SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 12-049461- -00000-0000
Fecha: 2012-03-23 14:55:11 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 411 PRESENTACION Folios: 363

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

SOLICITUD DE

PATENTE DE INVENCION
PCT ENTRADA EN FASE NACIONAL

21. EXPEDIENTE No. _____

54. TITULO: **DERIVADOS DE (TIO)MORFOLINA COMO MODULADORES DE S1P**

52. CLASIFICACION INTERNACIONAL: **C07D 265/30, C07D 265/32, C07D 413/12, C07D 419/12, C07D 471/04, A61K 31/5377, A61P 25/04, A61P 25/06, A61P 25/16, A61P 25/18, A61P 25/24, A61P 25/28, C07D278/12, C07D 417/12, C07D 487/04**

71. SOLICITANTES: **ABBOTT HELTHCARE PRODUCTS B.V.**

DOMICILIO: **C.J. van Houtenlaan 36, NL-1381 CP Weesp - HOLANDA**

74. APODERADO: **Dra. MARGARITA CASTELLANOS A.**

22. BOGOTA, D.C., _____

000001

PETITORIO

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

adicación

No. 12-049461- -00000-0000

Fecha: 2012-03-23 14:55:11 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 411 PRESENTACION Folios: 363

FORMULARIO UNICO D[illegible]
PCT
ENTRADA EN FASE NACIONAL

SOLICITUD DE:

① [X] **Patente de Invención.** [ ] **Patente de Modelo de Utilidad.**

[ ] **Capítulo I** [X] **Capítulo II**

② **SOLICITANTE (71)**	Nombre: **ABBOTT HEALTHCARE PRODUCTS B.V.** Dirección: **C.J. van Houtenlaan 36 NL-1381 CP Weesp HOLANDA** Domicilio: **NL-1381 CP Weesp HOLANDA** Lugar de Constitución: **HOLANDA** Teléfono: Fax: E-mail:	**IDENTIFICACIÓN** C.C. [ ] NIT [ ] C.E. [ ] Otro [ ] Cual Número
③ **REPRESENTANTE O APODERADO**	Nombre: **MARGARITA CASTELLANOS A.** Dirección: **CALLE 94A No. 7A-09** Teléfono: **7560770** Fax: **7550158** E-mail: info@castellanosyco.com	**IDENTIFICACIÓN** C.C. [X] NIT [ ] C.E. [ ] Otro [ ] Cual Número **39'779.654** TPA **70.819**
④ **INVENTOR (ES) (72)**	**VER ANEXO # 1**	

⑤ **PCT (86)**

Solicitud Internacional No. **PCT/EP2010/062552** Fecha **27/08/2010**

Publicación Internacional No. **WO 2011/023795 A1** Fecha **03/03/2011**

⑥ **Título (54)** **DERIVADOS DE (TIO)MORFOLINA COMO MODULADORES DE S1P**

⑦ **Clasificación Internacional (51)** C07D 265/30, C07D 265/32, C07D 413/12, C07D 419/12, C07D 471/04, A61K 31/5377, A61P 25/04, A61P 25/06, A61P 25/16, A61P 25/18, A61P 25/24, A61P 25/28, C07D278/12, C07D 417/12, C07D 487/04

⑧ **Prioridad** SI [X] NO [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	31/08/2009	61/238,518
EP	31/08/2009	09169075,0

⑨ **Comprobantes de pago Nos.** **12-0016979, 12-0016983** **Fecha** **Febrero 20 de 2012**

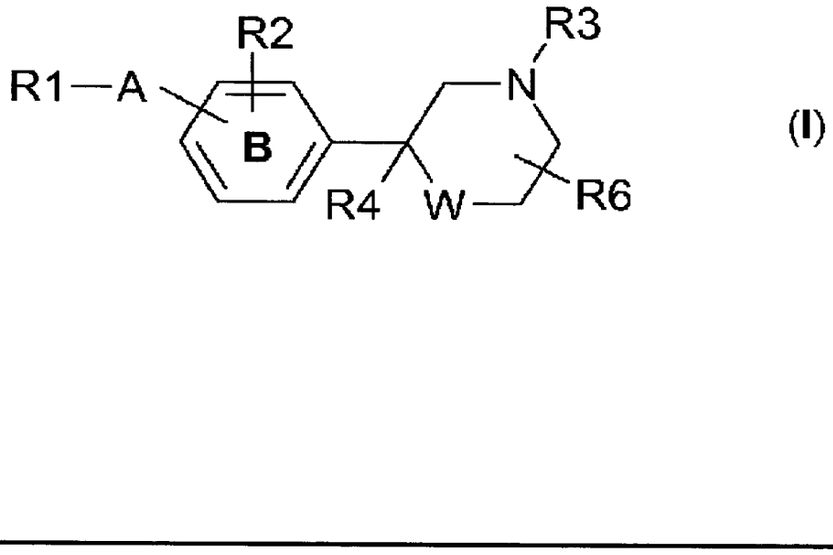
Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

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(10) Anexos

- [X] Comprobante de pago de la tasa de presentación de la solicitud.
- [X] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [X] Poderes, si fuere el caso, junto con la sustitución del mismo a mi favor
- [X] 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).
- [X] 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.
- [X] Arte final 12x12
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [X] Otros: **Tarjeta Propietario, Extracto para la publicación**

(11) FIGURA CARACTERISTICA:



(I)

(12) Solicito la concesión de la patente,

NOMBRE: **MARGARITA CASTELLANOS ABONDANO**

FIRMA:

C.C. No. 39.779.654 Usaquén - TPA 70.819 C.S.J.

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página. - MCA/gcb - P2424

PI02-F06 (2008-06-09)

22 MAR. 2012

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NIT : 800.176.089-2
- / -

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 12 - 0016979

Bogotá D.C., Febrero 20 de 2012 - 14:30:44

RECIBIDO DE : CASTELLANOS Y Y CO NI 800.174.641

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	444798933	20/02/2012	18.560.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE INVENCION	590.000.00	590.000.00
				$590.000.00

SON: **QUINIENTOS NOVENTA MIL PESOS MONEDA CORRIENTE***

Responsable: _____
-**-

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 12-049461- -00000-0000
Fecha: 2012-03-23 14:55:11 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
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NIT : 800.176.089-2
- / -

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 12 - 0016983

Bogotá D.C., Febrero 20 de 2012 - 14:30:44

RECIBIDO DE : CASTELLANOS Y Y CO NI 800.174.641

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	444798933	20/02/2012	18.560.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
2	50005-01-01 SOLICITUDES	1607 REIVINDICACION UNITARIA ADICIONAL A LAS 10 INICICIALES	30.000.00	60.000.00
				$60.000.00

SON: **SESENTA MIL PESOS MONEDA CORRIENTE***

Responsable: _____
****

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 12-049461- -00000-0000

Fecha: 2012-03-23 14:55:11 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 411 PRESENTACION Folios: 363

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NIT : 800.176.089-2
- / -

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 12 - 0011187

Bogotá D.C., Febrero 03 de 2012 - 14:20:26

RECIBIDO DE : CASTELLANOS Y Y CO NI 800.174.641

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	420505562	03/02/2012	7.335.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
7	50005-01-01 SOLICITUDES	1607 REIVINDICACION UNITARIA ADICIONAL A LAS 10 INICICIALES	30.000.00	210.000.00
				$210.000.00

==========

SON: **DOSCIENTOSDIEZ MIL PESOS MONEDA CORRIENTE***

Responsable: _____
-*********-

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 12-049461- -00000-0000
Fecha: 2012-03-23 14:55:11
Tra. 11 PATENTEIYII Dep. 2020 DIR.NUEVASCR
Act. 411 PRESENTACION Eve: 379 FASENACIONALII
Folios: 363

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DT

PATENT COOPERATION TREATY PCT/EP2010/062552

ADVANCE E-MAIL

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/naar

TERMIJN

21 FEB. 2012

BEANTWOORD

PCT

MAP P94071PC00

From the INTERNATIONAL BUREAU

To:

HOGENBIRK, Marijke
Octrooibureau Zoan B.V.
P.O. Box 140
NL-1380 AC Weesp
PAYS-BAS
Fax: +3170 416 67 99

NOTIFICATION OF THE RECORDING OF A CHANGE

(~~PCT Rule 92*bis*~~.1 and Administrative Instructions, Section 422)

Date of mailing *(day/month/year)* 21 February 2012 (21.02.2012)	
Applicant's or agent's file reference SPW0912 WO	**IMPORTANT NOTIFICATION**
International application No. PCT/EP2010/062552	International filing date *(day/month/year)* 27 August 2010 (27.08.2010)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address	State of Nationality	State of Residence
KAM, VAN DER, Elizabeth c/o Abbott Healthcare Products B.V. C.J. van Houtenlaan 36 NL-1381 CP Weesp Netherlands	NL	NL
	Telephone No.	
	Facsimile No.	
	E-mail address	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☒ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address	State of Nationality	State of Residence
VAN DER KAM, Elizabeth c/o Abbott Healthcare Products B.V. C.J. van Houtenlaan 36 NL-1381 CP Weesp Netherlands	NL	NL
	Telephone No.	
	Facsimile No.	
	E-mail address ☐ Notifications by e-mail authorized	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☐ the Authority(ies) specified for supplementary search
☐ the International Preliminary Examining Authority
☐ the designated Offices concerned
☒ the elected Offices concerned
☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 89 70

Authorized officer
Rochaix Thomas
e-mail pt06.pct@wipo.int
Telephone No. +41 22 338 74 06

BOEKEL DE NERÉE

Reference number : 20110008.01\S\S

000007 B2424

Seen for legalisation by me, mr. Antonius Lodewijk Maria Schulte, civil-law notary, practising in Amsterdam, the signature of:

- **Wouter Iwema Iwema Bakker**, born in Amsterdam on the 18th day of August 1965, holder of a Dutch passport with number NTB1L9PC9, issued in Weesp on the 8th day of September 2006;
- **Axel P. Stoit**, born in Amsterdam on the 7th day of April 1957, holder of a Dutch drivers license with number 4053910105, issued in Beemster on the 2nd day of April 2007
- **Harmen Mons**, born in Harderwijk on the 19th day of December 1961, holder of a Dutch passport with number NXRDFLDR6, issued in Almere on the 12th day of October 2009;
- **Hein Karel A.C. Coolen**, born in Roermond on the 10th day of January 1964, holder of a Dutch identity card with number IUKLD98C3, issued in Utrecht on the 11th day of July 2007;
- **Eric Ronken**, born in Arnhem on the 20th day of May 1963, holder of a Dutch drivers licence with number 4531979103, issued in Weesp on the 3rd day of Oktober 2007;
- **Elizabeth L. van der Kam**, born in Beek en Donk on the 25th day of February 1978, holder of a Dutch drivers license with number 4733231501, issued in Almere on the 25th day of May 2009; and
- **Jurjen Frankena**, born in IJlst on the 31st day of October 1955, holder of a Dutch drivers licence with numer 4516624001, issued in Wymbritseradiel on the 12th day of December 2006.

The aforementioned legalisation of a signature only relates to the signature and does not relate to any capacity in which the aforementioned might sign. I, mr. Antonius Lodewijk Maria Schulte, civil-law notary, practising in Amsterdam, have not given any information or advice about the content of the signed documentation.

