-[(3-bromobencil)amino]-2-hidroxipropil}-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzamida (E313)	D120	631.2	2.59

Ejemplo	Precursor	$[M+H]^+$	t.r. (min)
N-{(1S,2R)-1-Bencil-2-hidroxi-3-[(3-nitrobencil)amino]propil}-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzamida (E314)	D120	596.3	2.45
N-{(1S,2R)-1-Bencil-2-hidroxi-3-[(3-tienilmetil)-amino]propil}-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzamida (E315)	D120	557.3	2.36
N-((1S,2R)-1-Bencil-3-{[(4-bromo-1-metil-1*H*-pirazol-3-il)metil]amino}-2-hidroxipropil)-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzamida (E316)	D120	635.3	2. 33
N-((1S,2R)-1-Bencil-3-{[3-fluoro-5-(trifluorometil)-bencil]amino}-2-hidroxipropil)-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzamida (E317)	D120	637.3	2.68
ácido fórmico - N-{(1S,2R)-1-Bencil-2-hidroxi-3-[(3-vinilbencil)amino]propil}-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino benzamida) (1:1) (E318)	D120	577.3	2.43
ácido fórmico - N-((1S,2R)-1-Bencil-2-hidroxi-3-{[(4-metoxi-3-tienil)metil]amino}propil)-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzamida (1:1) (E319)	D120	587.3	2.31
Acido 3-{[((2R,3S)-3-{[3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzoil]amino}-2-hidroxi-4-fenilbutil)amino]metil}benzoico - ácido fórmico (1:1) (E320)	D120	595.3	2.27
ácido fórmico - N-{(1S,2R)-1-Bencil-3-[(3,4-dimetoxibencil)amino]-2-hidroxipropil}-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzamida (1:1) (E321)	D120	611.3	2.28
ácido fórmico - N-((1S,2R)-1-Bencil-3-{[(5-etil-2-furil)metil]amino}-2-hidroxipropil)-3-(1,1-dioxido-1,2-tiazinan-5-(etilamino)benzamida (1:1) (E322)	D120	567.4	2.34
ácido fórmico - N-{(1S,2R)-1-Bencil-3-[(2,3-dihidro-1,4-benzodioxin-6-ilmetil)amino]-2-hidroxipropil}-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzamida (1:1) (E323)	D120	609.4	2.32
ácido fórmico - N-{(1S,2R)-1-Bencil-3-[(3-etoxi-4-metoxibencil)amino]-2-hidroxipropil}-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzamida (1:1) (E324)	D120	625.4	2.36

Ejemplo	Precursor	$[M+H]^+$	t.r. (min)
ácido fórmico - N-((1S,2R)-1-Bencil-3-{[(5-etil-2-tienil)metil]amino}-2-hidroxipropil)-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzamida (1:1) (E325)	D120	585.3	2.46
ácido fórmico - N-{(1S,2R)-1-Bencil-3-[(3-cloro-4-fluorobencil)amino]-2-hidroxipropil}-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzamida (1:1) (E326)	D120	603.3	2.49
ácido fórmico - N-((1S,2R)-1-Bencil-3-{[(1-etil-1*H*-pirazol-4-il)metil]amino}-2-hidroxipropil)-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzamida (1: 1) E327	D120	569.4	2.13
ácido fórmico - N-((1S,2R)-1-Bencil-3-{[(1-etil-3-metil-1*H*-pirazol-4-il)metil]amino}-2-hidroxipropil)-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)-benzamida (1:1) (E328)	D120	583.4	2.17
ácido fórmico - N-((1S,2R)-1-Bencil-3-{[(2,2-dimetil-3,4-dihidro-2H-cromen-6-il)metil]amino}-2-hidroxipropil)-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzamida (1:1) (E329)	D120	635.4	2.60
ácido fórmico - N-{(1S,2R)-1-Bencil-3-{[4-cloro-3-(trifluorometil)bencil]amino}-2-hidroxipropil)-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)-benzamida (1:1) (E330)	D120	653.3	2.69
ácido fórmico - N-((1S,2R)-1-Bencil-2-hidroxi-3-{[(6-metilpiridin-2-il)metil]amino}propil)-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzamida (1: 1) (E331)	D120	566.3	2.22
ácido fórmico - N-{(1S,2R)-1-Bencil-3-[(3-etilbencil)amino]-2-hidroxipropil}-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzamida (1:1) (E332)	D120	579.5	2.40
N-((1S,2R)-1-bencil-2-{[(1-etil-1*H*-pirazol-4-il)metil]amino}-2-hidroxipropil)-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)-2-fluorobenzamida (E333)	D121	587.4	2.08
ácido fórmico - N-((1S,2R)-1-bencil-3-{[(1-etil-1*H*-pirazol-4-il)metil]amino}-2-hidroxipropil)-3-(etilamino)-5-(2-oxopirrolidin-1-il)benzamida (1:1) (E334)	E66	519.5	2.00

Ejemplo	Precursor	$[M+H]^+$	t.r. (min)
ácido fórmico - N-{(1S,2R)-1-bencil-2-hidroxi-3-[(3-metoxi-4-metilbencil)amino]propil}-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzamida (1:1) (E335)	D120	595.2	2.65
ácido fórmico - N-{(1S,2R)-1-bencil-2-hidroxi-3-[(3-metoxi-2-metilbencil)amino]propil}-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzamida (1:1) (E336)	D120	595.4	2.60
3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-N-[(1S,2R)-2-hidroxi-3-[(1-metilbutil)-amino]-1-(fenilmetil)propil]benzamida (E337)	D120	531.5	0.75
clorhidrato de 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-N-{(1S,2R)-2-hidroxi-1-(fenilmetil)-3-[(1-propilbutil)amino]-propil}benzamida (E338	D120	559.5	0.88
clorhidrato de 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-N-[(1S,2R)-2-hidroxi-3-[(1-metilpentil)amino]-1-(fenilmetil)propil]-benzamida (E339)	D120	545.5	0.84
clorhidrato de N-[(1S,2R)-3-[(1,4-dimetilpentil)-amino]-2-hidroxi-1-(fenilmetil)propil]-3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)benzamida (E340)	D120	559.5	0.88
clorhidrato de 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-N-[(1S,2R)-2-hidroxi-3-[(3-metilbutil)amino]-1-(fenilmetil)propil]-benzamida (E341)	D120	531.5	0.81
clorhidrato de 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-(propilamino)propil]-benzamida (E342)	D120	503.5	0.72
clorhidrato de N-[(1S,2R)-3-{[1-(3-clorofenil)-propil]amino}-2-hidroxi-1-(fenilmetil)propil]-3-(etilamino)-5-(2-oxo-1-pirrolidinil)benzamida (E343)	E66	563. 5	0.84
clorhidrato de N-[(1S,2R)-3-{[1-(3-clorofenil)-propil]amino}-2-hidroxi-1-(fenilmetil)propil]-3-ciclopentil-5-(2-oxo-1-pirrolidinil)benzamida (E344)	D122	588.4	1.01

Ejemplo	Precursor	$[M+H]^+$	t.r. (min)
clorhidrato de 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-N-[(1S,2R)-2-hidroxi-3-[(4-metilpentil)amino]-1-(fenilmetil)propil]-benzamida (E345)	D120	545.5	0.85
clorhidrato de 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-N-[(1S,2R)-2-hidroxi-3-[(5-metilhexil)amino]-1-(fenilmetil)propil]-benzamida (E346)	D120	559.6	0.89
clorhidrato de 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-N-[(1S,2R)-2-hidroxi-3-[(1-metilpropil)amino]-1-(fenilmetil)propil]-benzamida (E347)	D120	517.5	0.74
clorhidrato de 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-N-[(1S,2R)-2-hidroxi-3-[(1-metilhexil)amino]-1-(fenilmetil)propil]-benzamida (E348)	D120	559.6	0.89
N-[(1S,2R)-3-{[(3,5-dibromofenil)metil]amino}-2-hidroxi-1-(fenilmetil)propil]-3-[(1-metiletil)oxi]-5-(2-oxo-1-pirrolidinil)benzamida (E349)	D123	672.3	0.89
N-{(1S,2R)-2-hidroxi-1-(fenilmetil)-3- [(fenilmetil)-amino]propil}-3-[(1-metiletil)oxi]-5-(2-oxo-1-pirrolidinil)benzamida (E350)	D123	516.5	0.78
N-[(1S,2R)-3-{[(3-bromofenil)metil]amino}-2-hidroxi-1-(fenilmetil)propil]-3-[(1-metiletil)oxi]-5-(2-oxo-1-pirrolidinil)benzamida (E351)	D123	596.2	0.83
N-(1S,2R)-3-({[3-(etiloxi)fenil]metil}amino)-2-hidroxi-1-(fenilmetil)propil]-3-[(1-metiletil)oxi]-5-(2-oxo-1-pirrolidinil)benzamida (E352)	D123	560.4	0.82
N-[(1S,2R)-3-{[(3-clorofenil)metil]amino}-2-hidroxi-1-(fenilmetil)propil]-3-[(1-metiletil)oxi]-5-(2-oxo-1-pirrolidinil)benzamida (E353)	D123	550.3	0.82
N-{(1S,2R)-2-hidroxi-1-(fenilmetil)-3-[({3-[(trifluorometil)oxi]fenil}metil)amino]propil}-3-[(1-metiletil)oxi]-5-(2-oxo-1-pirrolidinil)benzamida (E354)	D123	600.3	0.87
N-[(1S,2R)-3-({[3,5-bis(metiloxi)fenil]metil}amino)-2-hidroxi-1-(fenilmetil)propil]-3-[(1-metiletil)oxi]-5-(2-oxo-1-pirrolidinil)benzamida (E355)	D123	576.4	0.81
N-[(1S,2R)-3-{[(3,5-diclorofenil)metil]amino}-2-hidroxi-1-(fenilmetil)propil]-3-[(1-metiletil)oxi]-5-(2-oxo-1-pirrolidinil)benzamida (E356)	D123	584.2	0.87

Ejemplo	Precursor	$[M+H]^+$	t.r. (min)
N-[(1S,2R)-3-{[(3,5-difluorofenil)metil]amino}-2-hidroxi-1-(fenilmetil)propil]-3-[(1-metiletil)oxi]-5-(2-oxo-1-pirrolidinil)benzamida (E357)	D 123	552.3	0.80
N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-({[3-(trifluorometil)fenil]metil}amino)propil]-3-[(1-metiletil)oxi]-5-(2-oxo-1-pirrolidinil)benzamida (E358)	D123	584.3	0.85
N-[(1S,2R)-3-({[3,5-bis(trifluorometil)fenil]-metil}amino)-2-hidroxi-1-(fenilmetil)propil]-3-[(1-metiletil)oxi]-5-(2-oxo-1-pirrolidinil)benzamida (E359)	D123	652.3	0.93
N-[(1S,2R)-2-hidroxi-3-{[(3-metilfenil)metil]amino}-1-(fenilmetil)propil]-3-[(1-metiletil)oxi]-5-(2-oxo-1-pirrolidinil)benzamida (E360)	D123	530.4	0.82
clorhidrato de 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-({[3-(trifluorometil)fenil]metil}amino)propil]-5-[(1-metiletil)oxi]benzamida (E361)	D124	634.3	0.88
clorhidrato de 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-N-[(1S,2R)-2-hidroxi-3-({[3-(metiloxi)fenil]metil}amino)-1-(fenilmetil)propil]-5-[(1-metiletil)oxi]benzamida (E362)	D124	596.3	0.82
clorhidrato de 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-[({3-[(trifluorometil)oxi]fenil}metil)amino]propil]-5-[(1-metiletil)oxi]benzamida (E363)	D124	650.3	0.89
clorhidrato de N-[(1S,2R)-3-({[3,5-bis(trifluorometil)fenil]metil}amino)-2-hidroxi-1-(fenilmetil)propil]-3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-[(1-metiletil)oxi]benzamida (E364)	D124	702.3	0.96
clorhidrato de N-[(1S,2R)-3-({[3,5-bis(metiloxi)fenil]metil}amino)-2-hidroxi-1-(fenilmetil)propil]-3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-[(1-metiletil)oxi]benzamida (E365)	D124	626.3	0.82
clorhidrato de N-[(1S,2R)-3-{[(3,5-dibromofenil)-metil]amino}-2-hidroxi-1-(fenilmetil)propil]-3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-[(1-metiletil)oxi]benzamida (E366)	D124	722.1	0.90
clorhidrato de 3-ciclopentil-5-(1,1-dioxido-tetrahidro-2*H*-1,2-tiazin-2-il)-N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-({[3-(trifluorometil)fenil]metil}-amino)propil]benzamida (E367)	D125	644.4	0.94

Ejemplo	Precursor	$[M+H]^+$	t.r. (min)
clorhidrato de 3-ciclopentil-5-(1,1-dioxido-tetrahidro-2*H*-1,2-tiazin-2-il)-N-[(1S,2R)-2hidroxi-3-({[3-(metiloxi)fenil]metil}amino)-1-(fenilmetil)propil]benzamida (E368)	D125	606.4	0.88
clorhidrato de 3-ciclopentil-5-(1,1-dioxido-tetrahidro-2*H*-1,2-tiazin-2-il)-N-{(1S,2R)-2-hidroxi-1-(fenilmetil)-3-[({3-[(trifluorometil)oxi]fenil}-metil)amino]propil}benzamida (E369)	D125	660.4	0.95
clorhidrato de N-[(1S,2R)-3-({[3,5-bis (trifluorometil)fenil]metil}amino)-2-hidroxi-1-(fenilmetil)propil]-3-ciclopentil-5-(1,1-dioxido-tetrahidro-2*H*-1,2-tiazin-2-il)benzamida (E370)	D125	712.4	1.02
clorhidrato de N-[(1S,2R)-3-({[3,5-bis (metiloxi)-fenil]metil}amino)-2-hidroxi-1-(fenilmetil)propil]-3-ciclopentil-5-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)benzamida (E371)	D125	636.4	0.90
clorhidrato de 3-ciclopentil-N-[(1S,2R)-3-{[(3,5-dibromofenil)metil]amino}-2-hidroxi-1-(fenilmetil)propil]-5-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)benzamida (E372)	D125	732.2	0.99
clorhidrato de 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-N-{(1S,2R)-2-hidroxi-1-(fenilmetil)-3-[({3-[(trifluorometil)oxi]fenil}-metil)amino]propil}benzamida (E373)	D120	635.3	0.83
clorhidrato de N-[(1S,2R)-3-({[3,5-bis (trifluorometil)fenil]metil}amino)-2-hidroxi-1-(fenilmetil)propil]-3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)benzamida (E374)	D120	687.3	0.89
clorhidrato de N-[(1S,2R)-3-({[3,5-bis (metiloxi)-fenil]metil}amino)-2-hidroxi-1-(fenilmetil)propil]-3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)benzamida (E375)	D120	611.4	0.77
clorhidrato de N-[(1S,2R)-3-{[(3,5-dibromofenil)-metil]amino}-2-hidroxi-1-(fenilmetil)propil]-3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-etilamino)benzamida (E376)	D120	707.2	0.85
clorhidrato de 3-(etiloxi)-N-{(1S,2R)-2-hidroxi-1-(fenilmetil-3-[({3-[(trifluorometil)oxi]fenil}metil)-amino]propil}-5-(2-oxo-1-pirrolidinil)-benzamida (E377)	D126	586.2	0.82

Ejemplo	Precursor	$[M+H]^+$	t.r. (min)
clorhidrato de N-[(1S,2R)-3-({[3,5-bis-(trifluorometil)fenil]-metil}amino)-2-hidroxi-1-(fenilmetil)propil]-3-(etiloxi)-5-(2-oxo-1-pirrolidinil)benzamida (E378)	D126	638.2	0.88
clorhidrato de N-[(1S,2R)-3-({[3,5-bis(metiloxi)-fenil]metil}amino)-2-hidroxi-1-(fenilmetil)propil]-3-(etiloxi)-5-(2-oxo-1-pirrolidinil)benzamida (E379)	D126	562.3	0.75
clorhidrato de N-[(1S,2R)-3-{[(3,5-dibromofenil)-metil]amino}-2-hidroxi-1-(fenilmetil)propil]-3-(etiloxi)-5-(2-oxo-1-pirrolidinil)benzamida (E380)	D126	658.0	0.83
clorhidrato de 3-ciclopentil-N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-[({3-[(trifluorometil)oxi]fenil}-metil)amino]propil]-5-(2-oxo-1-pirrolidinil)-benzamida (E381)	D122	610.3	0.92
clorhidrato de N-[(1S,2R)-3-({[3,5-bis-(trifluorometil)fenil]metil}amino)-2-hidroxi-1-(fenilmetil)propil]-3-ciclopentil-5-(2-oxo-1-pirrolidinil)benzamida (E382)	D122	662.3	0.99
clorhidrato de N-[(1S,2R)-3-({[3,5-bis(metiloxi)-fenil]metil}amino)-2-hidroxi-1-(fenilmetil)propil]-3-ciclopentil-5-(2-oxo-1-pirrolidinil)benzamida (E383)	D122	586.3	0.86
clorhidrato de 3-ciclopentil-N-[(1S,2R)-3-{[(3,5-dibromofenil)-metil]amino}-2-hidroxi-1-(fenilmetil)propil]-5-(2-oxo-1-pirrolidinil)benzamida (E384)	D122	682.1	0.94
clorhidrato de N-[(1S,2R)-3-({[3,5-bis(metiloxi)-fenil]metil}amino)-2-hidroxi-1-(fenilmetil)propil]-3-(etilamino)-5-(2-oxo-1-pirrolidinil)benzamida (E385)	E66	561.3	0.73
clorhidrato de N-[(1S,2R)-3-{[(3,5-dibromofenil)-metil]amino}-2-hidroxi-1-(fenilmetil)propil]-3-(etilamino)-5-(2-oxo-1-pirrolidinil)benzamida (E386)	E66	657.1	0.80
clorhidrato de N-[(1S,2R)-3-({[3,5-bis (trifluorometil)fenil]metil}amino)-2-hidroxi-1-(fenilmetil)propil]-3-(1,1-dioxido-2-isotiazolidinil)-5-(etiloxi)benzamida (E387)	D127	674.2	0.88
clorhidrato de N-[(1S,2R)-3-({[3,5-bis(metiloxi)-fenil]metil}amino)-2-hidroxi-1-(fenilmetil)propil]-3-(1,1-dioxido-2-isotiazolidinil)-5-(etiloxi)benzamida (E388)	D127	598.3	0.76

Ejemplo	Precursor	$[M+H]^+$	t.r. (min)
clorhidrato de N-[(1S,2R)-3-{[(3,5-dibromofenil)-metil]amino}-2-hidroxi-1-(fenilmetil)propil]-3-(1,1-dioxido-2-isotiazolidinil)-5-(etiloxi)benzamida (E389)	D127	694.1	0.84
clorhidrato de 3-(1,1-dioxido-2-isotiazolidinil)-N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-({[3-(trifluorometil)fenil]metil}amino)propil]-5-[(1-metiletil)oxi]benzamida (E390)	D128	620.2	0.84
clorhidrato de 3-(1,1-dioxido-2-isotiazolidinil)-N-[(1S,2R)-2-hidroxi-3-({[3-(metiloxi)fenil]metil}-amino)-1-(fenilmetil)propil]-5-[(1-metiletil)oxi]-benzamida (E391)	D128	582.3	0.77
clorhidrato de 3-(1,1-dioxido-2-isotiazolidinil)-N-{(1S,2R)-2-hidroxi-1-(fenilmetil)-3-[({3-[(trifluorometil)oxi]fenil}metil)amino]propil}-5-[(1-metiletil)oxi]benzamida (E392)	D128	636.2	0.85
clorhidrato de N-[(1S,2R)-3-({[3,5-bis(trifluorometil)fenil]metil}amino)-2-hidroxi-1-(fenilmetil)propil]-3-(1,1-dioxido-2-isotiazolidinil)-5-[(1-metiletil)oxi]benzamida (E393)	D128	688.2	0.91
clorhidrato de N-[(1S,2R)-3-({[3,5-bis-(trifluorometil)fenil]metil}amino)-2-hidroxi-1-(fenilmetil)propil]-3-(1,1-dioxido-2-isotiazolidinil)-5-[(1-metiletil)oxi]benzamida (E394)	D128	612.2	0.80
clorhidrato de N-[(1S,2R)-3-{[(3,5-dibromofenil)-metil]amino}-2-hidroxi-1-(fenilmetil)propil]-3-(1,1-dioxido-2-isotiazolidinil)-5-[(1-metiletil)oxi]-benzamida (E395)	D128	708.1	0.87
clorhidrato de 3-ciclopentil-5-(1,1-dioxido-2-isotiazolidinil)-N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-({[3-(trifluorometil)fenil]metil}amino)propil]-benzamida (E396)	D129	630.2	0.90
clorhidrato de 3-ciclopentil-5-(1,1-dioxido-2-isotiazolidinil)-N-[(1S,2R)-2-hidroxi-3-({[3-(metiloxi)fenil]metil}amino)-1-fenilmetil)propil]-benzamida (E397)	D129	592.3	0.84
clorhidrato de 3-ciclopentil-5-(1,1-dioxido-2-isotiazolidinil)-N-{(1S,2R)-2-hidroxi-1-(fenilmetil)-3-[({3-[(trifluorometil)oxi]fenil}metil)amino]propil}-benzamida (E398)	D129	646.3	0.91

Ejemplo	Precursor	$[M+H]^+$	t.r. (min)
clorhidrato de N-[(1S,2R)-3-({[3,5-bis (trifluorometil)fenil]metil}amino)-2-hidroxi-1-(fenilmetil)propil]-3-ciclopentil-5-(1,1-dioxido-2-isotiazolidinil)benzamida (E399)	D129	698.3	0.98
clorhidrato de N-[(1S,2R)-3-({[3,5-bis (metiloxi)-fenil]metil}amino)-2-hidroxi-1-(fenilmetil)propil]-3-ciclopentil-5-(1,1-dioxido-2-isotiazolidinil)-benzamida (E400)	D129	622.3	0.86
clorhidrato de 3-ciclopentil-N-[(1S,2R)-3-{[(3,5-dibromofenil)metil]amino}-2-hidroxi-1-(fenilmetil)-propil]-5-(1,1-dioxido-2-isotiazolidinil)benzamida (E401)	D129	718.1	0.94
clorhidrato de 3-(1,1-dioxido-2-isotiazolidinil)-5-(etilamino)-N-{(1S,2R)-2-hidroxi-1-(fenilmetil)-3-[({3-[(trifluorometil)oxi]fenil}metil)amino]propil}-benzamida (E402)	D130	621.3	0.80
clorhidrato de N-[(1S,2R)-3-({[3,5-bis-(trifluorometil)fenil]metil}amino)-2-hidroxi-1-(fenilmetil)propil]-3-(1,1-dioxido-2-isotiazolidinil)-5-(etilamino)benzamida (E403)	D130	673.3	0.86
clorhidrato de N-[(1S,2R)-3-({[3,5-bis-(metiloxi)-fenil]metil}amino)-2-hidroxi-1-(fenilmetil)propil]-3-(1,1-dioxido-2-isotiazolidinil)-5-(etilamino)-benzamida (E404)	D130	597.4	0.73
clorhidrato de N-[(1S,2R)-3-{[(3,5-dibromofenil)-metil]amino}-2-hidroxi-1-(fenilmetil)propil]-3-(1,1-dioxido-2-isotiazolidinil)-5-(etilamino)benzamida (E405)	D130	693.2	0.82
clorhidrato de 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etiloxi)-N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-({[3-(trifluorometil)fenil]metil}-amino)propil]benzamida (E406)	D131	620.3	0.83
clorhidrato de 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etiloxi)-N-[(1S,2R)-2-hidroxi-3-({[3-(metiloxi)fenil]metil}amino)-1-(fenilmetil)propil]-benzamida (E407)	D 131	582.4	0.78
clorhidrato de 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etiloxi)-N-{(1S,2R)-2-hidroxi-1-(fenilmetil)-3-[({3-[(trifluorometil)oxi]fenil}metil)-amino]propil}benzamida (E408)	D131	636.3	0.86

Ejemplo	Precursor	$[M+H]^+$	t.r. (min)
clorhidrato de N-[(1S,2R)-3-({[3,5-bis (trifluorometil)fenil]metil}amino)-2-hidroxi-1-(fenilmetil)propil]-3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etiloxi)benzamida (E409)	D131	688.3	0.93
clorhidrato de N-[(1S,2R)-3-({[3,5-bis(metiloxi)-fenil]metil}amino)-2-hidroxi-1-(fenilmetil)propil]-3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etiloxi)benzamida (E410)	D131	612.3	0.79
clorhidrato de N-[(1S,2R)-3-{[(3,5-dibromofenil)-metil]amino}-2-hidroxi-1-(fenilmetil)propil]-3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etiloxi)-benzamida (E411)	D131	708.1	0.88
clorhidrato de N-[(1S,2R)-3-{[1-(3-clorofenil)-propil]amino}-2-hidroxi-1-(fenilmetil)propil]-3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-benzamida (E412)	D120	613.3	0.92
clorhidrato de 3-ciclopentil-5-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-N-[(1S,2R)-2-hidroxi-3-[(1-metilbutil)amino]-1-fenilmetil)propil]-benzamida (E413)	D125	556.6	0.92
clorhidrato de N-[(1S,2R)-1-bencil-2-hidroxi-3-(1,2,3,4-tetrahidronaftalen-2-ilamino)propil]-3-ciclopentil-5-(2-oxopirrolidin-1-il)benzamida (E414)	D122	566.5	0.9
N-[(1S,2R)-1-bencil-3-(2,3-dihidro-1*H*-inden-2-ilamino)-2-hidroxipropil]-3-ciclopentil-5-(2-oxopirrolidin-1-il)benzamida (E415)	D122	552.6	0.9
clorhidrato de N-[(1S,2R)-1-bencil-3-(2,3-dihidro-1*H*-inden-2-ilamino)-2-hidroxipropil]-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzamida (E416)	D120	577.5	0.8
clorhidrato de N-[(1S,2R)-1-bencil-2-hidroxi-3-(1,2,3,4-tetrahidronaftalen-2-ilamino)propil]-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)-benzamida (E417)	D120	591.5	0.8
clorhidrato de N-[(1S,2R)-1-bencil-2-hidroxi-3-[(7-metoxi-1,2,3,4-tetrahidronaftalen-2-il)amino]-propil]-3-ciclopentil-5-(2-oxopirrolidin-1-il)-benzamida (E418)	D122	596.6	0.9
N-[(1S,2R)-1-bencil-3-[(3,5-diclorobencil)amino]-2-hidroxipropil}-3-ciclopentil-5-(2-oxopirrolidin-1-il)benzamida (E419)	D122	594.5	2.5

Ejemplo	Precursor	$[M+H]^+$	t.r. (min)
N-{(1S,2R)-1-bencil-3-[(3,5-diclorobencil)amino]-2-hidroxipropil}-3-(1,1-dioxidoisotiazolidin-2-il)-5-etoxibenzamida (E420)	D127	606.4	2.3
N-{(1S,2R)-1-bencil-3-[(3,5-diclorobencil)amino]-2-hidroxipropil}-3-(1,1-dioxidoisotiazolidin-2-il)-5-isopropoxibenzamida (E421)	D128	620.4	2.3
N-{(1S,2R)-1-bencil-3-[(3,5-diclorobencil)amino]-2-hidroxipropil}-3-ciclopentil-5-(1,1-dioxidoisotiazolidin-2-il)benzamida (E422)	D129	630.4	2.5
N-{(1S,2R)-1-bencil-3-[(3,5-diclorobencil)amino]-2-hidroxipropil}-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-etoxibenzamida (E423)	D131	620.3	2.3
N-{(1S,2R)-1-bencil-3-[(3,5-diclorobencil)amino]-2-hidroxipropil}-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-isopropoxibenzamida (E424)	D124	634.3	2.4
N-{(1S,2R)-1-bencil-3-[(3,5-diclorobencil)amino]-2-hidroxipropil}-3-ciclopentil-5-(1,1-dioxido-1,2-tiazinan-2-il)benzamida (E425)	D125	644.4	2.6
clorhidrato de N-{(1S,2R)-1-bencil-3-[(3,5-diclorobencil)amino]-2-hidroxipropil}-3-(etilamino)-5-(2-oxopirrolidin-1-il)benzamida (E426)	E66	568.8	2.2
clorhidrato de N-{(1S,2R)-1-bencil-3-[(3,5-diclorobencil)amino]-2-hidroxipropil)-3-(1,1-dioxidoisotiazolidin-2-il)-5-(etilamino)benzamida (E427)	D130	604.9	2.2

Ejemplos 428-570 (E428-E570)

Los compuestos de los ejemplos E428-E570 se prepararon de manera análoga al ejemplo 1, a partir del ácido apropiado y las aminas indicadas en el cuadro siguiente:

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
clorhidrato de 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-N-[(1S,2R)-2-hidroxi-3-{[1-(4-metilpentil)ciclopropil]amino}-1-(fenilmetil)propil]benzamida (E428)	A73	C73	585.6	0.90
clorhidrato de 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-N-[(1S,2R)-3-[(1-etilciclopropil)amino]-2-hidroxi-1-(fenilmetil)-propil]benzamida (E429)	A73	C74	529.5	0. 73
clorhidrato de 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-N-[(1S,2R)-2-hidroxi-3-{[1-(1-metiletil)ciclopropil]amino}-1-(fenilmetil)propil]benzamida (E430)	A73	C75	543.4	0.77
clorhidrato de N-[(1S,2R)-3-(butilamino)-2-hidroxi-1-(fenilmetil)propil]-3-(1,1-dioxido-tetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)benzamida (E431)	A73	C76	517.4	0.75
clorhidrato de 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-N-{(1S,2R)-2-hidroxi-1-(fenilmetil)-3-[(1-propilciclopropil)amino]propil}-benzamida (E432)	A73	C77	543.5	0.79
clorhidrato de 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-N-[(1S,2R)-2-hidroxi-3-{[1-(3-metilbutil)ciclopropil]amino}-1-(fenilmetil)propil]benzamida (E433)	A73	C78	571.6	0.88
clorhidrato de 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-N-[(1S,2R)-2-hidroxi-3-{[1-(2-metilpropil)ciclopropil]amino}-1-(fenilmetil)propil]benzamida (E434)	A73	C79	557.5	0.84
clorhidrato de N-[(1S,2R)-3-({1-[(3-clorofenil)metil]ciclopropil}amino)-2-hidroxi-1-(fenilmetil)propil]-3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)benzamida (E435)	A73	C80	625.4	0.90
clorhidrato de N-{(1S,2R)-1-bencil-2-hidroxi-3-[(1-metilciclohexil)amino]propil}-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzamida (E436)	A73	C81	557.5	0.78
clorhidrato de N-{(1S,2R)-1-bencil-3-[(1S,2S,4R)-biciclo[2.2.1]hept-2-ilamino]-2-hidroxipropil}-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzamida (E437)	A73	C82	555.4	0.78

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
clorhidrato de N-{(1S,2R)-1-bencil-3-[(4,4-dimetilciclohexil)amino]-2-hidroxipropil-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)-benzamida (E438)	A73	C83	571.3	0.82
clorhidrato de N-((1S,2R)-1-bencil-2-hidroxi-3-{[(1R)-1,2,2-trimetilpropil]amino}propil)-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)-benzamida (E439)	A73	C84	545.6	0.8
clorhidrato de N-((1S,2R)-1-bencil-2-hidroxi-3-{[(1S)-1,2,2-trimetilpropil]amino}propil)-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)-benzamida (E440)	A73	C85	545.6	0.81
clorhidrato de N-[(1S,2R)-1-bencil-3-[(2,2-dimetilciclohexil)amino]-2-hidroxipropil}-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)-benzamida (E441)	A73	C86	571.6	0.83
clorhidrato de N-[(1S,2R)-1-bencil-2-hidroxi-3-(pentilamino)propil]-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzamida (E442)	A73	C87	531.5	0.84
clorhidrato de N-[(1S,2R)-1-bencil-3-(hexilamino)-2-hidroxipropil]-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzamida (E443)	A73	C88	545.5	0.9
clorhidrato de N-{(1S,2R)-1-bencil-3-[(3,3-dimetilbutil)amino]-2-hidroxipropil}-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)-benzamida (E444)	A73	C89	545.5	0.86
clorhidrato de N-{(1S,2R)-1-bencil-3-[(1,1-dimetilpropil)amino]-2-hidroxipropil}-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)-benzamida (E445)	A73	C90	531.5	0.8
clorhidrato de N-{(1S,2R)-1-bencil-3-[(ciclopropilmetil)amino]-2-hidroxipropil}-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)-benzamida (E446)	A73	C91	515.5	0.76
clorhidrato de N-{(1S,2R)-1-bencil-3-[(3,3-dimetilciclopentil)amino]-2-hidroxipropil}-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)-benzamida (E447)	A73	C92	557.6	0.81
clorhidrato de N-[(1S,2R)-1-bencil-3-(etilamino)-2-hidroxipropil]-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzamida (E448)	A73	C24	489.5	0.7

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
clorhidrato de N-[(1S,2R)-1-bencil-2-hidroxi-3-(metilamino)propil]-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzamida (E449)	A73	C93	475.5	0.68
clorhidrato de N-[(1S,2R)-1-bencil-3-(ciclopropilamino)-2-hidroxipropil]-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)-benzamida (E450)	A73	C26	501.5	0.71
clorhidrato de N-[(1S,2R)-3-(1-adamantilamino)-1-bencil-2-hidroxipropil]-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)-benzamida (E451)	A73	C94	595.6	0.85
clorhidrato de N-[(1S,2R)-1-bencil-2-hidroxi-3-(1,2,3,4-tetrahidronaftalen-1-ilamino)propil]-3-ciclopentil-5-(2-oxopirrolidin-1-il)benzamida (E452)	A107	C95	566.5	0.91
clorhidrato de N-[(1S,2R)-1-bencil-2-hidroxi-3-(1,2,3,4-tetrahidronaftalen-1-ilamino)propil]-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)-benzamida (E453)	A73	C95	591.5	0.81
clorhidrato de N-((1S,2R)-1-bencil-2-hidroxi-3-{[2-(3-metoxifenil)etil]amino}propil)-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)-benzamida (E454)	A73	C96	595.6	0.79
clorhidrato de N-((1S,2R)-1-bencil-2-hidroxi-3-{[2-(4-metoxifenil)etil]amino}propil)-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)-benzamida (E455)	A73	C97	595.6	0.78
clorhidrato de N-((1S,2R)-1-bencil-2-hidroxi-3-{[2-(2-metoxifenil)etil]amino}propil)-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)-benzamida (E456)	A73	C98	595.4	0.79
clorhidrato de N-((1S,2R)-1-bencil-3-{[2-(2-clorofenil)etil]amino}-2-hidroxipropil)-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)-benzamida (E457)	A73	C99	599.5	0.81
clorhidrato de N-((1S,2R)-1-bencil-3-{[2-(3-clorofenil)etil]amino}-2-hidroxipropil)-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)-benzamida (E458)	A73	C100	599.5	0.82
clorhidrato de N-((1S,2R)-1-bencil-3-{[2-(4-clorofenil)etil]amino}-2-hidroxipropil)-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)-benzamida (E459)	A73	C101	599.5	0.82

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
clorhidrato de N-((1S,2R)-1-bencil-2-hidroxi-3-{[2-(4-metilfenil)etil]amino}propil)-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)-benzamida (E460)	A73	C102	579.5	2.02
clorhidrato de N-((1S,2R)-1-bencil-2-hidroxi-3-{[2-(2-metilfenil)etil]amino}propil)-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)-benzamida (E461)	A73	C103	580.5	2.02
clorhidrato de N-((1S,2R)-1-bencil-3-{[2-(3,4-diclorofenil)etil]amino}-2-hidroxipropil)-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)-benzamida (E462)	A73	C104	633.4	2.15
clorhidrato de N-((1S,2R)-1-bencil-3-{[2-(2,4-diclorofenil)etil]amino}-2-hidroxipropil)-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)-benzamida (E463)	A73	C105	633.4	0.86
clorhidrato de N-((1S,2R)-1-bencil-3-{[2-(3,5-dimetoxifenil)etil]amino}-2-hidroxipropil)-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)-benzamida (E464)	A73	C106	625.5	0.8
clorhidrato de N-((1S,2R)-1-bencil-3-{[2-(2,3-dimetoxifenil)etil]amino}-2-hidroxipropil)-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)-benzamida (E465)	A73	C107	625.4	0.79
clorhidrato de N-[(1S,2R)-1-bencil-3-(bencilamino)-2-hidroxipropil]-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzamida (E466)	A73	C108	551.5	0.75
clorhidrato de N-{(1S,2R)-1-bencil-2-hidroxi-3-[(2-feniletil)amino]propil}-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzamida (E467)	A73	C109	565.4	0.79
clorhidrato de N-{(1S,2R)-1-bencil-3-[(1-etilciclohexil)amino]-2-hidroxipropil}-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)-benzamida (E468)	A73	C110	571.6	0.82
clorhidrato de N-{(1S,2R)-1-bencil-2-hidroxi-3-[(1-metilciclopentil)amino]propil}-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzamida (E469)	A73	C111	544.5	1.81
clorhidrato de N-{(1S,2R)-1-bencil-2-hidroxi-3-[(1-propilciclopentil)amino]propil}-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)-benzamida (E470)	A73	C112	571.7	0.83