Signed in Amsterdam on 6th day of April 2011

mr. A.L.M. Schulte NOTARIS te AMSTERDAM

mr. A.L.M. Schulte
civil-law notary in Amsterdam

BOEKEL DE NERÉE

APOSTILLE
Convention de La Haye du 5 octobre 1961

1. Country: THE NETHERLANDS
   This public document
2. Has been signed by: mr. A.L.M. Schulte
3. Acting in the capacity of: civil law notary in Amsterdam
4. Bears the seal/stamp of:
   mr. A.L.M. Schulte
   Certified
5. At Amsterdam
6. On 6 april 2011
7. By the clerk of the Court of Amsterdam
8. No: 12749
9. Seal/Stamp:
10. Signature
    dhr. J. Hoogeveen



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SPW0912 CO

P A T E N T S

CESION

El (los) suscrito (s)

Axel STOIT, Wouter I. IWEMA BAKKER, Hein K.A.C. COOLEN, Harmen MONS, Eric RONKEN, Elizabeth VAN DER KAM and Jurjen FRANKENA

en consideración al pago de la suma de (.....), que he(mos) recibido, por el presente documento cedo (cedemos) a

ABBOTT HEALTHCARE PRODUCTS B.V

una compañía constituida de conformidad con las leyes de HOLANDA

con oficinas en C.J van Houtenlaan 36, 1381 CP Weesp, HOLANDA
Todos los derechos y titulo sobre la invencion titulada

DERIVADOS DE (TIO)MORFOLINA COMO MODULADORES DE S1P

EL CESIONARIO firma también el presente y declara que acepta dicha cesión

Dado y firmado hoy 11 de Febrero de 2012

en Weesp, Holanda

ASSIGNMENT

The undersigned

Axel STOIT, Wouter I. IWEMA BAKKER, Hein K.A.C. COOLEN, Harmen MONS, Eric RONKEN, Elizabeth VAN DER KAM and Jurjen FRANKENA

in consideration of the sum of 1 EUR (one Euro), the receipt of which is hereby acknowledged, by these presents do sell, assign and transfer unto

ABBOTT HEALTHCARE PRODUCTS B.V.

a corporation organized under the laws of The Netherlands

having a place of business at

C.J. van Houtenlaan 36, 1381 CP Weesp, The Netherlands

all rights and title to the invention related to

"(THIO)MORPHOLINE DERIVATIVES AS S1P MODULATORS"

THE ASSIGNEE signs these presents and declares that accepts the aforesaid assignment

Given an signed this February 11, 2011

in Weesp, The Netherlands

Inventors

Axel STOIT **Wouter I. IWEMA BAKKER** **Hein K.A.C. COOLEN** **Harmen MONS**

Eric RONKEN **Elizabeth VAN DER KAM** **Jurjen FRANKENA**

P A T E N T S

CERTIFICADO NOTARIAL INVENTORE(S)

Yo, Notario Público, CERTIFICO que el

de

Compareció (eron) ante mi

Axel STOIT, Wouter I. IWEMA BAKKER, Hein K.A.C. COOLEN, Harmen MONS, Eric RONKEN, Elizabeth VAN DER KAM and Jurjen FRANKENA

a quien(es) conozco y de quien (es) me consta que tiene (n) capacidad legal y reconoció(eron) como suya (s) la (s) firma (s) que aparece (n) en el documento anterior, cuyo contenido ratificó(aron)

Doy fé,

Firmado en

NOTARIO PUBLICO

NOTARIAL CERTIFICATE INVENTOR(S)

I, a Notary Public, CERTIFY that on

before me personally appeared

Axel STOIT, Wouter I. IWEMA BAKKER, Hein K.A.C. COOLEN, Harmen MONS, Eric RONKEN, Elizabeth VAN DER KAM and Jurjen FRANKENA

to me known and known to me to be of legal capacity and acknowledge his (their) signature (s) appearing on the foregoing instrument and ratified the same.

I attest,

Signed in

NOTARIO PUBLICO

TRADUCCION OFICIAL No. 053-12, DE UN DOCUMENTO ESCRITO EN INGLES, SELLADO CON EL SELLO DEL SUSCRITO TRADUCTOR OFICIAL, HOY MARZO 16 DEL 2012, EN LA CIUDAD DE BOGOTÁ D.C., REPUBLICA DE COLOMBIA.

Documento de cesion escrito en ingles y español

BOEKEL DE NEREE

Referencia numero: 20110008.01/S/S

Enviado para legislación por mi, Antonius Lodewijk Maria Schulte, , notario de ley civil en Amsterdam, la firma de

- Wouter Iwema Iwema Bakker, nacido en Amsterdam en Agosto 18 de 1965, titular del pasaporte Holandes con numero NTB1L9PC9, expedido en Weesp en Septiembre 8 de 2006.
- Axel P Stoit, nacido en Amsterdam en Abril 7 de 1957, titular de la licencia de conducción con numero 4053910105, expedido en Beemster en April 2 de 2007.
- Harmen Mons, nacido en harderwijk en Diciembre 19 de 1961, titular del pasaporte Holandes con numero NXRDFLDR6, expedido en Almere en octubre 12 de 2009
- Hein Karel A.C. Coolen, nacido en Roermond en Enero 10 de 1964, titular del pasaporte identificación con numero IUKLD98C3, expedido en Utrecht en Julio 11 de 2007

Sergio Eleuterio Lafaurie Mendoza
Traductor e Interprete Oficial
Resol. No. 2839 Minjusticia 1[illegible]

- Eric Ronken, nacido en Arnhem en mayo 20 de 1963, titular de la licencia de conducción holandesa con numero 4531979103, expedido en Weesp en Octubre 3 de 2007.
- Elizabeth L van der Kam, nacida en Beek en Fenrero 25 de 1978, titular de la licencia de conducción holandesa con numero 4733231501, expedido en Almere en mayo 25 de 2009 y
- Jurjen Frankena, nacido en Ijlst en Octubre 31 de 1955, titular de la licencia de conducción holandesa con numero 4516624001, expedido en Wymbritseradiel en SDiciembre 12 de 2006

La legislación antes mencionada de una firma solo se refiere a la firma y no se refiere a cualquier condición en la que los antes mencionados puedan firmar, Yo Antonius Lodewijk Maria Schukte. Notario de ley civil, practicante en Amsterdam, no dare ninguna información o aviso sobre el contenido del documento firmado

Firmado en Amsterdam este dia 6 de Abril de 2011.

A.L.M SCHULTE

Notario de ley civil en Emsterdam

Adjunto al documento se encuentra lo siguiente

APOSTILLE

(CONVENCION DE LA HAYE DE 5 OCTOBRE 1961)

1. PAIS: PAISES BAJOS

ESTE DOCUMENTO PUBLICO

Sergio Eleuterio Laborre Mendoza
Traductor e Interprete Oficial
Resol. No. 283 Minjusticia

2. HA SIDO FIRMADO POR: SR. A.L.M SCHULTE
3. ACTUANDO EN CAPACIDAD DE: NOTARIO DE LEY CIVIL EN AMSTERDAM
4. LLEVA EL SELLO/ESTAMPILLA SR. A.L.M SCHULTE

CERTIFICADO

5. EN: AMSTERDAM
6. EL DIA: 6 DE ABRIL DEL 2011
7. POR: EL REGISTRADOR DE LA CORTE EN ÁMSTERDAM
8. No. 12749

9. SELLO/ESTAMPILLA

10. FIRMA

J HOOGEVEEN

Sergio Eleuterio Latorre Mendoza
Traductor e Intérprete Oficial
Resol. No. 2839 Minjusticia 19[illegible]

000013

REPÚBLICA DE COLOMBIA
MINISTERIO DE RELACIONES EXTERIORES
LEGALIZACION

País: ***REPUBLICA DE COLOMBIA***
(Country: - Pays:)

El presente documento público
(This public document - Le présent acte public)

Ha sido firmado por: ***LATORRE MENDOZA SERGIO ELEUTERIO***
(Has been signed by: - A été signé par:)

Actuando en calidad de: ***TRADUCTOR OFICIAL***
(Acting in the capacity of: - Agissant en qualité de:)

Lleva el sello/estampilla de: ***TRADUCTOR E INTERPRETE OFICIAL***
(Bears the seal/stamp of: - Est revétu du sceau de / timbre de:)

Certificado
(Certified - Attesté)

En: ***BOGOTA D.C***
(At: - Á:)

El: ***3/22/2012 9:25:26 AM***
(On: - Le:)

Por: ***APOSTILLA Y LEGALIZACIÓN***
(By: The Ministry of Foreign Affairs of Colombia - Par: Ministère des Affaires Étrangères de la Colombie)

No: ***LMDW92526840***
(Under Number: - Sous le numéro:)

Nombre del Titular: ***12749***
(Name of the holder of document: - Nom du titulaire:)

Tipo de documento: ***TRADUCCION APOSTILLA***
(Type of document: - Type du document:)

Número de hojas: ***3***
(Number of pages: - Nombre de pages:)

01304100125363700485

Firmado Digitalmente por: (Digitally Signed by:)
Ministerio de Relaciones Exteriores de Colombia
AMPARO DE LA CRUZ TAMAYO RODRIGUEZ
Reason: DOCUMENT AUTHENTICITY
BOGOTA - COLOMBIA

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 March 2011 (03.03.2011)

PCT

(10) International Publication Number
WO 2011/023795 A1

(51) International Patent Classification:
C07D 265/30 (2006.01) *A61P 25/16* (2006.01)
C07D 265/32 (2006.01) *A61P 25/18* (2006.01)
C07D 413/12 (2006.01) *A61P 25/24* (2006.01)
C07D 419/12 (2006.01) *A61P 25/28* (2006.01)
C07D 471/04 (2006.01) *C07D 279/12* (2006.01)
A61K 31/5377 (2006.01) *C07D 417/12* (2006.01)
A61P 25/04 (2006.01) *C07D 487/04* (2006.01)
A61P 25/06 (2006.01)

(21) International Application Number:
PCT/EP2010/062552

(22) International Filing Date:
27 August 2010 (27.08.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/238,518 31 August 2009 (31.08.2009) US
09169075.0 31 August 2009 (31.08.2009) EP

(71) Applicant *(for all designated States except US)*: **ABBOTT HEALTHCARE PRODUCTS B.V.** [NL/NL]; C.J. van Houtenlaan 36, NL-1381 CP Weesp (NL).

(72) Inventors; and

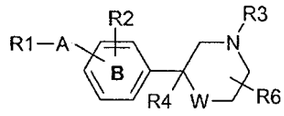
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[Continued on next page]

(54) Title: (THIO)MORPHOLINE DERIVATIVES AS S1P MODULATORS



(I)

(57) Abstract: The present invention relates to (thio)morpholine derivatives of the formula (I), wherein R1 is selected from cyano, (2-4C)alkynyl, (1-4C)alkyl, (3-6C)cycloalkyl, (4-6C)cycloalkenyl, (6-8C)bicycloalkyl, (8-10C)bicyclic group, each optionally substituted with (1-4C)alkyl, phenyl, biphenyl, naphthyl, each optionally substituted with one or more substituents independently selected from halogen, (1-4C)alkyloptionally substituted with one or more fluoro atoms, (2-4C)alkynyl, (1-4C)alkoxy optionally substituted with one or more fluoro atoms,amino, di(1-4C)alkylamino, -SO_2-(1-4C)alkyl, -CO-(1-4C)alkyl, -CO-O-(1-4C)alkyl, -NH-CO-(1-4C)alkyl and (3-6C)cycloalkyl, phenyl substituted with phenoxy, benzyl, benzyloxy, phenylethyl or monocyclic heterocycle, each optionally substituted with (1-4C)alkyl, monocyclic heterocycle optionally substituted with halogen, (1-4C)alkyl or with phenyl optionally substituted with (1-4C)alkyl, and bicyclic heterocycle optionally substituted with (1-4C)alkyl; A is selected from -CO-O-, -O-CO-, -NH-CO-, -CO-NH, -C=C-, -CCH_3-O- and the linking group –Y-$(CH_2)_n$-X- wherein Y is attached to R1 and selected from a bond, -O-, -S-, -SO-, -SO_2-, -CH_2-O-, -CO-, -O-CO-, -CO-O-, -CO-NH-, -NH-CO-, -C=C-and -C≡C-; n is an integer from 1 to 10; and X is attached to the phenylene / pyridyl group and selected from a bond, -O-, -S-, -SO-, -SO_2 -, -NH, -CO-, -C=C-and -C≡C-; ring structure B optionally contains one nitrogen atom; R2 is H, (1-4C)alkyl optionally substituted with one or more fluoro atoms, (1-4C)alkoxy optionally substituted with one or more fluoro atoms, or halogen; and R3 is (1-4C)alkylene-R5 wherein the alkylene group may be substituted with $(CH_2)_2$ to form a cyclopropyl moiety or one or two halogen atoms, or R3 is is (3-6C)cycloalkylene-R5 or -CO-CH_2-R5, wherein R5 is -OH, -PO_3H_2, -OPO_3H_2, -COOH, -COO(1-4C)alkyl or tetrazol-5-yl; R4 is H or (1-4C)alkyl; R6 is one or more substituents independently selected from H, (1-4C)alkyl or oxo; W is -O-, -S-, -SO- or -SO_2-; or a pharmaceutically acceptable salt, a solvate or hydrate thereof; with the proviso that the derivative of formula (I) is not 2-(4-ethylphenyl)-4-morpholinoethanol or 4-[4-(2-hydroxyethyl)-2-morpholinyl]benzeneacetonitrile or a pharmaceutically acceptable salt, a solvate or hydrate thereof. The compounds of the invention have affinity to S1P receptors and may be used in the treatment, alleviation or prevention of S1P receptor mediated diseases and conditions.

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(THIO)MORPHOLINE DERIVATIVES AS S1P MODULATORS

Field of the invention

This invention relates to new (thio)morpholine derivatives having affinity to S1P receptors, a pharmaceutical composition containing said compounds, as well as the use of said compounds for the preparation of a medicament for treating, alleviating or preventing diseases and conditions in which any S1P receptor is involved or in which modulation of the endogenous S1P signaling system via any S1P receptor is involved.