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
clorhidrato de N-{(1S,2R)-1-bencil-2-hidroxi-3-[(1-propilciclohexil)amino]propil}-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzamida (E471)	A73	C113	585.6	0.88
clorhidrato de N-((1S,2R)-1-bencil-3-{[2-(3-clorofenil)-1,1-dimetiletil]amino}-2-hidroxipropil)-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzamida (E472)	A73	C114	627.5	0.92
clorhidrato de 3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)-N-[(1S,2R)-2-hidroxi-3-[(3-metoxibencil)amino]-1-(piridin-3-ilmetil)propil]-benzamida (E473)	A73	C115	582.0	1.75
clorhidrato de 3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)-N-[(1S,2R)-2-hidroxi-3-[(3-metoxibencil)amino]-1-(1,3-tiazol-2-ilmetil)-propil]benzamida (E474)	A73	C116	588.0	1.91
clorhidrato de N-[(1S,2R)-3-(ciclohexilamino)-2-hidroxi-1-(1,3-tiazol-2-metil)propil]-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)-benzamida (E475)	A73	C117	550.0	1.88
clorhidrato de N-[(1S,2R)-3-[(1,5-dimetilhexil)-amino]-2-hidroxi-1-(1,3-tiazol-2-ilmetil)propil]-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)-benzamida (E476)	A73	C118	580.1	2.21
clorhidrato de 3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)-N-{(1S,2R)-1-(2-furilmetil)-2-hidroxi-3-[(3-metoxibencil)amino]propil}-benzamida (E477)	A73	C119	571.0	2.02
clorhidrato de N-[(1S,2R)-3-(ciclohexilamino)-1-(2-furilmetil)-2-hidroxipropil]-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzamida (E478)	A73	C120	533.0	2.01
clorhidrato de N-[(1S,2R)-3-[(1,5-dimetilhexil)-amino]-1-(2-furilmetil)-2-hidroxipropil]-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)-benzamida (E479)	A73	C121	563.1	2.32
clorhidrato de 3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)-N-{(1S,2R)-1-(2-furilmetil)-2-hidroxi-3-[(1,1,5-trimetilhexil)amino]propil}-benzamida (E480)	A73	C122	577.2	2.39

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)-N-[(1S)-2-hidroxi-3-[(3-metoxibencil)amino]-1-(piridin-2-ilmetil)propil]benzamida (E481)	A73	C123	581.9	1.84
clorhidrato de N-[(1S,2R)-1-[(4-clorofenil)metil]-3-(ciclohexilamino)-2-hidroxipropil]-3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)benzamida (E482)	A73	C124	577.4	0.82
clorhidrato de N-[(1S,2R)-1-[(4-clorofenil)metil]-2-hidroxi-3-({[3-(metiloxi)fenil]metil}amino)-propil]-3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)benzamida (E483)	A73	C125	615.4	0.82
clorhidrato de 3-ciclopentil-N-[(1S,2R)-1-[(3,5-difluorofenil)metil]-2-hidroxi-3-({[3-(trifluorometil)fenil]metil}amino)propil]-5-(2-oxo-1-pirrolidinil)benzamida (E484)	A107	C126	630.4	0.94
clorhidrato de N-[(1S,2R)-1-[(3,5-difluorofenil)-metil]-2-hidroxi-3-({[3-(trifluorometil)fenil]metil}-amino)propil]-3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)benzamida (E485)	A73	C126	655.4	0.85
clorhidrato de N-[(1S,2R)-1-[(3,5-difluorofenil)-metil]-2-hidroxi-3-({[3-(metiloxi)fenil]metil}-amino)propil]-3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)benzamida (E486)	A73	C127	617.3	0.8
clorhidrato de N-{(1S,2R)-1-[(3,5-difluorofenil)-metil]-3-[(1,5-dimetilhexil)amino]-2-hidroxipropil}-3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)benzamida (E487)	A73	C128	609.5	0.9
clorhidrato de N-{(1S,2R)-3-(ciclohexilamino)-1-[(3,5-difluorofenil)metil]-2-hidroxipropil}-3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)benzamida (E488)	A73	C129	579.4	0.8
clorhidrato de N-{(1S,2R)-1-[(3,5-difluorofenil)-metil]-2-hidroxi-3-[(1,1,5-trimetilhexil)amino]-propil}-3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)benzamida (E489)	A73	C130	623.6	0.93
clorhidrato de N-[(1S,2R)-1-[(3,4-difluorofenil)-metil]-2-hidroxi-3-({[3-(metiloxi)fenil]-metil}amino)propil]-3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)benzamida (E490)	A73	C131	617.5	0.81

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
clorhidrato de N-[(1S,2R)-3-(ciclohexilamino)-1-[(3,4-difluorofenil)metil]-2-hidroxipropil]-3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)benzamida (E491)	A73	C132	579.5	0.79
clorhidrato de N-[(1S,2R)-1-[(3,4-difluorofenil)-metil]-2-hidroxi-3-[(1,1,5-trimetilhexil)amino]-propil]-3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)benzamida (E492)	A73	C133	623.5	0.92
clorhidrato de N-[(1S,2R)-1-[(3-clorofenil)metil]-2-hidroxi-3-({[3-(metiloxi)fenil]metil}amino)-propil]-3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)benzamida (E493)	A73	C134	616.3	0.83
clorhidrato de N-[(1S,2R)-1-[(3-clorofenil)metil]-3-(ciclohexilamino)-2-hidroxipropil]-3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)benzamida (E494)	A73	C135	578.3	0.83
clorhidrato de N-[(1S,2R)-1-[(2-clorofenil)metil]-2-hidroxi-3-({[3-(metiloxi)fenil]metil}-amino)propil]-3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)benzamida (E495)	A73	C136	616.4	0.86
clorhidrato de N-[(1S,2R)-1-[(2-clorofenil)metil]-3-(ciclohexilamino)-2-hidroxipropil]-3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)benzamida (E496)	A73	C137	578.4	0.85
clorhidrato de N-[(1S,2R)-1-[(2-clorofenil)metil]-3-[(1,5-dimetilhexil)amino]-2-hidroxipropil}-3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)benzamida (E497)	A73	C138	608.5	0.98
clorhidrato de N-[(1S,2R)-1-[(3-clorofenil)metil]-3-[(1,5-dimetilhexil)amino]-2-hidroxipropil}-3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)benzamida (E498)	A73	C139	608.5	1
clorhidrato de 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-N-[(1S,2R)-1-[(3-fluorofenil)metil]-2-hidroxi-3-({[3-(metiloxi)fenil]-metil}amino)propil]benzamida (E499)	A73	C140	599.4	0.82
clorhidrato de N-[(1S,2R)-3-[(1,5-dimetilhexil)amino]-1-[(3-fluorofenil)metil]-2-hidroxipropil}-3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)benzamida (E500)	A73	C141	591.6	0.95

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
clorhidrato de 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-N-[(1S,2R)-2-hidroxi-3-({[3-(metiloxi)fenil]metil}amino)-1-(2-tienilmetil)-propil]benzamida (E501)	A73	C142	587.4	0.79
clorhidrato de N-[(1S,2R)-3-[(1,5-dimetilhexil)-amino]-2-hidroxi-1-(2-tienilmetil)-propil]-3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)benzamida (E502)	A73	C143	579.5	0.92
clorhidrato de 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-N-[(1S,2R)-2-hidroxi-3-({[3-(metiloxi)fenil]metil}amino)-1-(1H-pirazol-1-ilmetil)propil]benzamida (E503)	A73	C144	571.4	0.65
clorhidrato de N-[(1S,2R)-3-[(1,5-dimetilhexil)-amino]-2-hidroxi-1-(1H-pirazol-1-ilmetil)propil]-3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)benzamida (E504)	A73	C145	563.5	0.8
clorhidrato de 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-N-[(1S,2R)-2-hidroxi-3-({[3-(metiloxi)fenil]metil}amino)-1-(3-tienilmetil)-propil]benzamida (E505)	A73	C146	587.5	0.76
clorhidrato de N-[(1S,2R)-3-[(1,5-dimetilhexil)-amino]-2-hidroxi-1-(3-tienilmetil)propil]-3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)benzamida (E506)	A73	C147	579.5	0.85
ácido fórmico - N-[(1S,2R)-1-bencil-3-[(1,1-dimetilhexil)amino]-2-hidroxipropil]-3-(etilamino)-5-(2-oxopirrolidin-1-il)benzamida (1:1) (E507)	A31	C48	523.3	2.76
ácido fórmico - N-[(1S,2R)-1-bencil-2-hidroxi-3-({1-metil-1-[3-(trifluorometil)fenil]etil}amino)-propil]-3-(etilamino)-5-(2-oxopirrolidin-1-il)-benzamida (1:1) (E508)	A31	C40	597.3	3.03
ácido fórmico - N-((1S,2R)-1-bencil-2-hidroxi-3-{[2-metil-5-(trifluorometil)bencil]amino}propil)-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)-benzamida (1:1) (E509)	A73	C49	633.2	2.84
ácido fórmico - N-{(1S,2R)-1-bencil-3-[(1S)-2,3-dihidro-1*H*-inden-1-ilamino]-2-hidroxipropil}-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzamida (1:1) (E510)	A73	C50	577.2	2.68

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
ácido fórmico - N-((1S,2R)-1-bencil-2-hidroxi-3-{[(1S,2R)-2-hidroxi-2,3-dihidro-1*H*-inden-1-il]amino}propil)-3-etilamino)-5-(2-oxopirrolidin-1-il)benzamida (1:1) (E511)	A31	C51	543.1	2.55
N-[(1S,2R)-1-bencil-2-hidroxi-3-[(6-metoxi-2,3-dihidro-1H-inden-1-il)amino]propil]-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)-benzamida (E512)	A73	C52	607.5	2.55
ácido fórmico - N-((1S,2R)-1-bencil-2-hidroxi-3-{[(1R,2S)-2-hidroxi-2,3-dihidro-1*H*-inden-1-il]amino}propil)-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzamida (1:1) (E513)	A73	C53	593.4	2.40
N-((1S,2R)-1-bencil-2-hidroxi-3-[[2-(isobutiltio)-1,1-dimetiletil]amino}propil)-3-(etilamino)-5-(2-oxopirrolidin-1-il)benzamida (E514)	A31	C54	555.4	2.62
N-[(1S,2R)-1-bencil-3-[(1,1-dimetil-2-fenoxietil)-amino]-2-hidroxipropil]-3-(etilamino)-5-(2-oxopirrolidin-1-il)benzamida (E515)	A31	C55	559.4	2.56
N-((1S,2R)-1-bencil-3-{[2-(benciloxi)-1,1-dimetiletil]amino}-2-hidroxipropil)-3-(etilamino)-5-(2-oxopirrolidin-1-il)benzamida (E516)	A31	C56	573.5	2.58
N-[(1S,2R)-1-bencil-2-hidroxi-3-[(3-metoxifenil)amino]propil]-3-(etilamino)-5-(2-oxopirrolidin-1-il)benzamida (E517)	A31	C57	517.4	2.92
ácido fórmico - N-[(1S,2R)-1-bencil-2-hidroxi-3-({2-[3-(trifluorometil)fenil]etil}amino)propil]-3-(etilamino)-5-(2-oxopirrolidin-1-il)benzamida (1:1) (E518)	A31	C58	583.4	2.62
ácido fórmico - N-[(1S,2R)-1-bencil-3-[(1,1-dimetil-2-feniletil)amino]-2-hidroxipropil]-3-(etilamino)-5-(2-oxopirrolidin-1-il)benzamida (1:1) (E519)	A31	C59	543.5	2.55
ácido fórmico - N-((1S,2R)-1-bencil-2-hidroxi-3-{[2-(1-naftil)etil]amino}propil)-3-(etilamino)-5-(2-oxopirrolidin-1-il)benzamida (1:1) (E520)	A31	C60	565.5	2.63
ácido fórmico - N-((1S,2R)-1-bencil-2-hidroxi-3-{[2-(3-metoxifenil)-1,1-dimetiletil]amino}propil)-3-(etilamino)-5-(2-oxopirrolidin-1-il)benzamida (1:1) (E521)	A31	C61	573.5	2.57
N-[(1S,2R)-3-anilino-1-bencil-2-hidroxipropil]-3-etilamino)-5-(2-oxopirrolidin-1-il)benzamida (E522)	A31	C62	487.4	2.90

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
N-((1S,2R)-1-bencil-2-hidroxi-3-{[1-(3-metoxifenil)ciclopropil]amino}propil)-3-(etilamino)-5-(2-oxopirrolidin-1-il)benzamida (E523)	A31	C63	557.4	2.47
ácido fórmico - N-{(1S,2R)-1-bencil-3-[(ciclohexilmetil)amino]-2-hidroxipropil}-3-(etilamino)-5-(2-oxopirrolidin-1-il)benzamida (1:1) (E524)	A31	C64	507.5	2.48
ácido fórmico - N-{(1S,2R)-1-bencil-2-hidroxi-3-[(tetrahidro-2H-piran-4-ilmetil)amino]propil}-3-(etilamino)-5-(2-oxopirrolidin-1-il)benzamida (1:1) (E525)	A31	C65	509.4	2.15
N-[(1S,2R)-1-bencil-2-hidroxi-3-(tetrahidro-2*H*-tiopiran-4-ilamino)propil]-3-(etilamino)-5-(2-oxopirrolidin-1-il)benzamida (E526)	A31	C66	511.4	2.30
ácido fórmico - N-[(1S,2R)-1-bencil-2-hidroxi-3-(isopropilamino)propil]-3-etil-7-(2-oxopirrolidin-1-il)-1*H*-indol-5-carboxamida (1:1) (E527)	A141	C28	478.5	2.04
ácido fórmico - N-[(1S,2R)-1-bencil-3-(ciclohexilamino)-2-hidroxipropil]-3-etil-7-(2-oxopirrolidin-1-il)-1*H*-indol-5-carboxamida (1:1) (E528)	A141	C1	517.5	2.17
ácido fórmico - N-{(1S,2R)-1-bencil-2-hidroxi-3-[(1,1,5-trimetilhexil)amino]propil}-3-etil-7-(2-oxopirrolidin-1-il)-1H-indol-5-carboxamida (1:1) (E529)	A141	C5	561.5	2.56
ácido fórmico - N-{(1S,2R)-1-bencil-2-hidroxi-3-[(3-metoxibencil)amino]propil}-7-(1,1-dioxidoisotiazolidin-2-il)-3-etil-1*H*-indol-5-carboxamida (1:1) (E530)	A144	C14	591.4	2.36
N-{(1S,2R)-1-bencil-2-hidroxi-3-[(1,1,5-trimetilhexil)amino]propil}-7-(1,1-dioxidoisotiazolidin-2-il)-3-etil-1*H*-indol-5-carboxamida (E531)	A144	C5	597.5	2.72
ácido fórmico - N-[(1S,2R)-1-bencil-3-(ciclohexilamino)-2-hidroxipropil]-7-(1,1-dioxidoisotiazolidin-2-il)-3-etil-1*H*-indol-5-carboxamida (1: 1) (E532)	A144	C1	554.5	2.33
ácido fórmico - N-[(1S,2R)-1-bencil-2-hidroxi-3-(isopropilamino)propil]-7-(1,1-dioxidoisotiazolidin-2-il)-3-etil-1*H*-indol-5-carboxamida (1:1) (E533)	A144	C28	514.4	2.14

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
ácido fórmico - N-((1S,2R)-1-bencil-2-hidroxi-3-{[1-(3-metoxifenil)-1-metiletil]amino}propil)-7-(1,1-dioxidoisotiazolidin-2-il)-3-etil-1*H*-indol-5-carboxamida (1:1) (E534)	A144	C15	619.4	2.45
ácido fórmico - N-[(1S,2R)-1-bencil-2-hidroxi-3-({1-metil-1-[3-(trifluorometil)fenil]etil}amino)-propil]-7-(1,1-dioxidoisotiazolidin-2-il)-3-etil-1*H*-indol-5-carboxamida (1:1) (E535)	A144	C40	657.4	2.62
N-[(1S,2R)-1-bencil-3-(sec-butilamino)-2-hidroxipropil]-3-(etilamino)-5-(2-oxopirrolidin-1-il)benzamida (E536)	A31	C67	467.3	2.4
N-[(1S,2R)-1-bencil-3-[(4-ter-butilciclohexil)-amino]-2-hidroxipropil}-3-(etilamino)-5-(2-oxopirrolidin-1-il)benzamida (E537)	A31	C68	549.3	2.81
N-[(1S,2R)-1-bencil-3-[(1S)-2,3-dihidro-1*H*-inden-1-ilamino]-2-hidroxipropil}-3-(etilamino)-5-(2-oxopirrolidin-1-il)benzamida (E538)	A31	C50	527.2	2.56
N-[(1S,2R)-1-bencil-2-hidroxi-3-[(2-isobutoxi-1,1-dimetiletil)amino]propil}-3-(etilamino)-5-(2-oxopirrolidin-1-il)benzamida (E539)	A31	C70	539.2	2.64
N-[(1S,2R)-1-bencil-3-({1,1-dimetil-2-[(2-metilprop-2-en-1-il)oxi]etil}amino)-2-hidroxipropil]-3-(etilamino)-5-(2-oxopirrolidin-1-il)benzamida (E540)	A31	C71	537.2	2.61
N-[(1S,2R)-1-bencil-3-[(1R)-2,3-dihidro-1*H*-inden-1-ilamino]-2-hidroxipropil-3-(etilamino)-5-(2-oxopirrolidin-1-il)benzamida (E541)	A31	C72	527.2	2.54
N-[(1S,2R)-1-bencil-3-[(1R)-2,3-dihidro-1*H*-inden-1-ilamino]-2-hidroxipropil}-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzamida (E542)	A73	C72	577.2	2.64
N-[(1S,2R)-1-bencil-2-hidroxi-3-[(3-metoxibencil)amino]propil}-3-[etil(metil)amino]-5-(2-oxopirrolidin-1-il)benzamida (E543)	A128	C14	546.5	2.49
N-((1S,2R)-1-bencil-2-hidroxi-3-{[1-(3-metoxifenil)-1-metiletil]amino}propil)-3-[etil-(metil)amino]-5-(2-oxopirrolidin-1-il)benzamida (E544)	A128	C15	574.5	2.58
ácido fórmico - N-((1S,2R)-1-bencil-2-hidroxi-3-{[1-(3-metoxifenil)ciclohexil]amino}propil)-3-(etilamino)-5-(2-oxopirrolidin-1-il)benzamida (1:1) (E545)	A31	C41	599.5	2.60