Background of the invention

Sphingosine-1-phosphate (S1P) is a bioactive sphingolipid that mediates a wide variety of cellular responses, such as proliferation, cytoskeletal organization and migration, adherence- and tight junction assembly, and morphogenesis. S1P can bind with members of the endothelial cell differentiation gene family (EDG receptors) of plasma membrane-localized G protein-coupled receptors. To date, five members of this family have been identified as S1P receptors in different cell types, S1P1 (EDG-1), S1P2 (EDG-5), S1P3 (EDG-3), S1P4 (EDG-6) and S1P5 (EDG-8). S1P can produce cytoskeletal re-arrangements in many cell types to regulate immune cell trafficking, vascular homeostasis and cell communication in the central nervous system (CNS) and in peripheral organ systems.

It is known that S1P is secreted by vascular endothelium and is present in blood at concentrations of 200-900 nanomolar and is bound by albumin and other plasma proteins. This provides both a stable reservoir in extracellular fluids and efficient delivery to high-affinity cell-surface receptors. S1P binds with low nanomolar affinity to the five receptors S1P1-5. In addition, platelets also contain S1P and may be locally released to cause e.g. vasoconstriction. The receptor subtypes S1P1, S1P2 and S1P3 are widely expressed and represent dominant receptors in the cardiovascular system. Further, S1P1 is also a receptor on lymphocytes. S1P4 receptors are almost exclusively in the haematopoietic and lymphoid system. S1P5 is primarily (though not exclusively) expressed in central nervous system. The expression of S1P5 appears to be restricted to oligodendrocytes in mice, the myelinating cells of the brain, while in rat and man expression at the level of astrocytes and endothelial cells was found but not on oligodendrocytes.

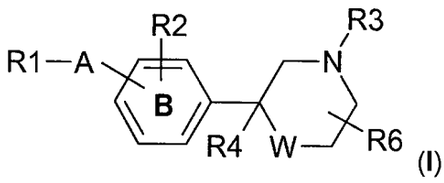
S1P receptor modulators are compounds which signal as (ant)agonists at one or more S1P receptors. The present invention relates to modulators of the S1P5 receptor, in particular agonists, and preferably to agonists with selectivity over S1P1

and/or S1P3 receptors, in view of unwanted cardiovascular and/or immunomodulatory effects. It has now been found that S1P5 agonists can be used in the treatment of cognitive disorders, in particular age-related cognitive decline.

Although research is ongoing to develop therapeutics that can be used to treat age related cognitive decline and dementia, this has not yet resulted in many successful candidates. Therefore, there is a need for new therapeutics with the desired properties.

Description of the invention

It has now been found that (thio)morpholine derivatives of the formula (**I**)



(**I**)

wherein

R1 is selected from

cyano,

(2-4C)alkynyl,

(1-4C)alkyl,

(3-6C)cycloalkyl,

(4-6C)cycloalkenyl,

(6-8C)bicycloalkyl, (8-10C)bicyclic group, each optionally substituted with (1-4C)alkyl,

phenyl, biphenyl, naphthyl, each optionally substituted with one or more substituents independently selected from halogen, (1-4C)alkyl optionally substituted with one or more fluoro atoms, (2-4C)alkynyl, (1-4C)alkoxy optionally substituted with one or more fluoro atoms, amino, di(1-4C)alkylamino, -SO_2-(1-4C)alkyl, -CO-(1-4C)alkyl, -CO-O-(1-4C)alkyl, -NH-CO-(1-4C)alkyl and (3-6C)cycloalkyl,

phenyl substituted with phenoxy, benzyl, benzyloxy, phenylethyl or monocyclic heterocycle, each optionally substituted with (1-4C)alkyl,

monocyclic heterocycle optionally substituted with halogen, (1-4C)alkyl or with phenyl optionally substituted with (1-4C)alkyl,

and

bicyclic heterocycle optionally substituted with (1-4C)alkyl;

A is selected from -CO-O-, -O-CO-, -NH-CO-, -CO-NH, -C=C-, -CCH_3-O- and the linking group –Y-$(CH_2)_n$-X- wherein

Y is attached to R1 and selected from a bond, -O-, -S-, -SO-, -SO_2-, -CH_2-O-, -CO-, -O-CO-, -CO-O-, -CO-NH-, -NH-CO-, -C=C- and -C≡C- ;

n is an integer from 1 to 10; and

X is attached to the phenylene / pyridyl group and selected from a bond, -O-, -S-, -SO-, -SO_2-, -NH, -CO-, -C=C- and -C≡C-;

ring structure **B** optionally contains one nitrogen atom;

R2 is H, (1-4C)alkyl optionally substituted with one or more fluoro atoms, (1-4C)alkoxy optionally substituted with one or more fluoro atoms, or halogen; and

R3 is (1-4C)alkylene-R5 wherein the alkylene group may be substituted with $(CH_2)_2$ to form a cyclopropyl moiety or one or two halogen atoms, or R3 is is (3-6C)cycloalkylene-R5 or -CO-CH_2-R5, wherein R5 is -OH, -PO_3H_2, -OPO_3H_2, -COOH, -COO(1-4C)alkyl or tetrazol-5-yl;

R4 is H or (1-4C)alkyl;

R6 is one or more substituents independently selected from H, (1-4C)alkyl or oxo;

W is -O-, -S-, -SO- or -SO_2-;

or a pharmaceutically acceptable salt, a solvate or hydrate thereof; with the proviso that the derivative of formula (**I**) is not

2-(4-ethylphenyl)-4-morpholinoethanol or

4-[4-(2-hydroxyethyl)-2-morpholinyl]benzeneacetonitrile.

display affinity for S1P receptors. In particular, compounds of the invention show selective affinity for the S1P5 receptor over the S1P1 and/or S1P3 receptor(s).

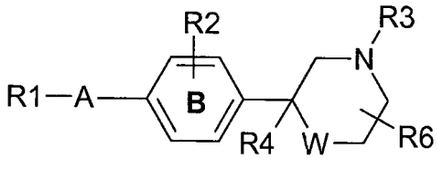
The use of the compound 2-(4-ethylphenyl)-4-morpholinoethanol as a reagent in the production of 2-(2-arylmorpholino)ethyl esters of naproxen is described in Database CA [Online] Chemical Abstracts Service, Columbus, OHIO, US; 2008, Hu, Ai-Xi et al, XP002558960 retrieved from STN database accession no. 2008:1527686; & Huaxue Xuebao, 66(22), 2553-2557 Coden: HHHPA4; ISSN: 0567-7351, 2008. No pharmacological activity of the compound is reported.

Similarly, in Farmatsiya (Sofia), Vol.45, no.1, 1998, pages 3-11, XP009126794 Yordanova, K. et al. describe the use of 4-[4-(2-hydroxyethyl)-2-morpholinyl]-benzeneacetonitrile as a reagent in the production of antidepressant phenylmorpholine derivatives. No pharmacological activity of the compound is reported.

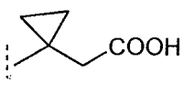
The compounds of the invention are modulators of the S1P receptor, in particular of the S1P5 receptor. More specifically, the compounds of the invention are S1P5 receptor agonists. The compounds of the invention are useful for treating, alleviating and preventing diseases and conditions in which (any) S1P receptor(s) - in particular S1P5 – is (are) involved or in which modulation of the endogenous S1P signaling system via any S1P receptor is involved. In particular, the compounds of the present invention may be used to treat, alleviate or prevent CNS (central nervous system) disorders, such as neurodegenerative disorders, in particular -but not limited to- cognitive disorders (in particular age-related cognitive decline) and related conditions, Alzheimer's disease, (vascular) dementia, Nieman's Pick disease, and cognitive deficits in schizophrenia, obsessive-compulsive behavior, major depression, autism, multiple sclerosis, pain, etc.. Preferably, the compounds of the present invention may be used to treat, alleviate or prevent cognitive disorders (in particular age-related cognitive decline) and related conditions.

In embodiments of the invention, the ring structure **B** is phenylene.

In an embodiment of the invention, the compounds have the structure (**II**)



(**II**).

In another embodiment of the invention, the compounds have formula (**I**) wherein R3 is selected from -$(CH_2)_2$-OH, -CH_2-COOH, -$(CH_2)_2$-COOH, -$(CH_2)_3$-COOH, -CH_2-$CHCH_3$-COOH, -CH_2-$C(CH_3)_2$-COOH, -$CHCH_3$-CH_2-COOH, 

, -CH_2-CF_2-COOH, -CO-CH_2-COOH, 1,3-cyclobutylene-COOH, -$(CH_2)_2$-PO_3H_2, -$(CH_2)_3$-PO_3H_2, -$(CH_2)_2$-OPO_3H_2, -$(CH_2)_3$-OPO_3H_2, -CH_2-tetrazol-5-yl, -$(CH_2)_2$-tetrazol-5-yl and -$(CH_2)_3$-tetrazol-5-yl. Preferred R3 groups are selected from -CH_2-COOH, -$(CH_2)_2$-COOH, -$(CH_2)_3$-COOH, -CH_2-$CHCH_3$-COOH, -CH_2-$C(CH_3)_2$-COOH, -$CHCH_3$-CH_2-COOH, -$(CH_2)_2$-PO_3H_2, -$(CH_2)_3$-PO_3H_2 and -$(CH_2)_2$-OPO_3H_2 and in particular -$(CH_2)_2$-COOH and -$(CH_2)_2$-PO_3H_2. Most preferred is -$(CH_2)_2$-COOH.

In another embodiment, W is -O- or -S-. In preferred embodiments, W is -O-.

In a further embodiment of the invention, R4 is H or methyl and in particular, R4 is H.

In another embodiment, the compounds have formula (**I**) wherein R2 is H, methyl, methoxy, trifluoromethyl, difluoromethyl, trifluoromethoxy, difluoromethoxy, Cl or F. In further preferred embodiments, R2 is H or trifluoromethyl.

Further, in an embodiment of the invention, A is selected from -CO-O-, -NH-CO-, -CO-NH, -C=C-, $-CCH_3-O-$ and the linking group $-Y-(CH_2)_n-X-$ wherein Y is attached to R1 and selected from a bond, -O-, $-SO_2-$, $-CH_2-O-$, -CO-, -CO-O-, -NH-CO-, -C=C- and -C≡C-; n is an integer from 1 to 7; and X is attached to the phenylene / pyridyl group and selected from a bond, -O-, -S- and -NH. Preferably, A selected from -CO-NH, -C=C-, $-CCH_3-O-$ and the linking groups $-(CH_2)_n-X-$ and $-O-(CH_2)_n-X-$. In preferred embodiments A is CH_2-O-.

In further embodiments of the invention, R1 is selected from cyano, ethynyl, (1-4C)alkyl, cyclopentyl, cyclohexyl, cyclohexenyl, 6,6-dimethyl-bicyclo[3.1.1]hept-2-yl, indanyl optionally substituted with methyl, biphenyl, naphthyl, phenyl optionally substituted with one, two or three substituents independently selected from chloro, fluoro, bromo, (1-4C)alkyl, (2-4C)alkynyl, (1-4C)alkoxy, dimethylamino, trifluoromethyl, trifluoromethoxy and (3-6C)cycloalkyl, and R1 is further selected from phenyl monosubstituted with phenoxy, benzyl, benzyloxy, phenylethyl, pyrazolyl or triazolyl, and R1 is further selected from pyrazolyl, thiazolyl, oxadiazolyl, thienyl, tetrahydrofuranyl, pyridinyl, tetrahydropyranyl, each optionally substituted with chloro, (1-4C)alkyl or phenyl substituted with (1-4C)alkyl, and R1 is further selected from indolyl, imidazopyridinyl, dihydrobenzofuranyl and benzdioxanyl each optionally substituted with (1-4C)alkyl. In preferred embodiments, R1 is selected from ethynyl, (1-4C)alkyl, cyclopentyl, cyclohexyl, cyclohexenyl, biphenyl, naphthyl, phenyl optionally substituted with one, two or three substituents independently selected from chloro, fluoro, bromo, (1-4C)alkyl, (1-4C)alkoxy, dimethylamino, trifluoromethyl and trifluoromethoxy, and further selected from phenyl monosubstituted with phenoxy, benzyl, benzyloxy, phenylethyl, pyrazolyl or triazolyl, and further selected from thiazolyl, thienyl, tetrahydrofuranyl, pyridinyl, tetrahydropyranyl, each optionally substituted with chloro or (1-4C)alkyl, and benzdioxanyl. In particular, R1 is selected from (1-4C)alkyl, cyclopentyl, cyclohexyl, pyridinyl and phenyl, wherein the latter two groups are optionally substituted with one or two substituents independently selected from chloro, fluoro, bromo, (1-4C)alkyl, (1-4C)alkoxy and trifluoromethyl. In preferred embodiments, R1 is (1-4C)alkyl or dichlorophenyl.

In a highly preferred embodiment of the invention, R1 is 2,6-dichlorophenyl; A is the linking group $-Y-(CH_2)_n-X-$, wherein Y is attached to R1 and is a bond, n is 1 and X is attached to the phenylene group and is -O-; R2 is H; R3 is $-(CH_2)_2-COOH$; and R4 is H.

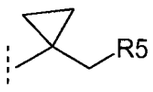
In further preferred embodiments of the invention, R1 is (1-4C)alkyl; A is the linking group $-Y-(CH_2)_n-X-$, wherein Y is attached to R1 and is a bond, n is an integer

selected from 1 to 6 and X is attached to the phenylene / pyridyl group and is -O- or a bond; R2 is H; R3 is selected from $-(CH_2)_2-COOH$, $-(CH_2)_3-COOH$, $-CH_2-CHCH_3-COOH$, $-CH_2-C(CH_3)_2-COOH$, $-CHCH_3-CH_2-COOH$, $-(CH_2)_2-PO_3H_2$, $-(CH_2)_3-PO_3H_2$ and $-(CH_2)_2-OPO_3H_2$; and R4 is H. Preferably, R1 and $-(CH_2)_n-$ together are a linear octyl group. Further preferred is R3 is $-(CH_2)_2-PO_3H_2$. In a further preferred embodiment, X is -O-.

The term halogen refers to fluoro, chloro, bromo, or iodo. Preferred halogens are fluoro and chloro, and in particular chloro.

The term (1-4C)alkyl means a branched or unbranched alkyl group having 1-4 carbon atoms, for example methyl, ethyl, propyl, isopropyl and butyl. A preferred alkyl group is methyl.

The term (1-4C)alkoxy means an alkoxy group having 1-4 carbon atoms, wherein the alkyl moiety is as defined above. A preferred alkoxy group is methoxy.

The term (1-4C)alkylene means a branched or unbranched alkylene group having 1-4 carbon atoms, for example methylene, $-CCH_3CH_2-$, and the like. In the definition of R3 which is (1-4C)alkylene-R5, one or more carbon atoms in the alkylene group may (amongst others) independently be substituted with $(CH_2)_2$ to form a cyclopropyl moiety, meaning to form a R3 group such as 

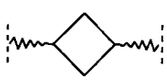
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The term (2-4C)alkynyl means a branched or unbranched alkynyl group having 2-4 carbon atoms, wherein the triple bond may be present at different positions in the group, for example ethynyl, propargyl, 1-butynyl, 2-butynyl, etc.

The term (3-6C)cycloalkyl means a cyclic alkyl group having 3-6 carbon atoms, thus cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. Preferred are cyclopentyl and cyclohexyl.

The term (4-6C)cycloalkenyl means a cyclic alkenyl group having 4-6 carbon atoms and comprising one or two double bonds, for example cyclohexenyl.

The term (3-6C)cycloalkylene means a cyclic alkyl group having two attachment points. Preferred is 1,3-cyclobutylene, having the structure


.

The term (6-8C)bicycloalkyl means a fused ring system of two cycloalkyl groups having together 6-8 carbon atoms, for example the group bicyclo[3.1.1]hept-2-yl.

The term (8-10C)bicyclic group means a fused ring system of an aromatic and a non-

aromatic ring structure having together 8-10 carbon atoms, for example the indane group.

The term monocyclic heterocycle encompasses monocyclic heteroaryl groups and non-aromatic heteromonocyclic groups, for example furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, oxadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, tetrahydrofuranyl, tetrahydropyranyl, dioxanyl, morpholinyl, and the like.

The term bicyclic heterocycle encompasses bicyclic heteroaryl groups and non-aromatic heterobicyclic groups, for example indolyl, indazolyl, isoindolyl, indolizinyl, benzimidazolyl, imidazothiazolyl, imidazopyridinyl, benzfuranyl, dihydrobenzofuranyl, benzdioxanyl, quinolinyl, isoquinolinyl, quinolizinyl, tetrahydroisoquinolinyl, and the like.

With reference to substituents, the term "independently" means that the substituents may be the same or different from each other in the same molecule.

The compounds of the invention may suitably be prepared by methods available in the art, and as illustrated in the experimental section of this description.

The compounds of the present invention may contain one or more asymmetric centers and can thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. Additional asymmetric centers may be present depending upon the nature of the various substituents on the molecule. Each such asymmetric center will independently produce two optical isomers and it is intended that all of the possible optical isomers and diastereomers in mixtures and as pure or partially purified compounds are included within the ambit of this invention. The present invention is meant to comprehend all such isomeric forms of these compounds. The independent syntheses of these diastereomers or their chromatographic separations may be achieved as known in the art by appropriate modification of the methodology disclosed herein. Their absolute stereochemistry may be determined by the x-ray crystallography of crystalline products or crystalline intermediates which are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration. If desired, racemic mixtures of the compounds may be separated so that the individual enantiomers are isolated. The separation can be carried out by methods well known in the art, such as the coupling of a racemic mixture of compounds to an enantiomerically pure compound to form a diastereomeric mixture, followed by

separation of the individual diastereomers by standard methods, such as fractional crystallization or chromatography.

Compounds may exist as polymorphs and as such are intended to be included in the present invention. In addition, compounds may form solvates with water (i.e., hydrates) or common organic solvents, and such solvates are also intended to be encompassed within the scope of this invention.

Isotopically-labeled compound of formula (**I**) or pharmaceutically acceptable salts thereof, including compounds of formula (**I**) isotopically-labeled to be detectable by PET or SPECT, also fall within the scope of the invention. The same applies to compounds of formula (I) labeled with [^{13}C]-, [^{14}C]-, [^{3}H]-, [^{18}F]-, [^{125}I]- or other isotopically enriched atoms, suitable for receptor binding or metabolism studies.

The term "pharmaceutically acceptable salt" refers to those salts that are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well-known in the art. They can be prepared *in situ* when isolating and purifying the compounds of the invention, or separately by reacting them with pharmaceutically acceptable non-toxic bases or acids, including inorganic or organic bases and inorganic or organic acids.

The compounds of the invention may be administered enterally or parenterally. The exact dose and regimen of these compounds and compositions thereof will be dependent on the biological activity of the compound *per se*, the age, weight and sex of the patient, the needs of the individual subject to whom the medicament is administered, the degree of affliction or need and the judgment of the medical practitioner. In general, parenteral administration requires lower dosages than other methods of administration which are more dependent upon adsorption. However, the dosages for humans are preferably 0.001 – 10 mg per kg body weight. In general, enteral and parenteral dosages will be in the range of 0.1 to 1,000 mg per day of total active ingredients.

Mixed with pharmaceutically suitable auxiliaries, *e.g.* as described in the standard reference "Remington, The Science and Practice of Pharmacy" (21st edition, Lippincott Williams & Wilkins, 2005, see especially Part 5: Pharmaceutical Manufacturing) the compounds may be compressed into solid dosage units, such as pills or tablets, or be processed into capsules or suppositories. By means of

pharmaceutically suitable liquids the compounds can also be applied in the form of a solution, suspension or emulsion.

For making dosage units, *e.g.* tablets, the use of conventional additives such as fillers, colorants, polymeric binders and the like, is contemplated. In general, any pharmaceutically suitable additive which does not interfere with the function of the active compounds can be used.

Suitable carriers with which the compounds of the invention can be administered include for instance lactose, starch, cellulose derivatives and the like, or mixtures thereof, used in suitable amounts. Compositions for intravenous administration may for example be solutions of the compounds of the invention in sterile isotonic aqueous buffer. Where necessary, the intravenous compositions may include for instance solubilizing agents, stabilizing agents and/or a local anesthetic to ease the pain at the site of the injection.

Pharmaceutical compositions of the invention may be formulated for any route of administration and comprise at least one compound of the present invention and pharmaceutically acceptable salts thereof, with any pharmaceutically suitable ingredient, excipient, carrier, adjuvant or vehicle.

By "pharmaceutically suitable" it is meant that the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

In an embodiment of the invention, a pharmaceutical pack or kit is provided comprising one or more containers filled with one or more pharmaceutical compositions of the invention. Associated with such container(s) can be various written materials such as instructions for use, or a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals products, which notice reflects approval by the agency of manufacture, use, or sale for human or veterinary administration.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention pertains. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described in this document.

LEGEND TO THE FIGURE

Figure 1 Percentage of alternation of young and old C57BL/6J male mice in the T-maze with either vehicle (control groups) or compound **34b** (10mg/kg; p.o.)

The following examples are intended to further illustrate the invention in more detail.

EXAMPLES

§1. MATERIALS AND METHODS

Nuclear magnetic resonance spectra (^{1}H NMR) were determined in the indicated solvent using a Bruker Avance-I 400 with a 9.4T magnet (^{1}H: 400 MHz, ^{13}C: 100 MHz), equipped with a BBI inversie broadband probehead with Z-gradient and ATM, or a Bruker Avance-DRX 600 with a 14.1T magnet, equipped with a TXI inverse triple resonance cryoprobehead with Z-gradient and ATM, at 300 K, unless indicated otherwise. The spectra were determined in deuterated chloroform ($CDCl_3$) with 99.8 atom% D; or in dimethylsulfoxide-d_6 (DMSO- d_6) containing 0.03 v/v% tetramethylsilane; both obtained from Aldrich Chemical shifts (δ) are given in ppm downfield from tetramethylsilane. Coupling constants *J* are given in Hz. Peakshapes in the NMR spectra are indicated with the symbols 'q' (quartet), 'dq' (double quartet), 't' (triplet), 'dt' (double triplet), 'd' (doublet), 'dd' (double doublet), 's' (singlet), 'bs' (broad singlet) and 'm' (multiplet). NH and OH signals were identified after mixing the sample with a drop of D_2O.

Melting points were recorded on a Büchi B-545 melting point apparatus.

All reactions involving **moisture sensitive** compounds or conditions were carried out under an anhydrous nitrogen atmosphere.

Reactions were monitored by using **thin-layer chromatography** (TLC) on silica coated plastic sheets (Merck precoated silica gel 60 F254) with the indicated eluent. Spots were visualised by UV light (254 nm) or I_2.

Liquid Chromatography- Mass Spectrometry (LC-MS)

System A: Column: Acquity UPLC BEH C18 1,7 µm, 50 x 2.1 mm with 1.7 µm particles. The column is thermo stated in a column oven at 45°C.

Detection: Diode array between 210 and 260 nm

step	total time(min)	flow (µl/min)	A(%)	B(%)
0	0	800	95	5
1	0.1	800	95	5
2	4.5	800	10	90
3	5	800	10	90
4	5.01	800	95	5

A= 99.9% Water with 0.1% CH_3COOH

B= 99.9% CH_3CN with 0.1% CH_3COOH

System B: Column: Waters Sunfire C18, 30 x 4.6 mm with 2.5 µm particles. The column is thermo stated in a column oven at 23°C.

Detection: UV/VIS meter with the wavelength set to 254 nm + evaporative light scattering detector operating at 70^0 Celsius and 1.7 bar N_2 pressure.

step	total time (min)	flow (ul/min)	A(%)	B(%)
0	0	1800	95	5
1	1.8	1800	0	100
2	2.6	1800	0	100
3	2.8	1800	95	5
4	3.0	1800	95	5

A= 99.9% Water with 0.1% HCOOH

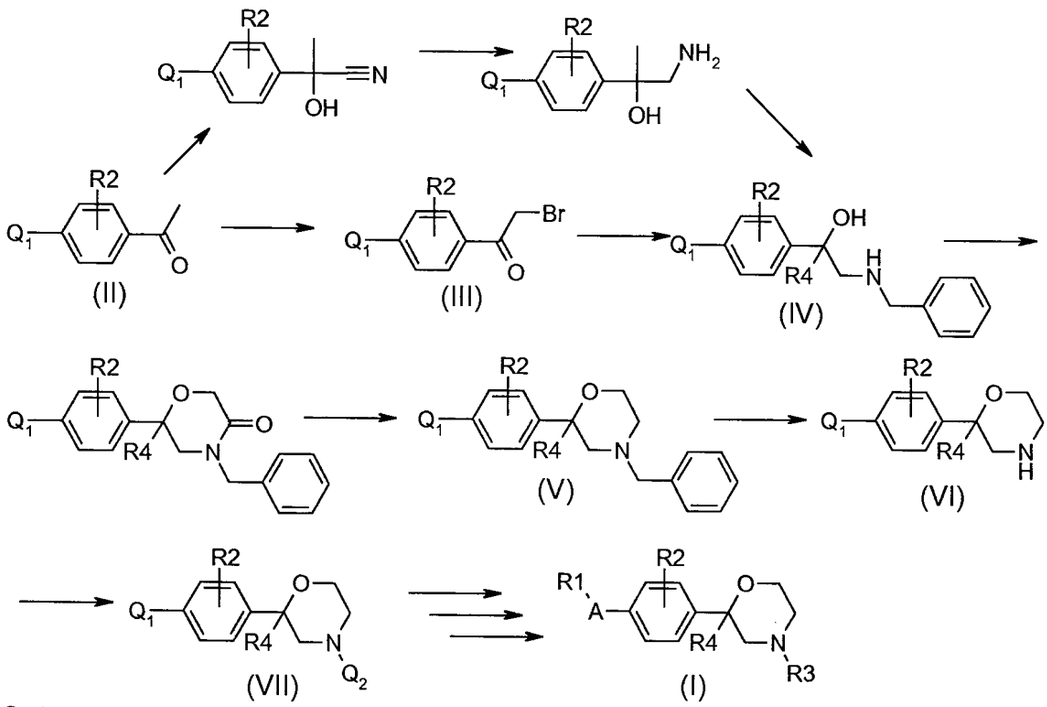
B= 99.9% CH_3CN with 0.1% HCOOH

The reported retention times (R_t), for System B, are for the peak in the Total Ion Current (TIC) chromatogram which showed the mass for [M+H]+ within 0.5 amu accuracy of the calculated exact MW and had an associated peak in the Evaporative Light Scattering (ELS) chromatogram with a relative area% (purity) of >85%.