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
ácido fórmico - N-((1S,2R)-1-bencil-2-hidroxi-3-{[1-(3-metoxifenil)ciclohexil]amino}propil)-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzamida (1:1) (E546)	A73	C41	649.5	2.70
ácido fórmico - N-((1S,2R)-1-bencil-2-hidroxi-3-{[1-metil-1H-pirazol-4-il)metil]amino}propil)-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzamida (1:1) (E547)	A73	C42	555.3	2.35
ácido fórmico - N-((1S,2R)-1-bencil-2-hidroxi-3-{[1-metil-1H-pirazol-4-il)metil]amino}propil)-3-(etilamino)-5-(2-oxopirrolidin-1-il)benzamida (1:1) (E548)	A31	C42	505.3	2.27
ácido fórmico - N-[(1S,2R)-1-bencil-3-(ciclohexilamino)-2-hidroxipropil]-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)-benzamida (1:1) (E549)	A73	C1	543.4	2.45
ácido fórmico - N-[(1S,2R)-1-bencil-2-hidroxi-3-(tetrahidro-2H-piran-4-ilamino)propil]-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)benzamida (1:1) (E550)	A73	C43	545.4	2.28
ácido fórmico - N-[(1S,2R)-1-bencil-3-(ciclohexilamino)-2-hidroxipropil]-3-ciclopentil-5-(1,1-dioxido-1,2-tiazinan-2-il)benzamida (1:1) (E551)	A126	C1	568.3	2.80
ácido fórmico - N-[(1S,2R)-1-bencil-2-hidroxi-3-(tetrahidro-2H-piran-4-ilamino)propil]-3-ciclopentil-5-(1,1-dioxido-1,2-tiazinan-2-il)-benzamida (1:1) (E552)	A126	C43	570.3	2.61
ácido fórmico - N-{(1S,2R)-1-bencil-3-[(3,3-dimetilbutil)amino]-2-hidroxipropil}-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)-2-fluorobenzamida (1:1) (E553)	A119	C44	563.4	2.53
N-{(1S,2R)-1-bencil-2-hidroxi-3-[(1,1,3,3-tetrametilbutil)amino]propil}-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)-2-fluorobenzamida (E554)	A119	C45	591.4	2.63
ácido fórmico - N-{(1S,2R)-1-bencil-3-[(1,3-dimetilbutil)amino]-2-hidroxipropil}-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-etilamino)-2-fluorobenzamida (1:1) (E555)	A119	C46	563.4	2.50

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
ácido fórmico - N-[(1S,2R)-1-bencil)-3-(ciclohexilamino)-2-hidroxipropil]-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(isopropilamino)-benzamida (1:1) (E556)	A127	C1	557.4	2.35
ácido fórmico - N-((1S,2R)-1-bencil-2-hidroxi-3-(isopropilamino)propil]-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(isopropilamino)benzamida (1:1) (E557)	A127	C28	517.4	2.20
ácido fórmico - N-[(1S,2R)-1-bencil-2-hidroxi-3-({1-metil-1-[3-(trifluorometil)fenil]etil}amino)-propil]-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(isopropilamino)benzamida (1:1) (E558)	A127	C40	661.4	2.70
ácido fórmico - N-[(1S,2R)-1-bencil-2-hidroxi-3-[(3-metoxibencil)amino]propil}-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(isopropilamino)benzamida (1:1) (E559)	A127	C14	595.4	2.41
N-((1S,2R)-1-bencil-2-hidroxi-3-{[3-(trifluorometil)bencil]amino}propil)-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(isopropilamino)-benzamida (E560)	A127	C16	633.4	2.66
ácido fórmico - N-[(1S,2R)-1-bencil-2-hidroxi-3-[(1,1,5-trimetilhexil)amino]propil}-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(isopropilamino)-benzamida (1:1) (E561)	A127	C5	601.5	2.80
ácido fórmico - N-((1S,2R)-1-bencil-3-{[4-fluoro-3-(trifluorometil)bencil]amino}-2-hidroxipropil)-3-(1,1-dioxido-1,2-tiazinan-2-il)-5-(etilamino)-2-fluorobenzamida (1:1) (E562)	A119	C47	655.4	2.50
ácido fórmico - 3-(etilamino)-N-[(1S,2R)-2-hidroxi-3-({[3-(metiloxi)fenil]metil}amino)-1-(fenilmetil)propil]-5-(2-oxo-1-piperidinil)-benzamida (1:1) (E563)	A59	C14	545.2	2.79
ácido fórmico - N-[(1S,2R)-3-[(1,5-dimetilhexil)amino]-2-hidroxi-1-(fenilmetil)-propil]-3-(etilamino)-5-(2-oxo-1-piperidinil)-benzamida (1:1) (E564)	A59	C20	537.3	2.81
3-(etilamino)-N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-({[3-(trifluorometil)fenil]metil}-amino)propil]-5-(2-oxo-1-piperidinil)benzamida (E565)	A59	C16	583.2	2.69

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
ácido fórmico - N-[(1S,2R)-2-hidroxi-3-({[3-(metiloxi)fenil]metil}amino)-1-(fenilmetil)propil]-3-(2-oxo-1-piperidinil)-5-propilbenzamida (1:1) (E566)	A116	C14	544.3	2.74
ácido fórmico - N-[(1S,2R)-3-[(1,5-dimetilhexil)amino]-2-hidroxi-1-(fenilmetil)-propil]-3-(2-oxo-1-piperidinil)-5-propilbenzamida (1:1) (E567)	A116	C20	536.3	3.01
N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-({[3-(trifluorometil)fenil]metil}amino)propil]-3-(2-oxo-1-piperidinil)-5-propilbenzamida (E568)	A116	C16	582.2	2.88
N-[(1S,2R)-3-{[(1S)-2-(ciclohexilamino)-1-metil-2-oxoetil]amino}-2-hidroxi-1-(fenilmetil)propil]-3-(2-oxo-1-piperidinil)-5-propilbenzamida (E569)	A116	C6	577.3	2.76
3-(1,1-dioxido-2-isotiazolidinil)-5-(etilamino)-N-{(1S,2R)-2-hidroxi-1-(fenilmetil)-3-[(1,1,5-trimetilhexil)amino]propil}benzamida (E570)	A70	C5	573.5	2.67

Ejemplos 571-572 (E571-E572)

Los siguientes compuestos se prepararon de manera análoga al ejemplo 183, a partir de la amina apropiada y el aldehído apropiado:

Ejemplo	Precursor	$[M+H]^+$	t.r (min)
ácido fórmico - 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-N-[(1S,2R)-2-hidroxi-3-[([1-(1-metiletil)-1*H*-pirazol-4-il]metil}amino)-1-(fenilmetil)propil]benzamida (1:1) (E571)	D120	583.5	2.24
ácido fórmico - 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-({[1-(2,2, 2-trifluoroetil)-1*H*-pirazol-4-il]metil}amino)propil]benzamida (1:1) (E572)	D120	623.4	2.28

524
527

Ejemplos 573-695 (E573-E695)

Los compuestos de los ejemplos E573-695 se prepararon de manera análoga al ejemplo 1, a partir del ácido apropiado y las aminas indicadas en el cuadro siguiente:

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
ácido fórmico - 5-(etilamino)-2-fluoro-N-[(1S,2R)-2-hidroxi-3-({[3-(metiloxi)fenil]metil}-amino)-1-(fenilmetil)propil]-3-(2-oxo-1-pirrolidinil)benzamida (1:1) (E573)	A118	C14	549.3	2.42
3-(etiloxi)-N-[(1S,2R)-2-hidroxi-3-({1-metil-1-[3-(trifluorometil)fenil]etil}amino)-1-(fenilmetil)-propil]-5-(2-oxo-1-pirrolidinil)benzamida (E574)	A11	C40	598.4	2.76
3-(1,1-dioxido-2-isotiazolidinil)-5-(etiloxi)-N-[(1S,2R)-2-hidroxi-3-({1-metil-1-[3-(trifluorometil)fenil]etil}amino)-1-(fenilmetil)-propil]benzamida (E575)	A18	C40	634.3	2.78
3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-N-[(1S,2R)-2-hidroxi-3-({1-metil-1-[3-(trifluorometil)fenil]etil}amino)-1-(fenilmetil)-propil]benzamida (E576)	A73	C40	647.4	2.78
1-etil-N-[(1S,2R)-2-hidroxi-3-({1-metil-1-[3-(trifluorometil)fenil]etil}amino)-1-(fenilmetil)-propil]-4-(2-oxo-1-pirrolidinil)-1*H*-indol-6-carboxamida (E577)	A140	C40	621.4	2.75
3-(etiloxi)-N-[(1S,2R)-2-hidroxi-3-({1-metil-1-[3-(metiloxi)fenil]etil}amino)-1-(fenilmetil)propil]-5-(2-oxo-1-pirrolidinil)benzamida (E578)	A11	C15	560.4	2.62
1-etil-N-[(1S,2R)-2-hidroxi-3-({1-metil-1-[3-(metiloxi)fenil]etil}amino)-1-(fenilmetil)propil]-4-2-oxo-1-pirrolidin)-1*H*-indol-6-carboxamida (E579)	A140	C15	583.4	2.61
3-etil-N-[(1S,2R)-2-hidroxi-3-({1-metil-1-[3-(trifluorometil)fenil]etil}amino)-1-(fenilmetil)propil]-7-(2-oxo-1-pirrolidinil)-1*H*-indol-5-carboxamida (E580)	A141	C40	621.4	2.81

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
3-(1,1-dioxido-2-isotiazolidinil)-5-(etiloxi)-N-[(1S,2R)-2-hidroxi-3-({1-metil-1-[3-(metiloxi)fenil]etil}amino)-1-(fenilmetil)propil]-benzamida (E581)	A18	C15	596.5	2.58
3-etil-N-[(1S,2R)-2-hidroxi-3-({1-metil-1-[3-(metiloxi)fenil]etil}amino)-1-(fenilmetil)propil]-7-(2-oxo-1-pirrolidinil)-1*H*-indol-5-carboxamida (E582)	A141	C15	583.5	2.62
3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-2-fluoro-N-[(1S,2R)-2-hidroxi-3-({[3-(metiloxi)fenil]metil}amino)-1-(fenilmetil)propil]-benzamida (E583)	A119	C14	599.4	2.27
3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-2-fluoro-N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-({[3-(trifluorometil)fenil]-metil}amino)propil]benzamida (E584)	A119	C16	637.4	2.48
3-(1,1-dioxido-2-isotiazolidinil)-5-(etilamino)-N-[(1S,2R)-2-hidroxi-3-({1-metil-1-[3-(trifluorometil)fenil]etil}amino)-1-(fenilmetil)-propil]-benzamida (E585)	A70	C40	633.3	2.73
3-(1,1-dioxido-2-isotiazolidinil)-5-(etilamino)-N-[(1S,2R)-2-hidroxi-3-({1-metil-1-[3-(metiloxi)-fenil]etil}amino)-1-(fenilmetil)propil]benzamida (E586)	A70	C15	595.3	2.57
5-(etilamino)-2-fluoro-N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-({[3-(trifluorometil)fenil]metil}-amino)propil]-3-(2-oxo-1-pirrolidinil)benzamida (E587)	A118	C16	587.3	2.60
2-fluoro-N-[(1S,2R)-2-hidroxi-3-({[3-(metiloxi)-fenil]metil}amino)-1-(fenilmetil)propil]-3-(2-oxo-1-pirrolidinil)-5-propilbenzamida (E588)	A120	C14	548.3	2.64
2-fluoro-N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-({[3-(trifluorometil)fenil]metil}amino)propil]-3-(2-oxo-1-pirrolidinil)-5-propilbenzamida (E589)	A120	C16	586.3	2.79
N-[(1S,2R)-2-hidroxi-3-({[3-(metiloxi)fenil]-metil}amino)-1-(fenilmetil)propil]-3-(2-oxo-5-fenil-1-piperidinil)-5-propilbenzamida (E590)	A121	C14	620.5	3.02
N-[(1S,2R)-2-hidroxi-3-[(1-metiletil)amino]-1-(fenilmetil)propil]-3-(2-oxo-5-fenil-1-piperidinil)-5-propilbenzamida (E591)	A121	C28	542.4	2.88

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
N-[(1S,2R)-3-(ciclohexilamino)-2-hidroxi-1-(fenilmetil)propil]-3-(2-oxo-5-fenil-1-piperidinil)-5-propilbenzamida (E592)	A121	C1	582.6	2.99
5-(etilamino)-2-fluoro-N-[(1S,2R)-2-hidroxi-3-({1-metil-1-[3-(trifluorometil)fenil]etil}amino)-1-(fenilmetil)propil]-3-(2-oxo-1-pirrolidinil)-benzamida (E593)	A118	C40	615.3	2.61
5-(etilamino)-2-fluoro-N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-[(1,1,5-trimetilhexil)amino]propil]-3-(2-oxo-1-pirrolidinil)benzamida (E594)	A118	C5	555.4	2.71
N-[(1S,2R)-3-(ciclohexilamino)-2-hidroxi-1-(fenilmetil)propil]-5-(etilamino)-2-fluoro-3-(2-oxo-1-pirrolidinil)benzamida (E595)	A118	C1	511.3	2.25
5-(etilamino)-2-fluoro-N-[(1S,2R)-2-hidroxi-3-[(1-metiletil)amino]-1-(fenilmetil)propil]-3-(2-oxo-1-pirrolidinil)benzamida (E596)	A118	C28	471.3	2.05
5-(etilamino)-2-fluoro-N-[(1S,2R)-2-hidroxi-3-({1-metil-1-[3-(metiloxi)fenil]etil}amino)-1-(fenilmetil)propil]-3-(2-oxo-1-pirrolidinil)benzamida (E597)	A118	C15	577.4	2.42
3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-2-fluoro-N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-[(1,1,5-trimetilhexil)amino]-propil]benzamida (E598)	A119	C5	605.4	2.87
N-[(1S,2R)-3-(ciclohexilamino)-2-hidroxi-1-(fenilmetil)propil]-3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-2-fluorobenzamida (E599)	A119	C1	561.4	2.42
3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-2-fluoro-N-[(1S,2R)-2-hidroxi-3-[(1-metiletil)amino]-1-(fenilmetil)propil]benzamida (E600)	A119	C28	521.3	2.20
4-(1,1-dioxido-2-isotiazolidinil)-1-etil-N-[(1S,2R)-2-hidroxi-3-({[3-(metiloxi)fenil]metil}-amino)-1-(fenilmetil)propil]-1*H*-indazol-6-carboxamida (E601)	A153	C14	592.3	2.39
4-(1,1-dioxido-2-isotiazolidinil)-1-etil-N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-({[3-(trifluorometil)fenil]metil}amino)propil]-1*H*-indazol-6-carboxamida (E602)	A153	C16	630.3	2.58

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
4-(1,1-dioxido-2-isotiazolidinil)-1-etil-N-[(1S,2R)-2-hidroxi-3-({1-metil-1-[3-(metiloxi)fenil]etil}amino)-1-(fenilmetil)propil]-1*H*-indazol-6-carboxamida (E603)	A153	C15	620.3	2.46
4-(1,1-dioxido-2-isotiazolidinil)-1-etil-N-[(1S,2R)-2-hidroxi-3-({1-metil-1-[3-(trifluorometil)fenil]etil}amino)-1-(fenilmetil)-propil]-1*H*-indazol-6-carboxamida (E604)	A153	C40	658.3	2.65
4-(1,1-dioxido-2-isotiazolidinil)-1-etil-N-{(1S,2R)-2-hidroxi-1-(fenilmetil)-3-[(1,1,5-trimetilhexil)amino]propil}-1*H*-indazol-6-carboxamida (E605)	A153	C5	598.5	2.47
N-[(1S,2R)-3-(ciclohexilamino)-2-hidroxi-1-(fenilmetil)propil]-4-(1,1-dioxido-2-isotiazolidinil)-1-etil-1*H*-indazol-6-carboxamida (E606)	A153	C1	554.4	2.08
4-(1,1-dioxido-2-isotiazolidinil)-1-etil-N-[(1S,2R)-2-hidroxi-3-[(1-metiletil)amino]-1-(fenilmetil)propil]-1H-indazol-6-carboxamida (E607)	A153	C28	514.4	1.91
3-etil-N-[(1S,2R)-2-hidroxi-3-({[3-(metiloxi)-fenil]metil}amino)-1-(fenilmetil)propil]-1-metil-7-(2-oxo-1-pirrolidinil)-1*H*-indol-5-carboxamida (E608)	A142	C14	569.5	2.38
3-etil-N-[(1S,2R)-2-hidroxi-3-({1-metil-1-[3-(metiloxi)fenil]etil}amino)-1-(fenilmetil)propil]-1-metil-7-(2-oxo-1-pirrolidinil)-1*H*-indol-5-carboxamida (E609)	A142	C15	597.5	2.45
3-etil-N-[(1S,2R)-2-hidroxi-3-({1-metil-1-[3-(trifluorometil)fenil]etil}amino)-1-(fenilmetil)-propil]-1-metil-7-(2-oxo-1-pirrolidinil)-1*H*-indol-5-carboxamida (E610)	A142	C40	635.4	2.71
N-[(1S,2R)-3-(ciclohexilamino)-2-hidroxi-1-(fenilmetil)propil]-3-etil-1-metil-7-(2-oxo-1-pirrolidinil)-1*H*-indol-5-carboxamida (E611)	A142	C1	531.5	2.33
3-etil-N-{(1S,2R)-2-hidroxi-1-(fenilmetil)-3-[(1,1,5-trimetilhexil)amino]propil}-1-metil-7-(2-oxo-1-pirrolidinil)-1*H*-indol-5-carboxamida (E612)	A142	C5	575.4	2.80
3-etil-N-{(1S,2R)-2-hidroxi-1-(fenilmetil)-3-[(1,1,5-trimetilhexil)amino]propil}-1-metil-7-(2-oxo-1-pirrolidinil)-1*H*-indol-5-carboxamida, sal formiato (1:1) (E613)	A122	C5	591.5	2.60