§2. GENERAL ASPECTS OF SYNTHESES

Suitable syntheses of claimed compounds and intermediates containing 2-aryl-morpholine moieties follow routes .**1Scheme** see ;as described below

Scheme 1



Q_1 is a group equal to R1-A, or a group that can be converted to R1-A. Q_2 is a group equal to R3, or a group that can be converted to R3. For details, see the full details given below.

The synthesis begins with a suitably substituted acetophenone (II). Suitably substituted acetophenones are commercially available or can be obtained from other commercially available acetophenones. For example by *O*-alkylation of (un)substituted 4-hydroxyacetophenones. This *O*-alkylation can be done with a suitable alkylating agent like 1-bromooctane or benzyl bromide, in solvents such as dimethylsulfoxide (DMSO), acetone, or acetonitrile, in the presence of a base like potassium hydroxide or potassium carbonate, at temperatures between 0°C and 60°C. As another example, 1-(4-benzyloxy-3-trifluoromethyl-phenyl)-ethanone was obtained from 4'-fluoro-3'-(trifluoromethyl)acetophenone by reaction with benzylalcohol in the presence of a strong base like potassium tert-butoxide, in a solvent like tetrahydrofuran, at a temperature of around 70°C.

The suitably substituted acetophenone (II) is brominated to afford 2'-bromo-acetophenones (III). Bromination can be done with copper(II) bromide in a suitable solvent like ethyl acetate with heating under reflux; via reaction of the corresponding silyl enol ether, prepared with DIPEA and TMSOTf, at 0°C, with NBS in a solvent like dichloromethane, at room temperature; or with tetra-*N*-butylammonium tribromide, in a solvent like methanol, at room temperature.

Reaction of the 2'-bromoacetophenones (III) with benzyl amine, in a solvent like ethanol and chloroform, at temperatures between 0°C and room temperature, afforded aminoketones (R4 = H) which where directly reduced with a reducing agent like sodium borohydride in a solvent like ethanol and chloroform, at temperatures between 0°C and room temperature, to afford amino alcohols (IV, R4 = H). Alternatively, 2'-bromoacetophenones (III) can be reduced with a suitable reducing agent like $NaBH_4$, in a solvent such as 1,4-dioxane, at room temperature, followed by treatment with a base, such as KOH, in a mixture of water and a suitable solvent, such as Et_2O, to afford 2-aryloxiranes, which on treatment with benzyl amine at a temperature of 80°C, afford amino alcohols (IV, R4 = H). Another method for the synthesis of aminoalcohols (IV, R4 = Me) is by the reaction of a suitably substituted acetophenone with trimethylsilyl cyanide in the presence of a lewis acid, like zinc iodide, at room temperature, in the neat. Followed by reduction of the intermediate cyanohydrin with a reducing agent, like lithium aluminum hydride, in a solvent like tetrahydrofuran, and subsequent imine formation with benzaldehyde in the presence of an acidic catalyst, like p-toluenesulfonic acid, in a solvent such as toluene, and finally reduction of the intermediate imine with sodium borohydride, in a solvent like methanol, at temperatures between -15°C and room temperature.

The amino alcohols (IV) can be reacted with an activated chloroacetic acid or bromoacetic acid in a solvent such as dichloromethane with a base such as triethylamine, and subsequently cyclized in a solvent such as 2-propanol with a base such as potassium hydroxide to afford morpholin-3-ones. Those morpholin-3-ones can then be reduced with a reducing agent such as borane in a solvent such as tetrahydrofuran, at temperatures between 0°C and room temperature, to afford the *N*-benzyl morpholines (V). Some of the *N*-benzyl morpholines (V) can be converted to other *N*-benzyl morpholines (V), see **Scheme 2**. For example *N*-benzyl-2-(4-bromophenyl)-morpholine (V-Br) was used as starting material in the following sequences:

Thus, treatment of V-Br with n-butyl lithium at -75°C, in a solvent like tetrahydrofuran or diethyl ether, followed by quenching with a formamide, like N,N-dimethylformamide or N-formylmorpholine, results in the formation of V-CHO. If the intermediate lithium species is quenched with a suitable isocyanate then the corresponding amides V-CONHG are formed.

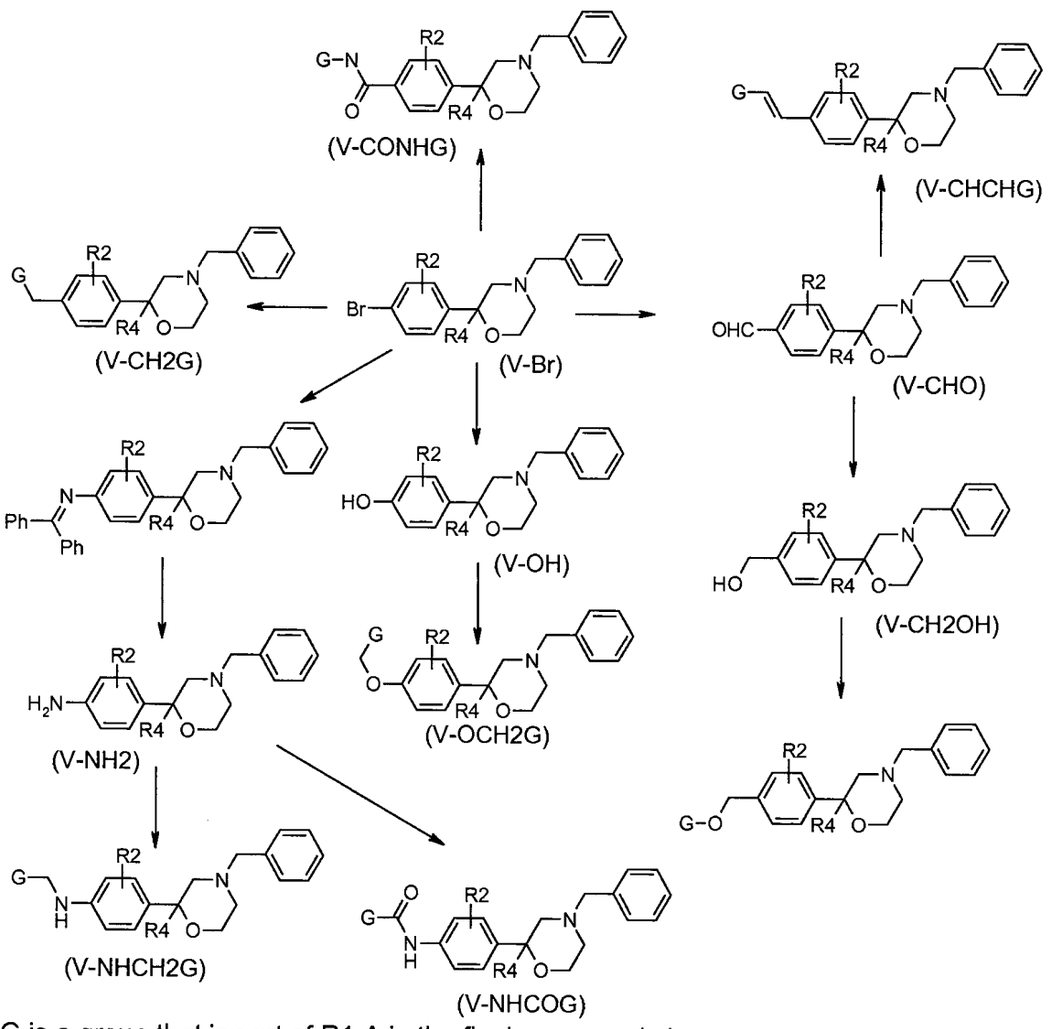
Reduction of V-CHO, with a reducing agent like sodium borohydride, in a solvent like methanol, at temperatures between 0°C and room temperature, afforded the benzylic alcohols V-CH2OH.

Compounds of type V-CH2OH can be coupled under Mitsunobu conditions with phenols, in a solvent such as tetrahydrofuran or dichloromethane, at room temperature.

Compounds of type V-CHO may also be coupled with a suitable phosphonium ylid, in a solvent such as tetrahydrofuran at a temperature around 70°C, to afford compounds of type V-CHCHG. The ylid can be generated from a suitable phosphonium salt with a strong base such as sodium hydride in a solvent such as tetrahydrofuran, at temperatures around 0°C.

V-Br could also be converted to V-OH, with a suitable palladium catalyst, in a solvent like 1,4-dioxane (Anderson K.W.; Ikawa T., Tundel R.E., Buchwald S.L. *J. Am. Chem. Soc.* **2006** *128(33),* 10694-10695). Compounds V-OH can be alkylated, for example under phase-transfer conditions in solvent such as water and 1,4-dioxane, with a base such potassium hydroxide and a phase-transfer catalyst like tetrabutylammonium bromide, at temperatures around the boiling point of the solvent.

Scheme 2



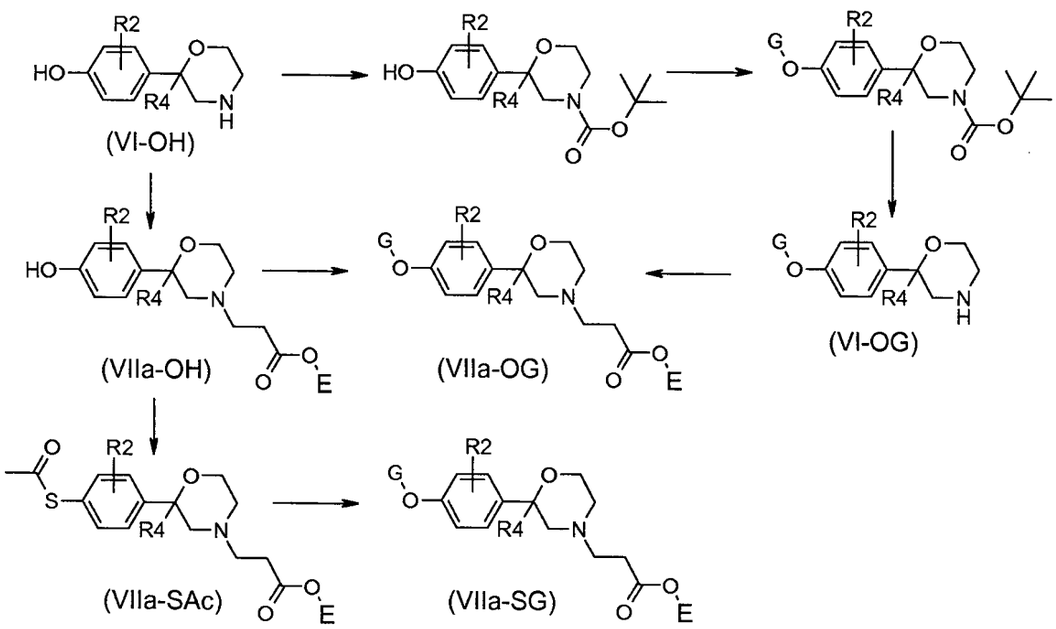
G is a group that is part of R1-A in the final compounds I.

Under palladium catalysis IV-Br can also be converted to V-CH2G with a suitable organometallic reagent like a boron reagent (Suzuki-reaction), or a zinc reagent (Negishi-reaction), in a solvent like toluene or tetrahydrofuran, at temperatures near the boiling point of the solvent. Also V-Br can be coupled with a suitable amine-donor, like benzophenone imine, under palladium catalysis in the presence of a base, like sodium tert-butoxide, in a solvent like toluene at temperatures around 100°C. Subsequent treatment with an aqueous acid, like hydrochloric acid, at room temperature, leads to intermediates V-NH2. V-NH2 can be reacted with a suitable alkylating agent and a base like N-ethyldiisopropylamine, in a solvent like methanol at room temperature to afford the secondary amines V-NHCH2G. V-NH2 can also be reacted with a suitable acylating reagent like an acyl chloride, with a suitable base

like N-ethyldiisopropylamine, in a solvent like acetonitrile, at temperatures between 0°C and room temperature to afford the amides V-NHCOG.