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
ácido fórmico - 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-N-{(1S,2R)-2-hidroxi-1-(fenilmetil)-3-[(1,1,5-trimetilhexil)amino]propil}-benzamida (1:1) (E614)	A73	C5	587.6	2.61
N-[(1S,2R)-3-(ciclohexilamino)-2-hidroxi-1-(fenilmetil)propil]-3-(1,1-dioxido-2-isotiazolidinil)-5-etilamino)-2-fluorobenzamida (E615)	A122	C1	547.5	2.08
7-(1,1-dioxido-2-isotiazolidinil)-3-etil-N-[(1S,2R)-2-hidroxi-3-({[3-(metiloxi)fenil]-metil}amino)-1-(fenilmetil)propil]-1-metil-1*H*-indol-5-carboxamida (E616)	A146	C14	605.5	2.49
7-(1,1-dioxido-2-isotiazolidinil)-3-etil-N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-({[3-(trifluorometil)fenil]metil}amino)propil]-1-metil-1*H*-indol-5-carboxamida (E617)	A146	C16	643.4	2.68
7-(1,1-dioxido-2-isotiazolidinil)-3-etil-N-[(1S,2R)-2-hidroxi-3-({1-metil-1-[3-(metiloxi)-fenil]etil}amino)-1-(fenilmetil)propil]-1-metil-1*H*-indol-5-carboxamida (E618)	A146	C15	633.4	2.57
7-(1,1-dioxido-2-isotiazolidinil)-3-etil-N-[(1S,2R)-2-hidroxi-3-({1-metil-1-[3-(trifluorometil)fenil]etil}amino)-1-(fenilmetil)-propil]-1-metil-1*H*-indol-5-carboxamida (E619)	A146	C40	671.4	2.74
7-(1,1-dioxido-2-isotiazolidinil)-3-etil-N-{(1S,2R)-2-hidroxi-1-(fenilmetil)-3-[(1,1,5-trimetilhexil)amino]propil}-1-metil-1*H*-indol-5-carboxamida (E620)	A146	C5	611.5	2.84
N-[(1S,2R)-3-(ciclohexilamino)-2-hidroxi-1-(fenilmetil)propil]-7-(1,1-dioxido-2-isotiazolidinil)-3-etil-1-metil-1*H*-indol-5-carboxamida (E621)	A146	C1	567.5	2.46
3-(etilamino)-N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-({[3-(trifluorometil)fenil]metil}-amino)propil]-4-metil-5-(2-oxo-1-pirrolidinil)-benzamida (E622)	A129	C16	583.2	2.70
3-(1,1-dioxido-2-isotiazolidinil)-5-(etilamino)-N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-({[3-(trifluorometil)fenil]metil}amino)propil]-4-metilbenzamida (E623)	A130	C16	619.2	2.77

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-({[3-(trifluorometil)fenil]metil}amino)propil]-4-metilbenzamida (E624)	A131	C16	633.2	2.84
3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-({[3-(trifluorometil)fenil]metil}amino)propil]-4-(metiloxi)benzamida (E625)	A132	C16	649.2	2.82
3-(etilamino)-N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-({[3-(trifluorometil)fenil]metil}-amino)propil]-4-(metiloxi)-5-(2-oxo-1-pirrolidinil)benzamida (E626)	A133	C16	599.2	2.71
3-(1,1-dioxido-2-isotiazolidinil)-5-(etilamino)-N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-({[3-(trifluorometil)fenil]metil}amino)propil]-4-(metiloxi)benzamida (E627)	A134	C16	635.2	2.76
3-(dietilamino)-5-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-({[3-(trifluorometil)fenil]metil}amino)propil]-4-metilbenzamida (E628)	A135	C16	661.2	2.94
3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-({[3-(trifluorometil)fenil]metil}amino)propil]-4-(metiloxi)-5-[(1E)-1-propen-1-il]benzamida (E629)	A136	C16	646.1	2.95
3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-({[3-(trifluorometil)fenil]metil}amino)propil]-4-(metiloxi)-5-propilbenzamida (E630)	A137	C16	648.2	2.99
N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-({[3-(trifluorometil)fenil]metil}amino)propil]-4-(2-oxo-1-pirrolidinil)-1*H*-indol-6-carboxamida (E631)	A154	C16	565.2	2.59
1-etil-N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-({[3-(trifluorometil)fenil]metil}amino)propil]-4-(2-oxo-1-pirrolidinil)-1*H*-indol-6-carboxamida (E632)	A140	C16	593.2	2.83
1-etil-N-[(1S,2R)-2-hidroxi-3-({[3-(metiloxi)-fenil]metil}amino)-1-(fenilmetil)propil]-4-(2-oxo-1-pirrolidinil)-1*H*-indol-6-carboxamida (E633)	A140	C14	555.2	2.36
4-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-N-[(1S,2R)-2-hidroxi-3-({[3-(metiloxi)fenil]-metil}amino)-1-fenilmetil)propil]-1*H*-indol-6-carboxamida (E634)	A155	C14	577.1	2.31

530
533

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
4-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-1-etil-N-[(1S,2R)-2-hidroxi-3-({[3-(metiloxi)fenil]-metil}amino)-1-(fenilmetil)propil]-1*H*-indol-6-carboxamida (E635)	A147	C14	605.4	2.60
N-[(1S,2R)-2-hidroxi-3-({[3-(metiloxi)fenil]metil}-amino)-1-(fenilmetil)propil]-3-(1-metiletil)-5-(2-oxo-1-pirrolidinil)benzamida (E636)	A104	C14	530.5	2.60
N-[(1S,2R)-2-hidroxi-3-({[3-(metiloxi)fenil]-metil}amino)-1-(fenilmetil)propil]-1-metil-4-(2-oxo-1-pirrolidinil)-1*H*-indol-6-carboxamida (E637)	A156	C14	541.2	2.50
3-(1,1-dioxido-2-isotiazolidinil)-N-[(1S,2R)-2-hidroxi-3-({[3-(metiloxi)fenil]metil}amino)-1-(fenilmetil)propil]-5-(2-oxo-1-pirrolidinil)-benzamida (E638)	A138	C14	607.2	2.43
1-butil-N-[(1S,2R)-2-hidroxi-3-({[3-(metoxi)-fenil]metil}amino)-1-(fenilmetil)propil]-4-(2-oxo-1-pirrolidinil)-1*H*-indol-6-carboxamida (E639)	A157	C14	583.2	2.78
N-[(1S,2R)-2-hidroxi-3-({[3-(metiloxi)fenil]-metil}amino)-1-(fenilmetil)propil]-4-(2-oxo-1-pirrolidinil)-1-pentil-1*H*-indol-6-carboxamida (E640)	A158	C14	597.2	2.90
3-(1,1-dioxido-2-isotiazolidinil)-5-(etilamino)-2-fluoro-N-[(1S,2R)-2-hidroxi-3-({[3-(metiloxi)-fenil]metil}amino)-1-(fenilmetil)propil]-benzamida (E641)	A122	C14	585.3	2.47
3-(1,1-dioxido-2-isotiazolidinil)-5-(etilamino)-2-fluoro-N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-({[3-(trifluorometil)fenil]metil}amino)propil]-benzamida (E642)	A122	C16	623.3	2.62
3-(1,1-dioxido-2-isotiazolidinil)-5-(etilamino)-2-fluoro-N-[(1S,2R)-2-hidroxi-3-({1-metil-1-[3-(metiloxi)fenil]etil}amino)-1-(fenilmetil)propil]-benzamida (E643)	A122	C15	613.3	2.56
3-(1,1-dioxido-2-isotiazolidinil)-5-(etilamino)-2-fluoro-N-[(1S,2R)-2-hidroxi-3-({1-metil-1-[3-(trifluorometil)fenil]etil}amino)-1-(fenilmetil)-propil]benzamida (E644)	A122	C40	651.3	2.70
3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-2-fluoro-N-[(1S,2R)-2-hidroxi-3-({1-metil-1-[3-(metiloxi)fenil]etil}amino)-1-(fenilmetil)propil]benzamida (E645)	A119	C15	627.3	2.63

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-2-fluoro-N-[(1S,2R)-2-hidroxi-3-({1-metil-1-[3-(trifluorometil)fenil]etil}amino)-1-(fenilmetil)propil]benzamida (E646)	A119	C40	665.3	2.77
4-(1,1-dioxido-2-isotiazolidinil)-1-etil-N-[(1S,2R)-2-hidroxi-3-({[3-(metiloxi)fenil]-metil}amino)-1-(fenilmetil)propil]-1*H*-indol-6-carboxamida (E647)	A143	C14	591.3	2.60
4-(1,1-dioxido-2-isotiazolidinil)-1-etil-N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-({[3-(trifluorometil)fenil]metil}amino)propil]-1*H*-indol-6-carboxamida (E648)	A143	C16	629.3	2.75
4-(1,1-dioxido-2-isotiazolidinil)-1-etil-N-[(1S,2R)-2-hidroxi-3-({1-metil-1-[3-(metiloxi)-fenil]etil}amino)-1-(fenilmetil)propil]-1*H*-indol-6-carboxamida (E649)	A143	C15	619.4	2.67
4-(1,1-dioxido-2-isotiazolidinil)-1-etil-N-[(1S,2R)-2-hidroxi-3-({1-metil-1-[3-(trifluorometil)fenil]etil}amino)-1-(fenilmetil)-propil]-1*H*-indol-6-carboxamida (E650)	A143	C40	657.4	2.80
3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-N-[(1S,2R)-2-hidroxi-3-({[3-(metiloxi)fenil]metil}amino)-1-(fenilmetil)propil]-2-(metiloxi)benzamida (E651)	A139	C14	611.4	2.59
3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-({[3-(trifluorometil)fenil]metil}amino)propil]-2-(metiloxi)benzamida (E652)	A139	C16	649.3	2.76
5-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-N'-[(1S,2R)-2-hidroxi-3-({1-metil-1-[3-(metiloxi)-fenil]etilamino)-1-(fenilmetil)propil]-N,N-dipropil-1,3-bencenodicarboxamida (E653)	A95	C15	693.5	2.82
5-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-N'-[(1S,2R)-2-hidroxi-3-({1-metil-1-[3-(trifluorometil)fenil]etil}amino)-1-(fenilmetil)-propil]-N,N-dipropil-1,3-bencenodicarboxamida (E654)	A95	C40	731.4	2.94
1-etil-N-[(1S,2R)-2-hidroxi-3-({[3-(metiloxi)-fenil]metil}amino)-1-(fenilmetil)propil]-4-(2-oxo-1-pirrolidinil)-1*H*-indazol-6-carboxamida (E655)	A152	C14	556.3	2.33

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
1-etil-N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-({[3-(trifluorometil)fenil]metil}amino)propil]-4-(2-oxo-1-pirrolidinil)-1*H*-indazol-6-carboxamida (E656)	A152	C16	594.3	2.42
1-etil-N-[(1S,2R)-2-hidroxi-3-({1-metil-1-[3-(metiloxi)fenil]etil}amino)-1-(fenilmetil)propil]-4-(2-oxo-1-pirrolidinil)-1*H*-indazol-6-carboxamida (E657)	A152	C15	584.4	2.42
1-etil-N-[(1S,2R)-2-hidroxi-3-({1-metil-1-[3-(trifluorometil)fenil]etil}amino)-1-(fenilmetil)-propil]-4-(2-oxo-1-pirrolidinil)-1*H*-indazol-6-carboxamida (E658)	A152	C40	622.4	2.61
4-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-1-etil-N-[(1S,2R)-2-hidroxi-3-({[3-(metiloxi)fenil]-metil}amino)-1-(fenilmetil)propil]-2,3-dihidro-1*H*-indol-6-carboxamida (E659)	A145	C14	607.4	2.61
4-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-1-etil-N-{(1S,2R)-2-hidroxi-1-(fenilmetil)-3-[(1,1,5-trimetilhexil)amino]propil}-1*H*-indol-6-carboxamida (E660)	A147	C5	611.5	2.92
4-(1,1-dioxido-2-isotiazolidinil)-1-etil-N-{(1S,2R)-2-hidroxi-1-(fenilmetil)-3-[(1,1,5-trimetilhexil)amino]propil}-1*H*-indol-6-carboxamida (E661)	A143	C5	597.5	2.85
1-etil-N-{(1S,2R)-2-hidroxi-1-(fenilmetil)-3-[(1,1,5-trimetilhexil)amino]propil}-4-(2-oxo-1-pirrolidinil)-1*H*-indol-6-carboxamida (E662)	A140	C5	561.5	2.83
N-[(1S,2R)-3-(ciclohexilamino)-2-hidroxi-1-(fenilmetil)propil]-4-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-1-etil-1*H*-indol-6-carboxamida (E663)	A147	C1	567.5	2.62
N-[(1S,2R)-3-(ciclohexilamino)-2-hidroxi-1-(fenilmetil)propil]-4-(1,1-dioxido-2-isotiazolidinil)-1-etil-1*H*-indol-6-carboxamida (E664)	A143	C1	553.5	2.54
N-[(1S,2R)-3-(ciclohexilamino)-2-hidroxi-1-(fenilmetil)propil]-1-etil-4-(2-oxo-1-pirrolidinil)-1*H*-indol-6-carboxamida (E665)	A140	C1	517.4	2.51
4-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-1-etil-N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-({[3-(trifluorometil)fenil]metil}amino)propil]-1*H*-indol-6-carboxamida (E666)	A147	C16	643.5	2.86

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
4-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-1-etil-N-[(1S,2R)-2-hidroxi-3-({1-metil-1-[3-(metiloxi)fenil]etil}amino)-1-(fenilmetil)propil]-1*H*-indol-6-carboxamida (E667)	A147	C15	633.5	2.75
4-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-1-etil-N-[(1S,2R)-2-hidroxi-3-({1-metil-1-[3-(trifluorometil)fenil]etil}amino)-1-(fenilmetil)-propil]-1*H*-indol-6-carboxamida (E668)	A147	C40	671.5	2.92
7-[acetil(etil)amino]-N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-({[3-(trifluorometil)fenil]metil}-amino)propil]-3-metil-1-benzofuran-5-carboxamida (E669)	A159	C16	580.2	2.81
ácido fórmico - N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-({[3-(trifluorometil)fenil]metil}-amino)propil]-3-metil-7-(2-oxo-1-pirrolidinil)-1*H*-indol-5-carboxamida (1:1) (E670)	A160	C16	579.2	2.68
N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-({[3-(trifluorometil)fenil]metil}amino)propil]-3-(1-metiletil)-7-(2-oxo-1-pirrolidinil)-1*H*-indol-5-carboxamida (E671)	A161	C 16	607.2	2.85
ácido fórmico - N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-({[3-(trifluorometil)fenil]metil}-amino)propil]-1-metil-3-(1-metiletil)-7-(2-oxo-1-pirrolidinil)-1*H*-indol-5-carboxamida (1:1) (E672)	A162	C16	621.2	2.89
3-etil-N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-({[3-(trifluorometil)fenil]metil}amino)propil]-7-(2-oxo-1-pirrolidinil)-1-benzofuran-5-carboxamida (E673)	A163	C16	594.2	2.90
ácido fórmico - N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-({[3-(trifluorometil)fenil]metil}-amino)propil]-4-metil-8-(2-oxo-1-pirrolidinil)-3,4-dihidro-2*H*-cromeno-6-carboxamida (1:1) (E674)	A164	C16	596.2	2.81
3-etil-N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-({[3-(trifluorometil)fenil]metil}amino)propil]-7-(2-oxo-1-pirrolidinil)-1*H*-indol-5-carboxamida (E675)	A141	C16	593.2	2.81
3-etil-N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-({[3-(trifluorometil)fenil]metil}amino)propil]-1-metil-7-(2-oxo-1-pirrolidinil)-1*H*-indol-5-carboxamida (E676)	A142	C16	607.2	2.83

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
7-(1,1-dioxido-2-isotiazolidinil)-3-etil-N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-({[3-(trifluorometil)fenil]metil}amino)propil]-1*H*-indol-5-carboxamida (E677)	A144	C16	629.1	2.87
N-[(1S,2R)-2-hidroxi-3-({[3-(metiloxi)fenil]-metil}amino)-1-(fenilmetil)propil]-3-(1-metiletil)-7-(2-oxo-1-pirrolidinil)-1*H*-indol-5-carboxamida (E678)	A161	C14	569.5	2.65
ácido fórmico - 3-etil-N-[(1S,2R)-2-hidroxi-3-({[3-(metiloxi)fenil]metil}amino)-1-(fenilmetil)-propil]-7-(2-oxo-1-pirrolidinil)-1*H*-indol-5-carboxamida (1:1) (E679)	A141	C14	555.1	2.44
ácido fórmico - 1-etil-N-[(1S,2R)-2-hidroxi-3-({[3-(metiloxi)fenil]metil}amino)-1-(fenilmetil)-propil]-4-(2-oxo-1-pirrolidinil)-1*H*-benzoimidazol-6-carboxamida (1:1) (E680)	A149	C14	556.5	2.24
ácido fórmico - 7-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-3-etil-N-[(1S,2R)-2-hidroxi-3-({[3-(metiloxi)fenil]metil}amino)-1-(fenilmetil)propil]-1H-indol-5-carboxamida (1:1) (E681)	A148	C14	605.5	2.63
ácido fórmico - 3-etil-N-[(1S,2R)-2-hidroxi-3-({[3-(metiloxi)fenil]metil}amino)-1-(fenilmetil)-propil]-7-(2-oxo-1-piperidinil)-1*H*-indol-5-carboxamida (1:1) (E682)	A165	C14	569.2	2.68
3-(1,1-dioxido-4-feniltetrahidro-2*H*-1,2-tiazin-2-il)-N-[(1S,2R)-2-hidroxi-3-({[3-(metiloxi)fenil]-metil}amino)-1-(fenilmetil)propil]-5-nitrobenzamida (E683)	A123	C14	659.3	2.95
3-(1,1-dioxido-4-feniltetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-N-[(1S,2R)-2-hidroxi-3-({[3-(metiloxi)fenil]metil}amino)-1-(fenilmetil)propil]-benzamida (E684)	A125	C14	657.4	2.85
3-amino-5-(1,1-dioxido-4-feniltetrahidro-2*H*-1,2-tiazin-2-il)-N-[(1S,2R)-2-hidroxi-3-({[3-(metiloxi)fenil]metil}amino)-1-(fenilmetil)propil]-benzamida (E685)	A124	C14	629.4	2.67
3-etil-N-[(1S,2R)-2-hidroxi-3-({[3-(metiloxi)-fenil]metil}amino)-1-(fenilmetil)propil]-7-(2-oxo-4-fenil-1-pirrolidinil)-1*H*-indol-5-carboxamida (E686)	A166	C14	631.4	2.92

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
N-[(1S,2R)-3-(ciclohexilamino)-2-hidroxi-1-(fenilmetil)propil]-3-(1,1-dioxido-4-feniltetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-benzamida (E687)	A125	C1	619.4	2.89
3-(1,1-dioxido-4-feniltetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-N-[(1S,2R)-2-hidroxi-3-[(1-metiletil)amino]-1-(fenilmetil)propil]benzamida (E688)	A125	C28	579.4	2.76
ácido fórmico - 1-etil-N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-({[3-(trifluorometil)fenil]metil}-amino)propil]-4-(2-oxo-1-pirrolidinil)-1*H*-1,2,3-benzotriazol-6-carboxamida (1:1) (E689)	A167	C16	595.3	2.67
ácido fórmico - 4-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-1-etil-N-[(1S,2R)-2-hidroxi-3-({[3-(metiloxi)fenil]metil}amino)-1-(fenilmetil)propil]-1H-benzoimidazol-6-carboxamida (1:1) (E690)	A151	C14	606.3	2.21
1-etil-N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-({[3-(trifluorometil)fenil]metil}amino)propil]-4-(2-oxo-1-pirrolidinil)-1*H*-benzoimidazol-6-carboxamida (E691)	A149	C16	594.5	2.21
1-etil-N-[(1S,2R)-2-hidroxi-3-({1-metil-1-[3-(trifluorometil)fenil]etil}amino)-1-(fenilmetil)propil]-4-(2-oxo-1-pirrolidinil)-1*H*-benzoimidazol-6-carboxamida (E692)	A149	C40	622.5	2.24
N-[(1S,2R)-3-(ciclohexilamino)-2-hidroxi-1-(fenilmetil)propil]-1-etil-4-(2-oxo-1-pirrolidinil)-1*H*-benzoimidazol-6-carboxamida (E693)	A149	C1	518.4	1.90
1-etil-N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-[(1,1,5-trimetilhexil)amino]propil]-4-(2-oxo-1-pirrolidinil)-1*H*-benzoimidazol-6-carboxamida (E694)	A149	C5	562.5	2.33
ácido fórmico - 1-etil-N-[(1S,2R)-2-hidroxi-3-({1-metil-1-[3-(metiloxi)fenil]etil}amino)-1-(fenilmetil)propil]-4-(2-oxo-1-pirrolidinil)-1*H*-benzoimidazol-6-carboxamida (1:1) E695	A149	C15	584.5	2.09

539

Ejemplo 696

3-(1,1-Dioxidotetrahidro-1,2-tiazepin-2(3H)-il)-N-[(1S,2R)-2-hidroxi-3-({[3-(metiloxi)fenil]metil}amino)-1-(fenilmetil)propil]-5-propilbenzamida (E696)

El compuesto del ejemplo 696 se preparó a partir del compuesto de la descripción 313, de manera análoga al ejemplo 213. $[M+H]^+$ = 594.4, t.r. = 2.77 min.

Ejemplo 697

3-(1,1-Dioxidotetrahidro-1,2-tiazepin-2(3H)-il)-N-1[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-({[3-(trifluorometil)fenil]metil}amino)propil]-5-propilbenzamida (E697)

El compuesto del ejemplo 697 se preparó a partir del compuesto de la descripción 312, de manera análoga al ejemplo 213. $[M+H]^+$ = 632.1, t.r. = 3.00 min.

Ejemplos 698-703 (E698-703)

Los siguientes compuestos se prepararon de manera análoga al ejemplo 183, a partir de la amina apropiada y el aldehído o cetona apropiada:

Ejemplo	Precursor	$[M+H]^+$	t.r. (min)
clorhidrato de N-[(1S,2R)-3-{[2-(3-clorofenil)-1-metiletil]amino}-2-hidroxi-1-(fenilmetil)propil]-3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)benzamida (E698)	D120	611.3	1.01
clorhidrato de N-[(1S,2R)-3-{[2-(3-clorofenil)-1-metiletil]amino}-2-hidroxi-1-(fenilmetil)propil]-1-ciclopentil-5-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)benzamida (E699)	D125	638.4	1.00
ácido fórmico - 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-N-[(1S,2R)-3-{[(5-etil-3-tienil)metil]amino}-2-hidroxi-1-(fenilmetil)propil]-benzamida (1:1) (E700)	D120	585.5	2.57
ácido fórmico - 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-N-[(1S,2R)-3-{[(4-etil-2-tienil)metil]amino}-2-hidroxi-1-(fenilmetil)propil]-benzamida (1:1) (E701)	D120	585.5	2.45
ácido fórmico - 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-N-[(1S,2R)-3-{[(1-etil-1*H*-pirazol-3-il)metil]amino}-2-hidroxi-1-(fenilmetil)propil]benzamida (1:1) (E702)	D120	569.5	2.31
ácido fórmico - 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-N-((1S,2R)-2-hidroxi-1-(fenilmetil)-3-{[(1-propil-1*H*-pirazol-4-il)-metil]amino}propil)benzamida (1:1) (E703)	D120	583.5	2.29

Ejemplo 704

El compuesto del ejemplo E704 se preparó de manera análoga al ejemplo 1, a partir del ácido apropiado y la amina indicada en el cuadro siguiente:

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
clorhidrato de N-[(1S,2R)-3-(biciclo[2.2.2]oct-1-ilamino)-2-hidroxi-1-(fenilmetil)propil]-3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)benzamida (E704)	A73	C153	589.5	2.02

Ejemplos 705-709 (E705-709)

Los siguientes compuestos se prepararon de manera análoga al ejemplo 183, a partir de la amina apropiada y el aldehído o cetona apropiada:

Ejemplo	Precursor	$[M+H]^+$	t.r. (min)
ácido fórmico - 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-N-[(1S,2R)-3-{[(5-etenil-3-tienil)metil]amino}-2-hidroxi-1-fenilmetil)propil]-5-(etilamino)benzamida (1:1) (E705)	D120	583.5	2.55
ácido fórmico - 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-N-[(1S,2R)-3-{[(4-etenil-2-furanil)-metil]amino}-2-hidroxi-1-fenilmetil)propil]-5-(etilamino)benzamida (1:1) (E706)	D120	587.5	2.44
ácido fórmico - 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-({[1-(2-propen-1-il)-1*H*-pirazol-4-il]-metil}amino)propil]benzamida (1:1) (E707)	D120	581.5	2.29
ácido fórmico - 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-N-[(1S,2R)-3-{[(4-etenil-2-tienil)-metil]amino}-2-hidroxi-1-(fenilmetil)propil]-5-(etilamino)benzamida (1:1) (E708)	D120	583.5	2.52
ácido fórmico - 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-N-[(1S,2R)-3-({[1-(2-fluoroetil)-1*H*-pirazol-4-il]metil}amino)-2-hidroxi-1-(fenilmetil)propil]benzamida (1:1) (E709)	D120	587.5	2.22

Ejemplos 710-744 (E710-744)

Los compuestos de los ejemplos E710-E744 se prepararon de manera análoga al ejemplo 1, a partir del ácido apropiado y las aminas indicadas en el cuadro siguiente:

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
3-ciclopentil-N-[(1S,2R)-3-{[(1-etil-1*H*-pirazol-4-il)metil]amino}-2-hidroxi-1-(fenilmetil)propil]-5-(2-oxo-1-pirrolidinil)-benzamida (E710)	A107	C154	544.7	2.51
3-(etiloxi)-N-[(1S,2R)-3-{[(1-etil-1*H*-pirazol-4-il)metil]amino}-2-hidroxi-1-(fenilmetil)-propil]-5-(2-oxo-1-pirrolidinil)benzamida (E711)	A11	C154	520.7	2.20
3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-N-[(1S,2R)-3-{[(1-etil-1*H*-pirazol-4-il)metil]amino}-2-hidroxi-1-(fenilmetil)propil]benzamida (E712)	A73	C154	569.6	2.19
3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-N-[(1S,2R)-3-{[(1-etil-1*H*-pirazol-4-il)metil]-amino}-2-hidroxi-1-(fenilmetil)propil]-5-propilbenzamida (E713)	A112	C154	568.6	2.46
ácido fórmico - N-[(1S,2R)-3-[(4,4-difluorociclohexil)amino]-2-hidroxi-1-(fenilmetil)propil]-3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-2-fluorobenzamida (1:1) (E714)	A119	C155	597.4	2.30
4-etil-N-[(1S,2R)-2-hidroxi-3-({[3-(metiloxi)fenil]metil}amino)-1-(fenilmetil)propil]-8-(2-oxo-1-pirrolidinil)-1,2,3,4-tetrahidro-6-quinoxalincarboxamida (E715)	A171	C14	572.5	2.61
4-(1,1-dioxido-2-isotiazolidinil)-1-etil-N-[(1S,2R)-2-hidroxi-3-({[3-(metiloxi)fenil]-metil}amino)-1-(fenilmetil)propil]-1*H*-benzoimidazol-6-carboxamida (E716)	A150	C14	592.4	2.21

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
4-(1,1-dioxido-2-isotiazolidinil)-1-etil-N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-({[3-(trifluorometil)fenil]metil}amino)propil]-1*H*-benzoimidazol-6-carboxamida (E717)	A150	C16	630.4	2.51
4-(1,1-dioxido-2-isotiazolidinil)-1-etil-N-[(1S,2R)-2-hidroxi-3-({1-metil-1-[3-(trifluorometil)fenil]etil}amino)-1-(fenilmetil)propil]-1*H*-benzoimidazol-6-carboxamida (E718)	A150	C40	658.4	2.51
4-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-1-etil-N-[(1S,2R)-2-hidroxi-3-({1-metil-1-[3-(trifluorometil)fenil]etil}amino)-1-(fenilmetil)propil]-2,3-dihidro-1*H*-indol-6-carboxamida (E719)	A145	C40	673.5	2.90
8-(1,1-dioxido-2-isotiazolidinil)-4-etil-N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-({[3-(trifluorometil)fenil]metil}amino)propil]-1,2,3,4-tetrahidro-6-quinoxalincarboxamida (E720)	A172	C16	646.5	2.65
ácido fórmico - 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-2-fluoro-N-{(1S,2R)-2-hidroxi-1-(fenilmetil)-3-[({3-[(trifluorometil)oxi]fenil}metil)amino]-propil}benzamida (1:1) (E721)	A119	C11	653.5	2.54
ácido fórmico - 3-(1,1-dioxido-2-isotiazolidinil)-N-[(1S,2R)-3-{[(1-etil-1*H*-pirazol-4-il)metil]amino}-2-hidroxi-1-(fenilmetil)propil]-2-fluoro-5-propilbenzamida (1:1) (E722)	A174	C154	572.4	2.37
3-(1,1-dioxido-2-isotiazolidinil)-2-fluoro-N-{(1S,2R)-2-hidroxi-1-(fenilmetil)-3-[(1,1,5-trimetilhexil)amino]propil}-5-propilbenzamida (E723)	A174	C5	590.5	2.92
3-(1,1-dioxido-2-isotiazolidinil)-2-fluoro-N-[(1S,2R)-2-hidroxi-3-({1-metil-1-[3-(metiloxi)fenil]etil}amino)-1-(fenilmetil)-propil]-5-propilbenzamida (E724)	A174	C15	612.5	2.66
3-(1,1-dioxido-2-isotiazolidinil)-2-fluoro-N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-({[3-(trifluorometil)fenil]metil}amino)propil]-5-propilbenzamida (E725)	A174	C16	622.4	2.68

Ejemplo	Acido	Amina	$[M+H]^+$	t.r. (min)
clorhidrato de N-[(1S,2R)-3-[(1r,4R)-biciclo-[2.2.1]hept-1-ilamino]-2-hidroxi-1-(fenilmetil)propil]-3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)benzamida (E726)	A73	C152	555.1	2.23
ácido fórmico - 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-N-[(1S,2R)-3-{[(1-etil-1*H*-pirazol-4-il)metil]amino}-2-hidroxi-1-(fenilmetil)propil]-2-fluoro-5-propilbenzamida (1:1) (E727)	A173	C154	586.4	2.50
3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-2-fluoro-N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-(tetrahidro-2*H*-piran-4-ilamino)propil]-5-propilbenzamida (E728)	A173	C43	562.4	2.45
ácido fórmico - 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-2-fluoro-N-[(1S,2R)-2-hidroxi-3-({1-metil-1-[3-(trifluorometil)fenil]etil}-amino)-1-(fenilmetil)propil]-5-propilbenzamida (1:1) (E729)	A173	C40	684.5	2.97
3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-2-fluoro-N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-({[3-(trifluorometil)fenil]metil}amino)propil]-5-propilbenzamida (E730)	A173	C16	636.4	2.84
3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-2-fluoro-N-[(1S,2R)-2-hidroxi-3-({[3-(metiloxi)-fenil]metil}amino)-1-(fenilmetil)propil]-5-propilbenzamida (E731)	A173	C14	598.4	2.70
2-fluoro-N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-(tetrahidro-2*H*-piran-4-ilamino)propil]-3-(2-oxo-1-pirrolidinil)-5-propilbenzamida (E732)	A120	C43	512.5	2.32
N-[(1S,2R)-3-{[(1-etil-1*H*-pirazol-4-il)-metil]amino}-2-hidroxi-1-(fenilmetil)propil]-2-fluoro-3-(2-oxo-1-pirrolidinil)-5-propilbenzamida (E733)	A120	C154	536.5	2.36
N-[(1S,2R)-3-({[3,4-bis(metiloxi)fenil]metil}-amino)-2-hidroxi-1-(fenilmetil)propil]-2-fluoro-3-(2-oxo-1-pirrolidinil)-5-propilbenzamida (E734)	A120	C156	578.5	2.40
2-fluoro-N-[(1S,2R)-2-hidroxi-3-[(1-metiletil)-amino]-1-(fenilmetil)propil]-3-(2-oxo-1-pirrolidinil)-5-propilbenzamida (E735)	A120	C28	470.5	2.26

Ejemplo	Acido	Amina	[M+H]+	t.r. (min)
N-[(1S,2R)-3-(ciclohexilamino)-2-hidroxi-1-(fenilmetil)propil]-2-fluoro-3-(2-oxo-1-pirrolidinil)-5-propilbenzamida (E736)	A120	C1	510.5	2.44
ácido fórmico - 2-fluoro-N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-[(1,1,5-trimetilhexil)amino]-propil}-3-(2-oxo-1-pirrolidinil)-5-propilbenzamida (1:1) (E737)	A120	C5	554.7	3.04
ácido fórmico - 2-fluoro-N-[(1S,2R)-2-hidroxi-3-({1-metil-1-[3-(trifluorometil)fenil]etil}-amino)-1-(fenilmetil)propil]-3-(2-oxo-1-pirrolidinil)-5-propilbenzamida (1:1) (E738)	A120	C40	614.6	2.77
ácido fórmico - 2-fluoro-N-[(1S,2R)-2-hidroxi-3-({1-metil-1-[3-(metiloxi)fenil]etil}amino)-1-(fenilmetil)propil]-3-(2-oxo-1-pirrolidinil)-5-propilbenzamida (1:1) (E739)	A120	C15	576.6	2.66
clorhidrato de 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-N-[(1S,2R)-3-[(1-etilciclobutil)-amino]-2-hidroxi-1-(fenilmetil)propil]-benzamida (E740)	A73	C69	542.9	1.05
clorhidrato de 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-N-{(1S,2R)-2-hidroxi-1-(fenilmetil)-3-[(1-propilciclobutil)-amino]propil}benzamida (E741)	A73	C148	556.9	1.08
clorhidrato de 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-N-[(1S,2R)-2-hidroxi-3-{[1-(1-metiletil)ciclobutil]amino}-1-(fenilmetil)propil]benzamida (E742)	A73	C149	556.9	1.07
clorhidrato de N-[(1S,2R)-3-({1-[(3-clorofenil)metil]ciclobutil}amino)-2-hidroxi-1-(fenilmetil)propil]-3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)benzamida (E743)	A73	C150	639.3	1.41
clorhidrato de 3-(1,1-dioxidotetrahidro-2*H*-1,2-tiazin-2-il)-5-(etilamino)-N-[(1S,2R)-2-hidroxi-1-(fenilmetil)-3-(triciclo[3.3.1.1~3,7~]-dec-2-ilamino)propil]benzamida (E744)	A73	C151	595.7	2.12

La actividad biológica *in vitro* de los compuestos de la invención se puede probar de acuerdo con las pruebas siguientes.

(I) Prueba de inhibición de Asp-2

Para cada compuesto a probar, se agrega en una placa de 384 cavidades:

(a) 1 µl de una solución del compuesto de prueba en DMSO (en la curva de CI_{50} se utilizan diez diluciones en serie de 1 en 2 desde 500 µM).

(b) 10 µl de solución de substrato (FAM- SEVNLDAEFK-TAMRA) en amortiguador. Esta se prepara diluyendo 2 ml de una solución del substrato en DMSO 2 mM, en 400 ml de amortiguador (acetato de sodio 100 mM, pH = 4.5, agua 1 l Milli-Q, Triton X-100 al 0.06% (0.5 ml/l), pH ajustado a 4.5 usando ácido acético glacial). La aminometilfluoresceína (FAM) y la tetrametilrodamina (TAMRA) son moléculas fluorescentes que cooperan para emitir fluorescencia a 535 nm tras la separación del péptido SEVNLDAEFK.

(c) 10 µl de solución de enzima. Esta se prepara diluyendo 16 ml de una solución 500 nM de enzima en 384 ml de amortiguador (preparado como arriba).

En cada placa se incluyen cavidades de blanco (la solución de enzima se reemplaza con amortiguador) como controles. Las cavidades se incuban 1 h a temperatura ambiente y la fluorescencia se lee usando un fluorímetro/espectrofotómetro Tecan Ultra (485 nm de excitación, 535 nm de emisión).

(II) Prueba de inhibición de catepsina D

Para cada compuesto a probar, se agrega en una placa de 384 cavidades:

(a) 1 µl de una solución del compuesto de prueba en DMSO (en la curva de CI_{50} se utilizan diez diluciones en serie de 1 en 2 desde 500 µM).

(b) 10 µl de solución de substrato (FAM-SEVNLDAEFK-TAMRA) en amortiguador. Esta se prepara diluyendo 2 ml de una solución del substrato en DMSO 2 mM, en 400 ml de amortiguador (acetato de sodio 100 mM, pH = 4.5, agua 1 l Milli-Q, Triton X-100 al 0.06% (0.5 ml/l), pH ajustado a 4.5 usando ácido acético glacial).

(c) 10 µl de solución de enzima. Esta se prepara diluyendo 1.6 ml de una solución de enzima de 200 unidades/ml (en HCl 10 mM), en 398.4 ml de amortiguador (preparado como arriba).

En cada placa se incluyen cavidades de blanco (la solución de enzima se reemplaza con amortiguador) como controles. Las cavidades se incuban 1 h a temperatura ambiente y la fluorescencia se lee usando un fluorímetro/espectrofotómetro Tecan Ultra (485 nm de excitación, 535 nm de emisión).

Datos farmacológicos

Los compuestos E1-E744 se analizaron en las pruebas (I) y (II) y mostraron inhibición en la siguiente escala: 1-10000 nM (Asp-2) y 10-10000 nM (CatD). Más particularmente, los compuestos de E12, 22, 30, 31, 33, 50, 54-56, 60, 65, 86,102, 179, 218, 222-223, 241, 245-246, 249, 255, 266, 270, 271, 277-278, 280-289, 296, 299, 303, 313-315, 317-318, 320-322, 325, 327, 329, 332-333, 361-363, 373, 375, 406-408, 559-560, 562, 583-584, 587, 632,

641-642, 647-648, 656, 680, 690-691, 694-695, 700, 703, 708, 713, 716-718, 720-721, 725, 727, 730-731 y 733, mostraron inhibición en la siguiente escala: 1-50 nM (Asp-2) y 100-10000 nM (CatD). Más particularmente, los compuestos de E30-31, 33, 270, 562, 584, 700 y 721, mostraron inhibición en la siguiente escala: 1-10 nM (Asp-2) y 500-10000 nM (CatD).