Removal of the *N*-benzyl group in the *N*-benzyl morpholines (V), can be done by hydrogenation in a solvent such as ethanol and a catalyst like palladium hydroxide, or alternatively by reaction with ACE-Cl in a solvent such as 1,2-dichloroethane, followed by reaction of the intermediate carbamate with methanol. The obtained morpholines (VI) can be converted to other morpholines (VI) in a sequence of steps. See **Scheme 3**. For example, (VI-OH) can be protected at the nitrogen with a suitable protecting group (P.G.M. Wuts, T.W. Greene Protective groups in organic synthesis, 4th ed., John Wiley & Sons, 2006), such as tert-butyloxycarbonyl (BOC), by reaction with di-tert-butyl dicarbonate in a solvent such as acetonitrile at room temperature. Subsequently, the phenolic group can be reacted with a suitable alkylating reagent in a solvent such as acetonitrile, in the presence of a base such as potassium carbonate, at room temperature. After which the tert-butyloxycarbonyl (BOC) group can be removed by the treatment with an acid, such as hydrogen chloride, in a solvent such as ethanol, at temperatures between room temperature and 60°C, to afford a modified morpholine (VI-OG).

Scheme 3



Morpholines (VI) can be reacted with an (meth)acrylic acid ester, in a so called Michael-addition, in a solvent such as acetonitrile, methanol, or *N,N*-dimethyl-formamide, at temperatures between room temperature and 85°C, and eventually with the addition of some base like triethylamine or 1,8-diazabicyclo[5.4.0]undec-7-

ene, to afford morpholin-4-yl-propionic acid esters (VIIa, Q2 = CH2CH2COOR'). In case those morpholin-4-yl-propionic acid esters (VIIa, Q2 = CH2CH2COOR') contain a phenolic group (VIIa-OH), those compounds can be modified in the following way: By reaction with a suitable alkylating reagent, such as a alkyl bromide or an alkyl chloride, in the presence of a base, such as potassium carbonate or cesium carbonate, in a solvent such as acetonitrile and / or tetrahydrofuran, at room temperature, to afford compounds of type VIIa-OG. Alternatively, VIIa-OH can be converted to VIIa-OG, by reaction with a suitable alcohol, in the presence of triphenylphosphine, and a suitable azo-reagent, like diisopropyl azodicarboxylate, in a solvent such as tetrahydrofuran or dichloromethane. Furthermore, VII-OH can be converted to the corresponding trifluoromethanesulfonic acid ester by reaction with *N*-phenylbis(trifluoromethane-sulfonimide) in the presence of a base, such as Et_3N, in a solvent, such as $CHCl_3$, at a temperature between room temperature 60°C. Those trifluoromethanesulfonic acid ester can than be reacted with thioacetate under palladium catalysis, in a solvent such as toluene, at 110°C, to afford the thioesters VIIa-SAc. Basic hydrolysis of the thioester, with a base such as NaOH, in a solvent such as EtOH and water, at 0°C, followed directly by alkylation with a suitable alkylating agent, at room temperature, affords thioethers VIIa-SG.

Compounds of type VIIa-OG and VIIa-SG can be converted into the final compounds I by basic or acidic hydrolysis of the ester, depending on the nature of group E. As an example, tert-butyl esters (E = $C(CH_3)_3$) can be treated with an acid, such as trifluoroacetic acid or hydrogen chloride, in a solvent such as CH_2Cl_2 or 1,4-dioxane, at room temperature. As a further example, ethyl esters (E = CH_2CH_3) can be treated with a base, such as sodium hydroxide or lithium hydroxide, in solvents such as ethanol, THF, and/or water, at temperatures between room temperature and 70°C.

Compounds of type VI can also be substituted on nitrogen by reaction with a suitable alkylating reagent like an alkyl bromide or alkyl chloride, in the presence of a base like potassium carbonate, triethylamine, or 1,8-diazabicyclo[5.4.0]undec-7-ene, optionally in the presence of sodium iodide, in a solvent such as acetonitrile or DMF, at temperatures between room temperature and 100°C. Furthermore, compounds of type VI can also be acylated on nitrogen, with an acid chloride or another activated acylating reagent, in the presence of a base such as N-ethyldiisopropylamine, in a solvent such as acetonitrile, at room temperature.

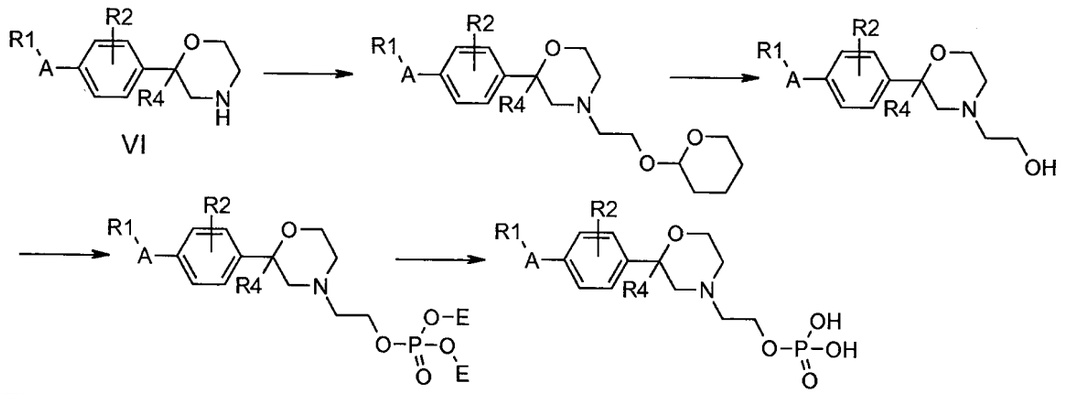
Compounds of type VI can also be modified on nitrogen with a 2,2-difluoro-propionic acid ester group, by the following sequence of steps (Cheguillaume A., Lacroix S., Marchand-Brynaert J. *Tetrahedron Letters* **2003**, *44*, 2375): First reaction with 1*H*-benzotriazole-1-methanol in a solvent such as ethanol, at temperatures around 50°C;

followed by reaction with a zinc reagent prepared from zinc dust, trimethylsilylchloride and a bromodifluoroacetate, in a solvent such as tetrahydrofuran, at temperatures around 70°C.

Morpholines of type VI can also be modified on nitrogen by reaction with a vinyl-phosphonate diester, in a solvent such as acetonitrile at temperatures around 85°C.

Compounds of type I wherein R3 = $(CH_2)_2OPO_3H_2$ can be synthesized as shown in **scheme 4.**

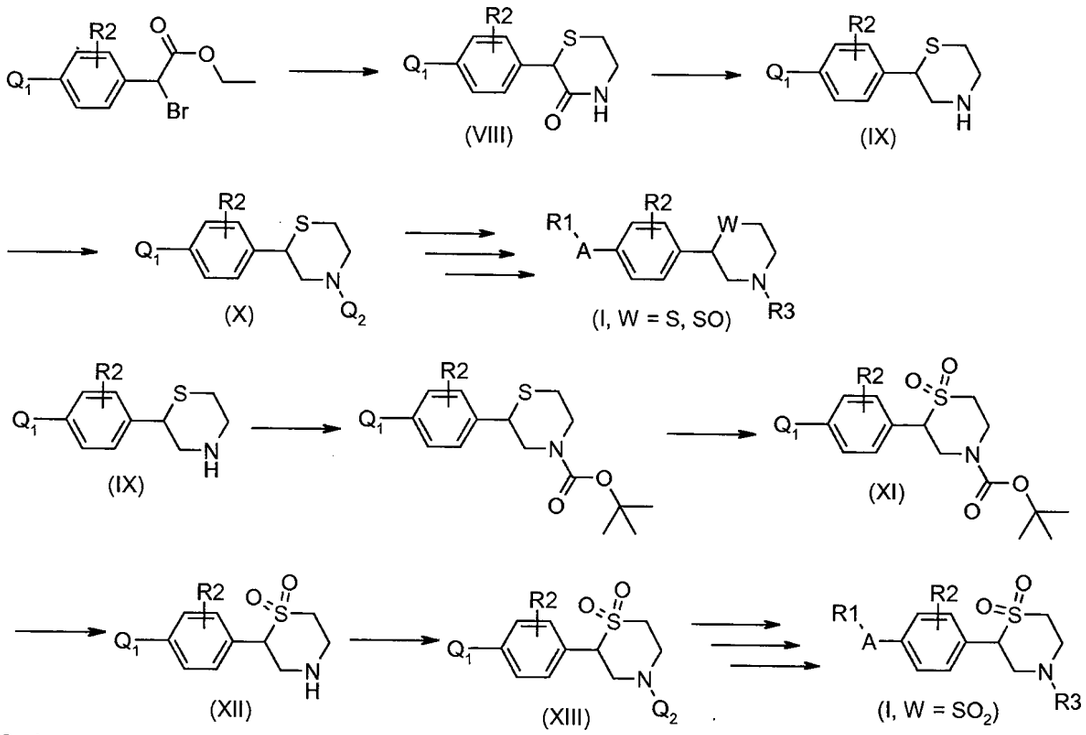
Scheme 4



Thus a suitable substituted morpholine VI is reacted with 2-(2-chloro-ethoxy)tetrahydro-2*H*-pyran, in the presence of a base, such as potassium carbonate, and sodium iodide, in a solvent such as DMF, at a temperature around 100°C. The tetrahydro-2*H*-pyran group is removed by treatment with an acid such as p-toluenesulfonic acid, in a solvent such as methanol, at room temperature. The formed alcohol is then treated with a phosphoramidite reagent such as di-tert-butyl *N,N*-diisopropylphosphoramidite, in the presence of tetrazole, in a mixture of solvents, such as THF, CH_2Cl_2, and CH_3CN, at room temperature, and subsequently oxidized with an oxidizing reagent such as hydrogen peroxide or tert-butylhydroperoxide in the same solvents, at room temperature. Partial hydrolysis of the phosphate esters can be done under conditions depending on the nature of the groups E. For example di-tert-butyl esters can be hydrolyzed by treatment with an acid, such as TFA, in a solvent such as CH_2Cl_2, at room temperature. As another example di-ethyl esters can be reacted with bromotrimethylsilane in a solvent such as CH_2Cl_2, at room temperature, followed by treatment with methanol to affect hydrolysis.

Compounds wherein W is -S-, -SO- or $-SO_2-$ may be prepared as described below and shown in **scheme 5.**

Scheme 5



Q_1 is a group equal to R1-A, or a group that can be converted to R1-A. Q_2 is a group equal to R3, or a group that can be converted to R3. For details, see the full details given below.

The synthesis begins with a suitably substituted bromo-phenyl-acetic acid ester. Suitably substituted bromo-phenyl-acetic acid esters are commercially available or can be obtained according to methods known in the literature. The bromo-phenyl-acetic acid ester is reacted with 2-aminoethanethiol, in the presence of a base, such as potassium carbonate, in a solvent such as ethanol, at room temperature, to obtain 2-aryl-thiomorpholin-3-ones (VIII). Those thiomorpholin-3-ones can then be reduced with a reducing agent such as borane in a solvent such as tetrahydrofuran, at temperatures between 0°C and room temperature, to afford the 2-aryl-thiomorpholines (IX). Thiomorpholines (IX) can be reacted with an (meth)acrylic acid ester, in a so called Michael-addition, in a solvent such as acetonitrile, methanol, or *N,N*-dimethylformamide, at temperatures between room temperature and 85°C, and eventually with the addition of some base like triethylamine or 1,8-diazabicyclo[5.4.0]undec-7-ene, to afford morpholin-4-yl-propionic acid esters (X, Q2 = CH2CH2COOR'). In case those thiomorpholin-4-yl-propionic acid esters (X, Q2 = CH2CH2COOR') are substituted with bromine (X, Q1 = Br), the bromine can be replaced by iodine (X, Q1 = I) in a reaction with sodium iodide, catalysed by copper(I)

iodide, in the presence of *N,N*-dimethylethylenediamine, in a solvent such as 1,4-dioxane, at temperatures around 130°C, in a closed vessel. Subsequently, the iodine (X, Q1 = I), can be substituted by a suitable alcohol, in the presence of a base such as cesium carbonate, and catalyzed by copper(I) iodide and 1,10-phenanthroline, in a solvent such as toluene, at a temperature around 110°C, to obtain compounds in which Q1 is equal to R1-A, and Q2 = CH2CH2COOR'. In case R' is tert-butyl, the ester can be hydrolyzed with acid, such as hydrochloric acid, in a solvent such as 1,4-dioxane, at temperatures between room temperature and 80°C, to afford compounds (I, W = S). Thiomorpholines (X, W = S, Q1 = R1-A, Q2 = CH2CH2COOR'), can be oxidized with an oxidizing reagent such as potassium peroxymonosulfate (Oxone®), in a solvent such as methanol/water, at temperatures between 0°C and room temperature to afford the thiomorpholine 1-oxides (X, W = SO, Q1 = R1-A, Q2 = CH2CH2COOR'). In case R' is tert-butyl acid hydrolysis as described for the thiomorpholines affords compounds (I, W = SO).