Abreviaciones

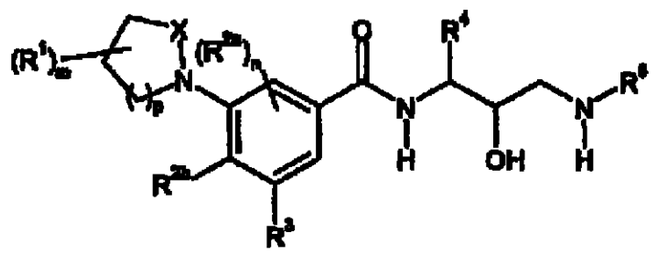
DMF	dimetilformamida
DMSO	sulfóxido de dimetilo
DMAP	dimetilaminofenol
DABCO	1,4-diazabiciclo[2.2.2]octano
DME	éter dimetílico
EDAC	N-etil-N-(3-dimetilaminopropil)carbodiimida
THF	tetrahidrofurano
DEAD	dicarboxilato de dietilacetileno
DCM	diclorometano
TFA	ácido trifluoroacético
HOBT	N-hidroxibenzotriazol
FAM	carboxifluoresceína
TAMRA	carboxitetrametilrodamina
[ ]	código de aminoácido de una letra para la secuencia de péptido

546
549

NOVEDAD DE LA INVENCION

REIVINDICACIONES

1.- Un compuesto de fórmula (I):



(I)

en donde: R^1 representa alquilo de C_{1-6}, alquenilo de C_{2-6}, halógeno, alcoxi de C_{1-6}, amino, ciano, hidroxi, arilo, heteroarilo o heterociclilo; R^{2a} representa hidrógeno, alquilo de C_{1-3}, alcoxi de C_{1-3} o halógeno; m y n representan, independientemente, 0, 1 ó 2; X representa CO, SO o SO_2; p representa un entero de 1 a 3; R^{2b} representa hidrógeno, alquilo de C_{1-6}, alquenilo de C_{2-6}, halógeno, alcoxi de C_{1-6}, amino, ciano, hidroxi, arilo, heteroarilo o heterociclilo; R^3 representa halógeno, alquilo de C_{1-6}, alquenilo de C_{2-6}, arilo, heteroarilo, heterociclilo, -alquil(C_{1-6})-arilo, -alquil(C_{1-6})-heteroarilo, -alquil(C_{1-6})-heterociclilo, -alquenil(C_{2-6})-arilo, -alquenil(C_{2-6})-heteroarilo, -alquenil(C_{2-6})-heterociclilo, cicloalquilo de C_{3-8}, -alquil(C_{1-6})-cicloalquilo de C_{3-8}, ciano, azido, nitro, $-NR^7R^8$, $-NR^9COR^{10}$, $-NR^{11}SO_2R^{12}$, $-OR^{13}$, $-SO_2R^{14}$, $-SR^{15}$, $-C{=}CR^{16}$, -alquil(C_{1-6})-$(CF_2)_qCF_3$, $-CONR^{17}R^{18}$, $COOR^{19}$, -alquil(C_{1-6})-$NR^{20}R^{21}$ o –

alquil(C_{1-6})-N_3, o R^3 y R^{2b} junto con el grupo fenilo al que están unidos, forman un anillo naftilo, o heterocíclico o heteroarilo benzofusionado, sustituido opcionalmente con uno o dos grupos alquilo de C_{1-6}; R^4 representa –alquinilo de C_{2-6}, -alquil(C_{1-6})-arilo, -alquil(C_{1-6})-heteroarilo o –alquil(C_{1-6})-heterociclilo; R^5 representa hidrógeno, alquilo de C_{1-10}, cicloalquilo de C_{3-10}, cicloalquenilo de C_{3-10}, arilo, heteroarilo, heterociclilo, -alquil(C_{1-6})-cicloalquilo de C_{3-10}, -cicloalquil(C_{3-10})-alquilo de C_{1-10}, -cicloalquil(C_{3-10})-alquil(C_{1-6})-arilo, -cicloalquil(C_{3-10})-arilo, -alquil(C_{1-6})-aril-heteroarilo, -C(R^aR^b)-CONH-alquilo de C_{1-6}, -C(R^cR^d)-CONH-cicloalquilo de C_{3-10}, -alquil(C_{1-6})-S-alquilo de C_{1-6}, -alquil(C_{1-6})-NR^eR^f, -alquil(C_{1-6})-arilo, -alquil(C_{1-6})-heteroarilo, -alquil(C_{1-6})-heterociclil-alquil(C_{1-6})-alcoxi(C_{1-6})-arilo, -alquil(C_{1-6})-alcoxi(C_{1-6})-heteroarilo o –alquil(C_{1-6})-alcoxi(C_{1-6})-heterociclilo; R^7, R^8, R^9, R^{10}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20} y R^{21}, representan independientemente hidrógeno, alquilo de C_{1-6}, alquenilo de C_{2-6}, cicloalquilo de C_{3-8}, arilo, heteroarilo, heterociclilo, alquil(C_{1-6})-cicloalquilo de C_{3-8}, -alquil(C_{1-6})-arilo, -alquil(C_{1-6})-heteroarilo, -alquil(C_{1-6})-heterociclilo o –CO-alquilo de C_{1-6}; R^{11}, R^{12}, R^a, R^c, R^e y R^f representan independientemente hidrógeno, alquilo de C_{1-6} o cicloalquilo de C_{3-8}; R^b y R^d representan independientemente hidrógeno, alquilo de C_{1-6}, cicloalquilo de C_{3-8} o -alquil(C_{1-6})-SO_2-alquilo de C_{1-6}; q representa 1 a 3; en donde dichos grupos alquilo pueden estar sustituidos opcionalmente con uno o más grupos (por ejemplo, 1, 2 ó 3) halógeno, alquilo de C_{1-6}, alcoxi de C_{1-6}, alquenoxi de C_{2-6}, cicloalquilo de C_{3-8}, amino, ciano o hidroxi; y en donde dichos grupos cicloalquilo, arilo, heteroarilo o heterociclilo pueden estar sustituidos

opcionalmente con uno o más grupos (por ejemplo 1, 2 ó 3) alquilo de C_{1-6}, alquenilo de C_{2-6}, alquinilo de C_{2-6}, halógeno, haloalquilo de C_{1-6}, $-OCF_3$, oxo, alcoxi de C_{1-6}, -alcoxi(C_{1-6})-CN, amino, ciano, nitro, $-NR^{22}COR^{23}$, $-CONR^{22}R^{23}$, $-COOR^{22}$, $-SO_2R^{22}$, -alquil(C_{1-6})-$NR^{22}R^{23}$ (en donde R^{22} y R^{23} representan independientemente hidrógeno o alquilo de C_{1-6}), -alquil(C_{1-6})-alcoxi de C_{1-6}, -alcanol de C_{1-6} o hidroxi; o una sal o solvato farmacéuticamente aceptable del mismo.

2.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque es un compuesto de la fórmula E1-E744, o una sal farmacéuticamente aceptable del mismo.

3.- Una composición farmacéutica que comprende un compuesto de fórmula (I) como el que se define en la reivindicación 1 o la reivindicación 2, o una sal o solvato farmacéuticamente aceptable del mismo, en mezcla con uno o más diluyentes o vehículos farmacéuticamente aceptables.

4.- Un compuesto de fórmula (I) como el que se define en la reivindicación 1 o la reivindicación 2, o una sal o solvato farmacéuticamente aceptable del mismo, para su uso como un agente farmacéutico.

5.- El uso de un compuesto de fórmula (I) como el que se define en la reivindicación 1 o la reivindicación 2, o una sal o solvato farmacéuticamente aceptable del mismo, en el tratamiento de enfermedades caracterizadas por concentración elevada de β-amiloide o depósitos de β-amiloide.

6.- El uso de un compuesto de fórmula (I) como el que se

reclama en la reivindicación 1 o la reivindicación 2, o una sal o solvato farmacéuticamente aceptable del mismo, en la fabricación de un medicamento para el tratamiento de enfermedades caracterizadas por concentración elevada de β-amiloide o depósitos de β-amiloide.

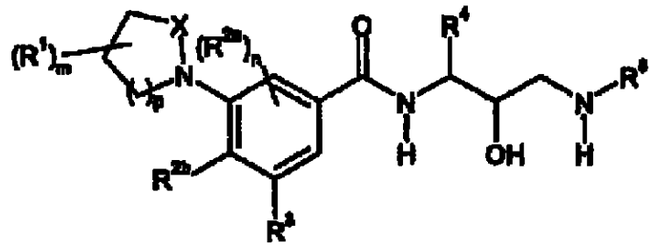
7.- Un método de tratamiento o profilaxis de enfermedades caracterizadas por concentración elevada de β-amiloide o depósitos de β-amiloide, que comprende administrar a un paciente una cantidad efectiva de un compuesto de fórmula (I) como el que se define en la reivindicación 1 o la reivindicación 2, o una sal o solvato farmacéuticamente aceptable del mismo.

8.- Una composición farmacéutica que comprende un compuesto de fórmula (I) como el que se define en la reivindicación 1 o la reivindicación 2, o una sal o solvato farmacéuticamente aceptable del mismo, para su uso en el tratamiento de enfermedades caracterizadas por concentración elevada de β-amiloide o depósitos de β-amiloide.

550
553

RESUMEN DE LA INVENCION

La presente invención se refiere a compuestos de hidroxietilamina novedosos de fórmula (I):



(I)

que tienen actividad inhibidora de Asp2, secretasa, BACE1 o Memapsina; procedimientos para su preparación; composiciones que los contienen; y su uso en el tratamiento de enfermedades caracterizadas por concentración elevada de β-amiloide o depósitos β-amiloides, particularmente la enfermedad de Alzheimer.

EA

P05/670F

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

GlaxoSmithKline
Corporate IP
Received BRENTFORD
07 FEB 2005
ATTY: CG JR ADMIN: KA
FOR: N/A ON UPDATED ON:
ATTY CHECKED/FILE CG

To:

THOMPSON, Clive Beresford
Glaxo Smith Kline
Corporate Intellectual Property
980 Great West Road
Brentford, Middlesex TW8 9EP
GRANDE BRETAGNE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

	Date of mailing *(day/month/year)* 04.02.2005
Applicant's or agent's file reference MXG/P33154	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 03/13806	03.12.2003	05.12.2002

Applicant
GLAXO GROUP LIMITED

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report 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 examination report. 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 invention 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	Cherqui, E Tel. +31 70 340-2643

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
MXG/P33154		
International application No.	**International filing date** *(day/month/year)*	**Priority date** *(day/month/year)*
PCT/EP 03/13806	03.12.2003	05.12.2002

International Patent Classification (IPC) or both national classification and IPC

C07D207/26

Applicant

GLAXO GROUP LIMITED

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
11.06.2004	04.02.2005

Name and mailing address of the international preliminary examining authority:

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

Authorized Officer

Seitner, I

Telephone No. +31 70 340-2389

INTERNATIONAL PRELIMINARY EXAMINATION REPORT International application No. PCT/EP 03/13806

I. Basis of the report

1. With regard to the **elements** of the international application *(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 since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-194 as originally filed

Claims, Numbers

1-8 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

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. 7 (with respect to industrial applicability)

   because:

   ☒ the said international application, or the said claims Nos. 7 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.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

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	1-8
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-8
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-6,8
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item III

N n-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 7 relates 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 document:

D1: WO 02/02512 A (UPJOHN CO ;ELAN PHARM INC (US)) 10 January 2002 (2002-01-10)

V.1 Novelty:

The compounds according to present formula (I) of claim 1 are not encompassed by the prior art. Consequently, the subject matter of **claims 1-8 is new (Article 33(2) PCT).**

V.2. Inventive Step:

Document D1, which is considered to represent the most relevant state of the art, discloses (cf. claims 1, 218-255) compounds for the treatment of Alzheimer's disease.

The subject-matter of claim 1 differs from these known compounds in that the phenyl ring is further substituted by a nitrogen containing heterocycle.

The problem to be solved by the present application may therefore be regarded as the provision of further compounds for the treatment of Alzheimer's disease.

From the teaching of the prior art, the skilled person would not have had any incentive to incorporate a nitrogen containing heterocycle and consequently, the subject matter of **claims 1-8 is 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 Alzheimer's disease and the **subject matter of claims 1-6,8** is therefore considered as **industrially applicable (Article 33(4) PCT)**.

For the assessment of the present claim 7 on the question whether it is 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.

588 560

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN MODELO DE UTILIDAD	( )	( )
- **Indicación de que se solicita la concesión de una patente.**	( )	( )
- **Datos de identificación del solicitante o de la persona que se 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 o 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 solicita el registro de un Esquema de trazado.**	( )	( )
- **Datos de identificación del solicitante o de la persona que presenta La solicitud.**	( )	( )
Representación gráfica del esquema de trazado	( )	( )
Comprobante de pago de las tasas establecidas.	( )	( )
COMPLETA ( ) **INCOMPLETA**	( )	( )

Firma Responsable:

SUPERINDUSTRIA Y COMERCIO
Radicacion : 05054272 DOC32200
Fecha: 2005-06-03 14:23:12 Folios: 527
Tramite : 011 PCT-PATENT 379 FASE NPCI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Fecha:

461
589

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
OLARTE GARCIA CARLOS REINALDO
Apoderado(a) y/o Representante de
GLAXO GROUP LIMITED

REFERENCIA	Radicación No.	5 54176
	Solicitud internacional	EP2003/13806
	Fecha inicio fase nacional	05/07/2005
	Trámite	11
	Evento	379
	Actuación	430
	Oficio No.	7119

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 29 AGO. 2005
adpal

SUPERINDUSTRIA Y COMERCIO
Radicacion : 05054176 00000002 Folios: 24
Fecha (HOY): 2005-08-26 18:44:25
Tramite : 011 PCT-PATENT 379 FASE NACI 444 RESPUESTA
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

562 y 560

SEÑORES
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES
E. S. D.

Ref.: Expediente Nº. 05-054.176
Solicitud de Patente de Invención Titulada: "DERIVADOS DE HIDROXIETILAMINA PARA EL TRATAMIENTO DE LA ENFERMEDAD DE ALZHEIMER"
Solicitante: GLAXO GROUP LIMITED.

RESPUESTA AL OFICIO Nº. 7110 NOTIFICADO POR FIJACION EN LISTA No. 327, DE FECHA 19 DE AGOSTO DE 2005, (EXAMEN DE FORMA)

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, identificado tal como aparece al pie de mi firma, en mi carácter de apoderado de la sociedad en referencia, me permito dar respuesta al auto proferido por ese Despacho, dentro del término legal previsto en el artículo 39 de la Decisión 486, en los siguientes términos:

1. En respuesta a la única observación del Examinador, me permito aportar junto al presente memorial, el documento de cesión debidamente legalizado, junto con su correspondiente traducción, según lo previsto en el Art. 26- k de la Decisión 486.

2. Igualmente, me permito adjuntar el Reporte del Examen Preliminar Internacional, junto con su correspondiente traducción.

Atentamente,

CARLOS R. OLARTE
C.C. No. 79.782.747 de Bogotá
T.P. 74.295

Anexo: Documento de Cesión
Reporte del Examen Preliminar Internacional

P33154

Nosotros,
Emmanuel H. DEMONT
Andrew FALLER
David Timothy MACPHERSON
Peter Henry MILNER
Alan NAYLOR
Sally REDSHAW
Steven James STANWAY
David R VESEY
Daryl S WALTER

Por medio de la presente cedemos a

Glaxo Group Limited

una compañía organizada bajo las leyes de Gran Bretaña domiciliada en
Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex, UB6 0NN, Gran Bretaña,

(en adelante el "Cesionario"), todos mis (nuestros) derechos, título e interés sobre mi(nuestra) invención tal como describe en:

DERIVADOS DE HIDROXIETILAMINA PARA EL TRATAMIENTO DE LA ENFERMEDAD DE ALZHEIMER.

En lo que concierne a la República de Colombia.

564 562

Lugar y Fecha: Harlow, UK 11 de mayo de 2005

(Fdo) Emmanuel H. DEMONT
Emmanuel H. DEMONT

Lugar y Fecha:

_____
Andrew FALLER

Lugar y Fecha: Harlow, UK 11 de mayo de 2005

(Fdo) David Timothy MACPHERSON
David Timothy MACPHERSON

Lugar y Fecha: Harlow, UK 11 de mayo de 2005

(Fdo) Peter Henry MILNER
Peter Henry MILNER

Lugar y Fecha: Harlow, UK 12 de mayo de 2005

(Fdo) Alan NAYLOR
Alan NAYLOR

Lugar y Fecha: Harlow, UK 11 de mayo de 2005

(Fdo) Sally REDSHAW
Sally REDSHAW

563
505

Lugar y Fecha: Harlow, UK 16 de mayo de 2005

(Fdo) Steven James STANWAY

Steven James STANWAY

Lugar y Fecha: Harlow, UK 11 de mayo de 2005

(Fdo) David R VESEY

David R VESEY

Lugar y Fecha: Harlow, UK 11 de mayo de 2005

(Fdo) Daryl S WALTER

Daryl S WALTER

564

P33154

Nosotros,
Emmanuel H. DEMONT
Andrew FALLER
David Timothy MACPHERSON
Peter Henry MILNER
Alan NAYLOR
Sally REDSHAW
Steven James STANWAY
David R VESEY
Daryl S WALTER

Por medio de la presente cedemos a

Glaxo Group Limited

Una compañía organizada bajo las leyes de Gran Bretaña
Domiciliada en
Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex, UB6 0NN, Gran Bretaña,

(en adelante el "Cesionario"), todos mis (nuestros) derechos, título e interés sobre mi(nuestra) invención tal como describe en:

DERIVADOS DE HIDROXIETILAMINA PARA EL TRATAMIENTO DE LA ENFERMEDAD DE ALZHEIMER.

En lo que concierne a la República de Colombia.

Lugar y Fecha:

_____

Emmanuel H. DEMONT

Lugar y Fecha: Erl Wood, Surrey 16 de mayo de 2005

(Fdo.) Andrew FALLER

Andrew FALLER

Lugar y Fecha:

_____

David Timothy MACPHERSON

Lugar y Fecha:

_____

Peter Henry MILNER

Lugar y Fecha:

_____

Alan NAYLOR

Lugar y Fecha:

_____

Sally REDSHAW

566
568

Lugar y Fecha:

_____

Steven James STANWAY

Lugar y Fecha:

_____

David R VESEY

Lugar y Fecha:

_____

Daryl S WALTER

EN ESPAÑOL viene Certificación de la firma anterior por parte de James Kerr MILLIGAN, Notario Público de Londres, Inglaterra.

APOSTILLA

(Convención de la Haya del 5 de Octubre de 1961)

REINO UNIDO DE GRAN BRETAÑA E IRLANDA DEL NORTE

1. País: Reino Unido de Gran Bretaña e Irlanda del Norte
   El presente documento público
2. Ha sido firmado por: **James Kerr Milligan**
3. Que actuó en su calidad de Notario Público
4. Lleva el sello del mencionado Notario Público
   Se certifico
5. En Londres
6. El 02 de junio de 2005
7. Por parte del Principal Secretario de Estado de su Majestad para Asuntos Extranjeros y de la Mancomunidad.
8. Bajo el Número **G715875**
9. Lleva el Sello de la Oficina de Asuntos Extranjeros y de la Mancomunidad de Londres.
10. Firmado por **S. Gardiner**
    Por el Secretario de Estado.

570

Yo, el infrascrito, **James Kerr MILLIGAN**, Notario Público de la Ciudad de Londres, Inglaterra, por la Autoridad Real debidamente admitido y juramentado,

C E R T I F I C O:

QUE las páginas anexas forman en conjunto un documento único de Cesión que fue firmado por:

Don **Emmanuel Hubert DEMONT**, titular de pasaporte francés **03FE36141** expedido el día 29 de abril de 2004;

Don **Andrew FALLER**, titular de pasaporte británico número **034451324** expedido por la Agencia de Pasaportes del Reino Unido el día 6 de marzo de 1999;

Don **David Timothy MACPHERSON**, cuya identidad me consta;

Don **Peter Henry MILNER**, titular de pasaporte británico número **029578254** expedido por la Agencia de Pasaportes del Reino Unido el día 16 de diciembre de 1997;

Don **Alan NAYLOR**, titular del carnet de conducir británico número **NAYLO 507100 A99HX** expedido el día 17 de julio de 1976;

Doña **Sally Davina REDSHAW**, titular del carnet de conducir británico número **REDSH 555094 SD9UJ** expedido el día 1 de octubre de 1979;

Don **Steven James STANWAY**, titular de pasaporte británico número **450040406** expedido por la Agencia de Pasaportes del Reino Unido el día 10 de julio de 2000;

Don **David Robert VESEY**, titular de pasaporte británico número **304395998** expedido por la Agencia de Pasaportes del Reino Unido el día 24 de febrero de 2005; y

Don **Daryl Simon WALTER**, titular del carnet de conducir británico número **WALTE 604105 DS9DA** expedido el día 10 de mayo de 1994.

Y PARA QUE CONSTE donde y como convenga y fuere necesario expido el presente Certificado que firmo y sello en dicha Ciudad de Londres, el día de hoy primero de junio del año dos mil cinco.

SCRIVENER NOTARIES

James Kerr MILLIGAN
Notario Público de Londres, Inglaterra

APOSTILLE
(Hague Convention of 5 October 1961 / Convention de La Haye du 5 octobre 1961)

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

1. Country: United Kingdom of Great Britain and Northern Ireland
   Pays: Royaume-Uni de Grande-Bretagne et d'Irlande du Nord

   This public document / Le présent acte public

2. Has been signed by **James Kerr Milligan**
   a été signé par

3. Acting in the capacity of **Notary Public**
   agissant en qualité de

4. Bears the seal/stamp of **The Said Notary Public**
   est revêtu du sceau/timbre de

Certified/Attesté

5. at London/à Londres
6. the/le **02 June 2005**

7. by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs /
   par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth.

8. Number/sous No **G715875**

9. Stamp:
   timbre:

10. Signature: **S. Gardiner**

For the Secretary of State / Pour le Secrétaire d'Etat

If this document is to be used in a country which is not party to the Hague Convention of 5 October 1961, it should be presented to the consular section of the mission representing that country. An apostille or legalisation certificate only confirms that the signature, seal or stamp on the document is genuine. It does not mean that the contents of the document are correct or that the Foreign & Commonwealth Office approves of the contents.

571 569

Colombia

P33154

ASSIGNMENT	CESION
Emmanuel H DEMONT **Andrew FALLER** **David Timothy MACPHERSON** **Peter Henry MILNER** **Alan NAYLOR** **Sally REDSHAW** **Steven James STANWAY** **David R VESEY** **Daryl S WALTER**	por medio de la present cedo (cedemos) a una _____ organizada baja las leyes de
By means of this document assign to **Glaxo Group Limited** A company organized under the laws of **Great Britain**	domiciliada en (de ahora en adelante el CESIONARIO), todos mis (nuestros) derechos, titulo e interes sobre mi (nuestra) invencion tal como describe en:
Domiciled in **Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex, UB6 0NN, Great Britain** (hereinafter referred to as the ASSIGNEE). All my (our) rights, title and interest in and to my (our) invention for a new and useful improvement entitled and as fully set forth and described in: **HYDROXYETHYLAMINE DERIVATIVES FOR THE TREATMENT OF ALZHEIMER'S DISEASE** So far as the Republic of Colombia is concerned.	En lo que concierne a la Republica de Colombia. Place and date:
Place and date: Harlow, UK 4/05/2005 _____ **Emmanuel H DEMONT** Place and date: _____ **Andrew FALLER**	

Place and date:
Harlow UK 11/5/05

D.T. MacPherson
David Timothy MACPHERSON

Place and date:
HARLOW, U.K 11 May 2005

P. Milner
Peter Henry MILNER

Place and date:
HARLOW UK, 12th May 2005

Alan NAYLOR

Place and date:
Harlow UK 11/05/05

Sally REDSHAW

Place and date:
Harlow, UK 16th May 2005

Steven James STANWAY

Place and date:
Harlow UK 11/5/05

David R VESEY

Place and date:
HARLOW UK 11/5/05

Daryl S WALTER

ASSIGNMENT	CESION
Emmanuel H DEMONT **Andrew FALLER** **David Timothy MACPHERSON** **Peter Henry MILNER** **Alan NAYLOR** **Sally REDSHAW** **Steven James STANWAY** **David R VESEY** **Daryl S WALTER**	por medio de la present cedo (cedemos) a una _____ organizada baja las leyes de
By means of this document assign to **Glaxo Group Limited** A company organized under the laws of **Great Britain**	domiciliada en (de ahora en adelante el CESIONARIO), todos mis (nuestros) derechos, titulo e interes sobre mi (nuestra) invencion tal como describe en:
Domiciled in **Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex, UB6 0NN, Great Britain** (hereinafter referred to as the ASSIGNEE). All my (our) rights, title and interest in and to my (our) invention for a new and useful improvement entitled and as fully set forth and described in: **HYDROXYETHYLAMINE DERIVATIVES FOR THE TREATMENT OF ALZHEIMER'S DISEASE** So far as the Republic of Colombia is concerned.	En lo que concierne a la Republica de Colombia. Place and date:
Place and date: _____ **Emmanuel H DEMONT** Place and date: Erl Wood, Surrey 16 MAY 2005 Andrew Faller **Andrew FALLER**	

Place and date: _____ **David Timothy MACPHERSON** **Place and date:** _____ **Peter Henry MILNER** **Place and date:** _____ **Alan NAYLOR** **Place and date:** _____ **Sally REDSHAW** **Place and date:** _____ **Steven James STANWAY** **Place and date:** _____ **David R VESEY** **Place and date:** _____ **Daryl S WALTER**	

REPORTE DE EXAMEN PRELIMINAR INTERNACIONAL
(PCT Artículo 36 y Regla 70)

Referencia del solicitante o representante: MXG/P33154
No. de Solicitud Internacional: PCT/EP03/13806
Fecha de presentación internacional: 03/12/2003
Fecha de prioridad: 05/12/2002
Clasificación Internacional de Patentes: C07D207/26
Solicitante: GLAXO GROUP LIMITED

1. El reporte de examen preliminar internacional ha sido preparado por esta Autoridad de Revisión Preliminar Internacional y es transmitido al solicitante según el Artículo 36.

2. Este REPORTE consta de 5 hojas, incluyendo esta cubre hoja.

__ Este reporte también está acompañado de ANEXOS, es decir, hojas de la descripción, reivindicaciones, y/o dibujos los cuales han sido modificados y son la base para este reporte y/o hojas que contengan rectificaciones hechas ante esta Autoridad (ver Regla 70.16 y Sección 607 de las Instrucciones Administrativas bajo el PCT).

Estos anexos constan de hojas.

3. Este reporte contiene indicaciones con relación a los siguientes ítems:

I. X Base para el reporte
II. _ Prioridad
III. X Ninguna opinión con respecto a la novedad, nivel inventivo y aplicación industrial.
IV. _ Falta de unidad inventiva
V. X Declaración razonada según Regla 66.2(a) (ii) con respecto a la novedad, nivel inventivo o aplicación industrial; citas y explicaciones soportando dicha declaración.
VI. _ Ciertos documentos citados
VII _ Ciertos defectos en la solicitud internacional
VIII _ Ciertas observaciones sobre la solicitud internacional

Fecha de radicación de la demanda: 11.06.2004
Fecha de elaboración de este reporte: 04.02.2005

Nombre y dirección de correspondencia de la Autoridad de Revisión Preliminar Internacional:
Oficina de Patentes Europea - 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.

Funcionario Autorizado: Seitner, I
Tel: + 31 70 340-2389

575
577

REPORTE DE EXAMEN PRELIMINAR INTERNACIONAL

No. de Solicitud Internacional: PCT/EP03/13806

I. **Base del reporte**

1. Con respecto a los **elementos** de la solicitud internacional (Hojas de reemplazo, entregadas a la Oficina receptora en respuesta a un requerimiento según el Artículo 14, son referidas en este reporte como "presentadas originalmente" y no están anexadas al presente puesto que no contienen enmiendas (Reglas 70.16 y 70.17)):

Descripción, páginas:

1-194 tal como se presentó originalmente

Reivindicaciones, Nos.:

1-8 tal como se presentó originalmente

2. Con respecto al **idioma**, todos los elementos marcados anteriormente estuvieron disponibles o fueron suministrados a esta Autoridad en el idioma en el cual fue presentada la solicitud internacional, a menos que se indique de otra manera bajo este punto.

Estos elementos estuvieron disponibles o fueron suministrados a esta Autoridad en el siguiente idioma: , el cual es:

- ☐ el idioma de una traducción suministrada con fines de la búsqueda internacional (bajo Regla 23.1(b)).
- ☐ el idioma de la publicación de la solicitud internacional (bajo Regla 48.3 (b)).
- ☐ el idioma de una traducción suministrada con fines del examen preliminar internacional (bajo Regla 55.2 y/o 55.3).

3. Con respecto a cualquier **secuencia nucleótida y/o de amino ácidos** divulgada en la solicitud internacional, el examen preliminar internacional fue realizado con base en el listado de secuencias:

- ☐ contenido en la solicitud internacional por escrito.
- ☐ presentado junto con la solicitud internacional en forma electrónica
- ☐ suministrado subsecuentemente a esta Autoridad por escrito
- ☐ suministrado subsecuentemente a esta Autoridad en forma electrónica

☐ Ha sido suministrada la declaración donde indica que el listado suministrado de secuencias escrito no va más allá de la divulgación encontrada en la solicitud internacional tal como se presentó

☐ Ha sido suministrada la declaración que indica que la información registrada en forma electrónica es idéntica al listado de secuencias escrito.

4. Las enmiendas han resultado en la cancelación de:

☐ la descripción, páginas:
☐ las reivindicaciones, Nos.:
☐ los dibujos, hojas:

5. Este reporte ha sido establecido como si no estuvieran hechas las enmiendas, puesto que se consideró que iban más allá de la divulgación tal como se presentó (Regla 70.2(c)).

(Cualquier hoja de reemplazo que contenga tales enmiendas debe referirse al ítem 1 y estar adjunto a este reporte.)

6. Observaciones adicionales, si son necesarias:

III. Ninguna formulación de opinión con respecto a la novedad, nivel inventivo, y aplicación industrial

1. Las preguntas con respecto a si el invento reivindicado parece ser novedoso, tener nivel inventivo (no ser obvio), o ser industrialmente aplicable no han sido examinadas con respecto a:

☐ toda la solicitud internacional,
X reivindicaciones Nos. 7 (con respecto a la aplicación industrial)

puesto que:

X dicha solicitud internacional, o dichas reivindicaciones Nos. 7 se relacionan con el siguiente tema el cual no requiere examen preliminar internacional (especifique):

ver página adjunta

☐ la descripción, reivindicaciones, o dibujos (indique elementos en particular a continuación) o tales reivindicaciones Nos. están tan ambiguas que ninguna opinión significativa pudo formularse (especifique):

☐ las reivindicaciones, o dichas reivindicaciones No. están tan inapropiadamente soportadas que no se pudo formar una opinión significativa.

☐ no se ha establecido ninguna búsqueda internacional para dichas reivindicaciones Nos.

2. Un examen preliminar internacional significativo no puede efectuarse debido a que el listado de secuencias nucleótidas y/o de amino ácidos no cumple con el estándar suministrado en el Anexo C de las Instrucciones Administrativas:

☐ la forma escrita no ha sido suministrada o no cumple con el estándar
☐ la forma electrónica no ha sido suministrada o no cumple con el estándar

V. Declaración razonada según el Artículo 35(2) con respecto a la novedad, nivel inventivo o aplicación industrial: anterioridades y explicaciones que soportan tal declaración

1. Declaración

Novedad (N)	Si:	Reivindicaciones 1-8
	No:	Reivindicaciones
Nivel Inventivo (NI)	Si:	Reivindicaciones 1-8
	No:	Reivindicaciones
Aplicación Industrial (AI)	Si:	Reivindicaciones 1-6,8
	No:	Reivindicaciones

2. Anterioridades y explicaciones

ver hoja adjunta.

REPORTE DE EXÁMEN PRELIMINAR INTERNACIONAL
– HOJA SEPARADA

Solicitud Internacional No. PCT/EP 03/13806

Re Sección III

La reivindicación 7 está relacionada con la materia-sujeto considerada por esta Autoridad que esta cubierta por las provisiones establecidas en la Regla 67.1 (iv) del PCT. Por lo tanto, ninguna opinión será formulada con respecto a la aplicación industrial de la materia-sujeto de estas reivindicaciones (Artículo 34(4)(a)(I) del PCT).

Re Sección IV

Declaración razonada con respecto a novedad, nivel inventivo o aplicabilidad industrial; citaciones y explicaciones que sustentan dicha declaración

Se hace referencia al siguiente documento

D1: WO 02/02512 A (UPJHON CO; ELAN PHARM INC (US)) Enero 10 del 2002 (2002-01-10)

V.1. Novedad:
Los compuestos de acuerdo con la presente fórmula (I) de la reivindicación 1 no están comprendidos en el artículo previo. Por lo tanto, la materia sujeto de las reivindicaciones 1-8 es nueva (Artículo 33(2) PCT).

2. Nivel Inventivo:
El documento D1, el cual se considera representa el punto mas relevante del artículo, discute (cf. Reivindicaciones 1, 218-255) compuestos para el tratamiento de la enfermedad de Alzheimer.

La materia-sujeto de la reivindicación 1 difiere de aquellos compuestos conocidos en que el anillo fenil es de lejos sustituido por un heterocíclico que contiene nitrógeno.

El problema a resolver por la presente aplicación podría por lo tanto ser considerado como la provisión de novedosos compuestos para el tratamiento de la enfermedad de Alzheimer.

Como enseñanza del artículo previo, el personal entrenado no habría tenido ningún incentivo en incorporar un heterocíclico conteniendo nitrógeno, y por ende, la materia sujeto de las **reivindicaciones 1–8 es considerada como implicando un nivel inventivo (Artículo 33 (3) PCT).**

REPORTE DE EXÁMEN PRELIMINAR INTERNACIONAL
– HOJA SEPARADA

Solicitud Internacional No. PCT/EP 03/13806

V.3. Aplicabilidad Industrial:
La presente aplicación está relacionada con compuestos que son útiles para el tratamiento de la enfermedad de Alzheimer y la materia sujeto de las **reivindicaciones 1-6, 8** que por consiguiente se considera como **industrialmente aplicable (Artículo 34(4) PCT).**

Para la evaluación de la presente reivindicación 7 en cuestión de cuando es industrialmente aplicable, no existen criterios unificados en los Estados de Contratación PCT. La patentabilidad puede también ser dependiente por la formulación de las reivindicaciones. La EPO, por ejemplo, no reconoce si es industrialmente aplicable la materia sujeto para el uso de un compuesto en tratamiento médico, pero es permitido, así mismo, las reivindicaciones para un compuesto conocido para primer uso en tratamiento médico y el uso de tal compuesto para la fabricación de un medicamento para un nuevo tratamiento médico.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference MXG/P33154	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/13806	International filing date *(day/month/year)* 03.12.2003	Priority date *(day/month/year)* 05.12.2002
International Patent Classification (IPC) or both national classification and IPC C07D207/26		
Applicant GLAXO GROUP LIMITED		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
11.06.2004	04.02.2005
Name and mailing address of the international preliminary examining authority: 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	Authorized Officer Seitner, I Telephone No. +31 70 340-2389

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/13806

I. **Basis of the report**

1. With regard to the **elements** of the international application *(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 since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-194 as originally filed

Claims, Numbers

1-8 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

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. 7 (with respect to industrial applicability)

   because:

   ☒ the said international application, or the said claims Nos. 7 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.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

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	1-8
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-8
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-6,8
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 7 relates 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 document:

D1: WO 02/02512 A (UPJOHN CO ;ELAN PHARM INC (US)) 10 January 2002 (2002-01-10)

V.1 Novelty:

The compounds according to present formula (I) of claim 1 are not encompassed by the prior art. Consequently, the subject matter of **claims 1-8 is new (Article 33(2) PCT).**

V.2. Inventive Step:

Document D1, which is considered to represent the most relevant state of the art, discloses (cf. claims 1, 218-255) compounds for the treatment of Alzheimer's disease.

The subject-matter of claim 1 differs from these known compounds in that the phenyl ring is further substituted by a nitrogen containing heterocycle.

The problem to be solved by the present application may therefore be regarded as the provision of further compounds for the treatment of Alzheimer's disease.

From the teaching of the prior art, the skilled person would not have had any incentive to incorporate a nitrogen containing heterocycle and consequently, the subject matter of **claims 1-8 is 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 Alzheimer's disease and the **subject matter of claims 1-6,8** is therefore considered as **industrially applicable (Article 33(4) PCT).**

For the assessment of the present claim 7 on the question whether it is 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.