Thiomorpholines (IX) can be protected at the nitrogen with a suitable protecting group (P.G.M. Wuts, T.W. Greene Protective groups in organic synthesis, 4th ed., John Wiley & Sons, 2006), such as tert-butyloxycarbonyl (BOC), by reaction with di-tert-butyl dicarbonate in a solvent such as acetonitrile at room temperature. Subsequently, the thiomorpholines can be oxidized with an oxidizing reagent such as 3-chloroperoxybenzoic acid, in a solvent such as dchloromethane, at temperatures between 0°C and room temperature, to obtain thiomorpholine 1,1-dioxides (XI). After which the tert-butyloxycarbonyl (BOC) group can be removed by the treatment with an acid, such as hydrogen chloride, in a solvent such as ethanol, at temperatures between room temperature and 60°C, to afford modified thiomorpholine 1,1-dioxides (XII). Thiomorpholine 1,1-dioxides can then be reacted in a so called Michael reaction as described above for the thiomorpholines, to obtain compounds XIII (Q2 = CH2CH2COOR'). In case compounds XIII are substituted with bromine (Q1 = Br), they can be substituted by a suitable alcohol, in the presence of a base such as cesium carbonate, and catalyzed by a palladium catalyst, such as $Pd(AcO)_2$, and a suitable phosphine ligand, in a solvent such as toluene, at a temperature around 100°C, to obtain compounds XIII (W = SO_2, Q1 = R1-A, Q2 = CH2CH2COOR'). In case R' is tert-butyl acid hydrolysis as described for the thiomorpholines affords compounds (I, W = SO_2).

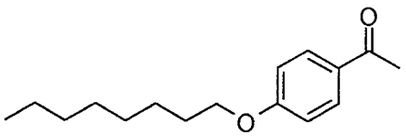
Abbreviations

ACE-Cl	1-Chloroethyl chloroformate
AcCl	Acetyl chloride
$AlCl_3$	Aluminum chloride
9-BBN	9-borabicyclo[3.3.1]nonane dimer
BH_3·THF	Borane tetrahydrofuran complex
n-BuLi	n-Butyl lithium
nBu_4NBr	Tetrabutylammonium chloride
$CHCl_3$	Chloroform
CH_2Cl_2	Dichloromethane
CH_3CN	Acetonitrile
Cs_2CO_3	Cesium carbonate
$CuBr_2$	Copper(II) bromide
CuI	Copper(I) iodide
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DIAD	Diisopropyl azodicarboxylate
DIPEA	*N,N*-Diisopropylethylamine
DMF	*N,N*-dimethylformamide
DMSO	Dimethyl sulfoxide
Et_3N	Triethylamine
Et_2O	Diethyl ether
EtOH	Ethanol
EtOAc	Ethyl acetate
HCl	Hydrogen chloride
H_2SO_4	Sulfuric acid
K_2CO_3	Potassium carbonate
$KHCO_3$	Potassium bicarbonate
KI	Potassium iodide
KOH	Potassium hydroxide
KOtBu	Potassium *tert*-butoxide
$LiAlH_4$	Lithium aluminum hydride
LiHMDS	Lithium bis(trimethylsilyl)amide
LiOH	Lithium hydroxide
MeI	Methyl iodide
MeMgBr	Methylmagnesium bromide
MeOH	Methanol
min.	minutes

$NaBH_4$	Sodium borohydride
$NaHCO_3$	Sodium bicarbonate
NaI	Sodium iodide
NaN_3	Sodium azide
NaOH	Sodium hydroxide
NaOtBu	Sodium *tert*-butoxide
Na_2SO_4	Sodium sulfate
NBS	*N*-Bromosuccinimide
PBr_3	Phosphorus tribromide
Pd_2dba_3	Tris(dibenzylideneacetone)dipalladium(0)
$Pd(dppf)Cl_2$	[1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)
$PdCl_2(PPh_3)_2$	Bis(triphenylphosphine)palladium(II) dichloride
$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine)palladium(0)
iPr_2O	Diisopropyl ether
RT	Room Temperature
SiO_2	Silica gel
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMSCl	Chlorotrimethylsilane
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
p-TsOH	p-Toluenesulfonic acid monohydrate
ZrCl4	Zirconium tetrachloride

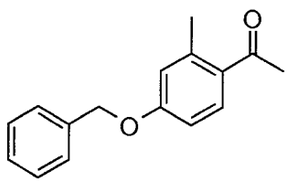
§3. SYNTHESES OF INTERMEDIATES

ARYL(THIO)MORPHOLINES

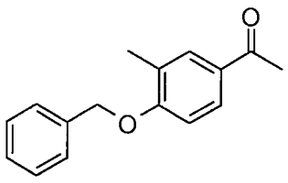


1-(4-Octyloxy-phenyl)-ethanone: To a solution of 4'-hydroxyacetophenone (25.0 g; 183.6 mmol) in DMSO (300. mL) was added KOH (11.3 g; 201.9 mmol.) and the reaction mixture was stirred for 1 hour at RT. After 1 hour the reaction mixture was cooled (0°C) and 1-bromooctane (34.9 mL; 201.9 mmol) was added. The ice bath was removed and the reaction mixture was stirred overnight at RT. The reaction mixture was extracted with EtOAc/ 5% aqueous $NaHCO_3$ solution. The organic layer

was dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, Et_2O: hexanes 1:3) to afford 1-(4-octyloxy-phenyl)-ethanone (43.08 g)



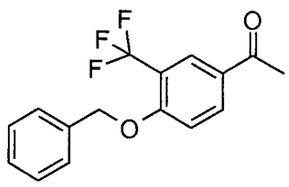
1-(4-benzyloxy-2-methylphenyl)-ethanone: A mixture of 4'-hydroxy-2'-methylacetophenone (24.88 g; 165.7 mmol)), KI (5.50 g; 33.1 mmol), K_2CO_3 (34.3 g; 248.5 mmol) and benzyl bromide (21.7 mL; 182.2 mmol) in acetone (200 mL) was stirred overnight at RT. Subsequently the resulting mixture was filtered and partitioned between EtOAc and 5% aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo to afford 1-(4-benzyloxy-2-methylphenyl)-ethanone , which was used as such.



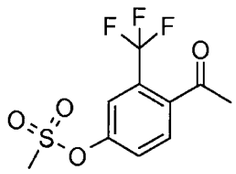
1-(4-benzyloxy-3-methylphenyl)-ethanone : A mixture of 4'-hydroxy-3'-methylacetophenone (10.00 g; 66.6 mmol) and K_2CO_3 (13.80 g; 99.9 mmol) in acetone (100 mL) was stirred, at RT for 40 minutes. Subsequently, benzyl bromide (7.9 mL; 66.6 mmol) was added and the resulting mixture was heated under reflux for 2,5 h. After cooling to RT the mixture was concentrated in vacuo. The residue was dissolved in EtOAc, washed with 5% aqueous ammonia, water, and brine, dried ($MgSO_4$), filtered and concentrated in vacuo to afford 1-(4-benzyloxy-3-methylphenyl)-ethanone (15.86 g).

The following compound was obtained according to a similar manner:

1-(4-Benzyloxy-3-methoxy-phenyl)-ethanone



1-(4-Benzyloxy-3-trifluoromethyl-phenyl)-ethanone : A mixture of benzyl alcohol (10.9 mL; 104.98 mmol) and KOtBu (12.96 g; 115.5 mmol) in THF (500 mL) was heated under reflux for 10 minutes. Subsequently, 4'-fluoro-3'-(trifluoromethyl)acetophenone (21.64 g; 105 mmol) was added and the mixture heated under reflux for another 2 hours. After cooling to RT, the mixture was partitioned between EtOAc and a 5% aqueous $NaHCO_3$ solution. The organic layer was separated, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, Et_2O: hexanes 1:2.5) to afford 1-(4-Benzyloxy-3-trifluoromethyl-phenyl)-ethanone (22.37 g).

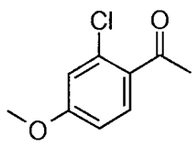


Methanesulfonic acid 4-acetyl-3-trifluoromethyl-phenyl ester: To a solution of 1-(4-hydroxy-2-trifluoromethyl-phenyl)-ethanone (29.74 g; 145.7 mmol) in CH_2Cl_2 (300 mL) and THF (120 mL) was added Et_3N (24.4 mL; 174.8 mmol), at 0°C. To the resulting mixture was added dropwise a solution of methanesulfonyl chloride (12. 5 mL; 160.3 mmol) in CH_2Cl_2 (60 mL), at 0°C. Subsequently the mixture was stirred overnight at RT, and poured in ice-water. The layers were separated and the organic layer was washed with 1 M aqueous HCl and water; dried ($MgSO_4$), filtered and concentrated in vacuo to afford methanesulfonic acid 4-acetyl-3-trifluoromethyl-phenyl ester (40.47 g), which was used as such.

The following compounds were prepared in an analogues manner:

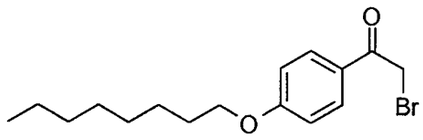
Methanesulfonic acid 4-acetyl-2-chloro-phenyl ester

Methanesulfonic acid 4-acetyl-3-fluoro-phenyl ester

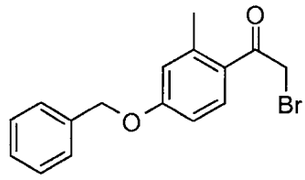


1-(2-Chloro-4-methoxy-phenyl)-ethanone

To a mixture of $AlCl_3$ (42.08 g; 315.60 mmol) in CH_2Cl_2 (300 mL) was added dropwise 3-chloroanisole (22.50 g; 157.80 mmol), at -30°C. To the resulting mixture was added dropwise a solution of AcCl (10.50 mL; 147.63 mmol) in CH_2Cl_2 (100 mL) at such a rate to keep the temperature below -15°C. The resulting mixture was stirred for 4 hours at -10°C. Subsequently, the mixture was poured onto ice and extracted with CH_2Cl_2. The combined organic layers, were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, Et_2O/hexanes 1:9) to afford 1-(2-chloro-4-methoxy-phenyl)-ethanone (17.68 g).



2-Bromo-1-(4-octyloxy-phenyl)-ethanone : To a solution of 1-(4-octyloxy-phenyl)-ethanone (43.0 g; 173.1 mmol) in EtOAc (200 mL) was added $CuBr_2$ (77.3 g; 346.2 mmol) and heated to reflux for 2 hours. The reaction mixture was filtered over Kieselguhr. The reaction mixture was washed with 10% aqueous solution of Sodium thiosulfate and brine. The organic layer was dried over Na_2SO_4, concentrated in vacuo and purified by column chromatography (SiO_2, Et_2O: hexanes 1:7)) to afford 2-bromo-1-(4-octyloxy-phenyl)-ethanone (36.3 g)

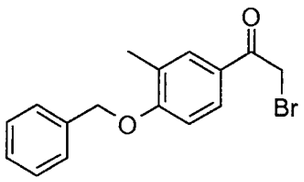


1-(4-Benzyloxy-2-methyl-phenyl)-2-bromo-ethanone: To a solution of 1-(4-benzyloxy-2-methylphenyl)-ethanone (42.00 g; 174.8 mmol) in MeOH (300 mL) was added tetra-*N*-butylammonium tribromide (84.28 g; 174.8 mmol) and the mixture was stirred overnight at RT. Subsequently, the MeOH was evaporated in vacuo, and the residue partitioned between EtOAc (300 mL) and 5% aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4), filtered, concentrated in vacuo and purified by column

chromatography (SiO_2, Et_2O: hexanes 1:1) to afford 1-(4-benzyloxy-2-methyl-phenyl)-2-bromo-ethanone (49.93 g).

The following compound was obtained according to a similar manner:

1-(4-Benzyloxy-3-trifluoromethyl-phenyl)-2-bromo-ethanone



1-(4-Benzyloxy-3-methyl-phenyl)-2-bromo-ethanone : To a solution of 1-(4-benzyloxy-3-methyl-phenyl)-ethanone (12.89 g; 53.1 mmol) in CH_2Cl_2 was added, dropwise, at 0°C, DIPEA (10.9 mL; 63.7 mmol) and trimethylsilyl trifluoromethanesulfonate (11.1 mL; 61.1 mmol). The resulting mixture was stirred at 0°C for 1 hour, and subsequently, NBS (10.87 g; 61.1 mmol) was added in one portion. The mixture was allowed to warm to RT stirred overnight. Then the mixture was concentrated in vacuo, the residue dissolved in EtOAc, washed with water twice, and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo to afford 1-(4-benzyloxy-3-methyl-phenyl)-2-bromo-ethanone (11.90 g).

The following compound was obtained according to a similar manner:

1-(4-Benzyloxy-3-methoxy-phenyl)-2-bromo-ethanone

Methanesulfonic acid 4-(2-bromo-acetyl)-3-trifluoromethyl-phenyl ester

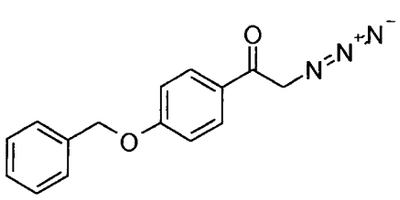
Methanesulfonic acid 4-(2-bromo-acetyl)-2-chloro-phenyl ester

Methanesulfonic acid 4-(2-bromo-acetyl)-3-fluoro-phenyl ester

1-(3-Benzyloxy-phenyl)-2-bromo-ethanone

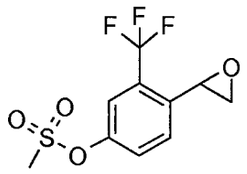
2-Bromo-1-(2-chloro-4-methoxy-phenyl)-ethanone

2-Bromo-1-(5-bromo-pyridin-2-yl)-ethanone



2-Azido-1-(4-benzyloxy-phenyl)-ethanone

To a mixture of 1-(4-benzyloxy-phenyl)-2-bromo-ethanone (28.55 g; 93.6 mmol) in CH_2Cl_2 (300 mL) and water (30 mL) was added nBu_4NBr (1.51 g; 4.7 mmol) and NaN_3 (6.69 g; 102.9 mmol) in one portion. After 4h at RT, the layers were separated. The organic layer was washed water, dried (Na_2SO_4), filtered and concentrated in vacuo to afford 2-azido-1-(4-benzyloxy-phenyl)-ethanone (23.64 g).



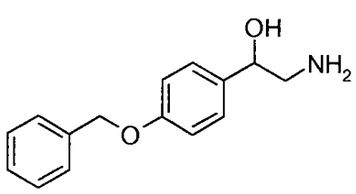
Methanesulfonic acid 4-oxiranyl-3-trifluoromethyl-phenyl ester: To a solution of methanesulfonic acid 4-(2-bromo-acetyl)-3-trifluoromethyl-phenyl ester (33.95 g; 89.3 mmol) in 1,4-dioxane (150 mL) was added dropwise a solution of $NaBH_4$ (2.37 g; 62.5 mmol) in water (47 mL). The resulting mixture was stirred at RT for 2.5 hours, subsequently, quenched with 0.5M aqueous HCl (125 mL), and extracted with EtOAc. The combined organic layers were washed with water, dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was dissolved in Et_2O (500 mL) and treated with a solution of KOH (4.19 g; 74.7 mmol) in water (100 mL). The resulting mixture was heated under reflux for 4 hours. After cooling to RT, the volatiles were removed in vacuo and the residue was partitioned between EtOAc and water. The organic layer was washed with water, dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by column chromatography (CH_2Cl_2) to afford methanesulfonic acid 4-oxiranyl-3-trifluoromethyl-phenyl ester (23.54 g).

The following compounds were prepared in an analogues manner:

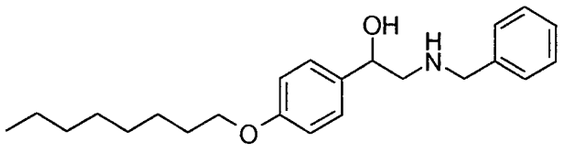
Methanesulfonic acid 4-oxiranyl-3-fluoro-phenyl ester

Methanesulfonic acid 4-oxiranyl-2-chloro-phenyl ester

2-(2-Chloro-4-methoxy-phenyl)-oxirane



2-Amino-1-(4-benzyloxy-phenyl)-ethanol: To a suspension of $LiAlH_4$ (8.18 g; 215.6 mmol) in THF (100 mL), was added dropwise a solution of 2-azido-1-(4-benzyloxy-phenyl)-ethanone (23.05 g; 86.2 mmol) in THF (200 mL), at 0°C. The mixture was stirred at 0°C for 20 min. and subsequently 2 hours at RT. Thereafter, water (50 mL), and 2M aqueous NaOH-solution (150 mL) were added consecutively. The formed precipitate was removed by filtration over kieselguhr, and washed with MeOH. The filtrate was concentrated in vacuo and the remaining aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo to afford 2-amino-1-(4-benzyloxy-phenyl)-ethanol (20.10 g)



2-Benzylamino-1-(4-octyloxy-phenyl)-ethanol: To a cooled (0°C) suspension of 2-Bromo-1-(4-octyloxy-phenyl)-ethanone (36.1 g; 110.3 mmol) in EtOH (500 mL) and $CHCl_3$ (100 mL) was added benzylamine (48.2 mL; 441.2 mmol). After 30 minutes the ice-bath was removed and the mixture stirred for another 2 hours at RT. Subsequently the reaction mixture was cooled again to 0°C and $NaBH_4$ (6.26 g; 165.5 mmol) was added in small portions. The resulting mixture was stirred at 0°C for 1 hour and thereafter another 4 hours at RT. The reaction mixture was quenched with 1M aqueous HCl (750 mL) at 0°C and stirred at RT for 1 hour. The reaction mixture was concentrated in vacuo and the residue was partitioned between EtOAc and 2 N aqueous NaOH. The organic layer was dried (Na_2SO_4), filtered, concentrated in vacuo, and purified by column chromatography (SiO_2, EtOAc) to give 2-benzylamino-1-(4-octyloxy-phenyl)-ethanol (22.58 g)

The following compounds were obtained according to a similar manner:

2-Benzylamino-1-(4-bromo-phenyl)-ethanol

2-Benzylamino-1-(4-benzyloxy-phenyl)-ethanol

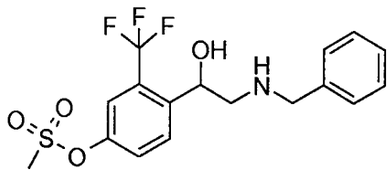
2-Benzylamino-1-(4-benzyloxy-2-methyl-phenyl)-ethanol

2-Benzylamino-1-(4-benzyloxy-3-methyl-phenyl)-ethanol

2-Benzylamino-1-(4-benzyloxy-3-trifluoromethyl-phenyl)-ethanol

2-Benzylamino-1-(4-benzyloxy-3-methoxy-phenyl)-ethanol 2-Benzylamino-1-(3-benzyloxy-phenyl)-ethanol

2-(Benzhydryl-amino)-1-(5-bromo-pyridin-2-yl)-ethanol



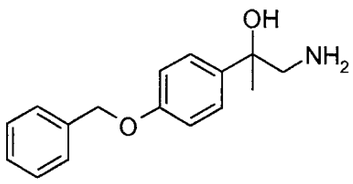
Methanesulfonic acid 4-(2-benzylamino-1-hydroxy-ethyl)-3-trifluoromethyl-phenyl ester: Methanesulfonic acid 4-oxiranyl-3-trifluoromethyl-phenyl ester (23.54 g; 79.2 mmol) was dissolved in benzylamine (26 mL). The resulting mixture was stirrred at 80°C for 4h. After cooling to RT, Et_2O was added and the mixture cooled to 0°C. The formed precipitate was collected by filtration, washed with Et_2O, and dried under vacuum, at 40°C, to afford methanesulfonic acid 4-(2-benzylamino-1-hydroxy-ethyl)-3-trifluoromethyl-phenyl ester as a white solid (26.87 g) which was used as such.

The following compounds were prepared in a similar manner:

Methanesulfonic acid 4-(2-benzylamino-1-hydroxy-ethyl)-3-fluoro-phenyl ester

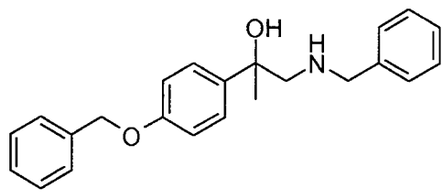
Methanesulfonic acid 4-(2-benzylamino-1-hydroxy-ethyl)-2-chloro-phenyl ester

2-Benzylamino-1-(2-chloro-4-methoxy-phenyl)-ethanol

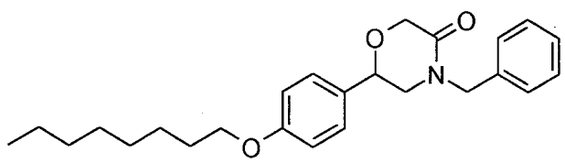


1-Amino-2-(4-benzyloxy-phenyl)-propan-2-ol: A mixture of 1-(4-benzyloxy-phenyl)-ethanone (18.50 g; 81.8 mmol), zinc iodide (0.52 g; 1.6 mmol), and trimethylsilyl cyanide (33.8 mL; 269.8 mmol) was stirred overnight at RT. Subsequently, the excess trimethylsilyl cyanide was removed in vacuo, and the residue dissolved in THF (100 mL). The resulting solution was added, dropwise, to a mixture of lithium aluminum hydride (12.7 g; 335.2 mmol) in THF (200 mL). The resulting mixture was heated under reflux for 2 h. Next, the mixture was cooled to 0°C and treated successively with water (13 mL), 2M aqueous NaOH (26 mL), and water (13 mL). Thereafter the mixture was heated under reflux for 15 minutes, cooled again to RT,

filtered over Kieselguhr, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, MeOH) to afford 1-Amino-2-(4-benzyloxy-phenyl)-propan-2-ol (18.15 g).



1-Benzylamino-2-(4-benzyloxy-phenyl)-propan-2-ol: A mixture of 1-amino-2-(4-benzyloxy-phenyl)-propan-2-ol (1.26 g; 4.9 mmol), benzaldehyde (0.55 mL; 5.4 mmol), and p-toluenesulfonic acid (0.04 g; 0.24 mmol) in toluene (30 mL) was heated under reflux in a Dean-Stark apparatus, overnight. Subsequently, the mixture was cooled to RT and the solvent was removed in vacuo. The residue was suspended in MeOH (30 mL), cooled to -15°C, and treated with $NaBH_4$ (0.74 g; 19.6 mmol), portionwise. After the addition was complete the mixture was warmed to RT and stirred for one hour. Subsequently, the MeOH was removed in vacuo. The residue was partitioned between Et_2O and 5% aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, Et_2O: hexanes 2:1) to give 1-benzylamino-2-(4-benzyloxy-phenyl)-propan-2-ol (1.07 g).



4-Benzyl-6-(4-octyloxy-phenyl)-morpholin-3-one: To a solution of 2-benzylamino-1-(4-octyloxy-phenyl)-ethanol (22.50 g; 63.3 mmol) and Et_3N (9.7 mL; 69.6 mmol) in CH_2Cl_2 (500 mL) was added dropwise a solution of chloroacetyl chloride (5.5 mL; 69.6 mmol) in CH_2Cl_2 (25 mL), at 0°C. After 1 hour at 0°C the reaction mixture was quenched with 1M aqueous HCl (200 mL). The layers were separated and the organic layer washed with a 5% aqueous $NaHCO_3$ solution, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was dissolved in 2-propanol (250 mL) and KOH (4.26 g; 76 mmol) was added. The resulting mixture was stirred at RT for 1 hour and subsequently concentrated *in vacuo*. The crude product was partitioned between EtOAc and 0.5 M aqueous HCl. The layers were separated and the organic layer was

washed with 5% aqueous $NaHCO_3$ solution, dried (Na_2SO_4) and evaporated in vacuo to afford 4-benzyl-6-(4-octyloxy-phenyl)-morpholin-3-one (22.30 g) which was used as such in the next step.

The following compounds were obtained according to a similar manner:

4-Benzyl-6-(4-bromo-phenyl)-morpholin-3-one

4-Benzyl-6-(4-benzyloxy-phenyl)-morpholin-3-one

4-Benzyl-6-(4-benzyloxy-2-methyl-phenyl)-morpholin-3-one

4-Benzyl-6-(4-benzyloxy-3-methyl-phenyl)-morpholin-3-one

4-Benzyl-6-(4-benzyloxy-3-methoxy-phenyl)-morpholin-3-one

4-Benzyl-6-(4-benzyloxy-3-trifluoromethyl-phenyl)-morpholin-3-one

4-Benzyl-6-(4-benzyloxy-phenyl)-6-methyl-morpholin-3-one

4-Benzyl-6-(3-benzyloxy-phenyl)-morpholin-3-one

4-Benzyl-6-(2-chloro-4-methoxy-phenyl)-morpholin-3-one

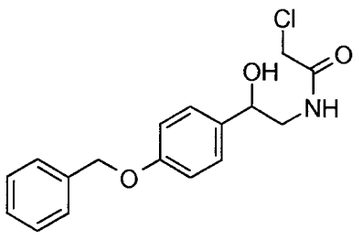
4-Benzhydryl-6-(5-bromo-pyridin-2-yl)-morpholin-3-one

The following compounds were obtained according to a similar manner from methanesulfonic acid phenyl esters using 2.5 equivalents of KOH instead of 1.25 equivalents.

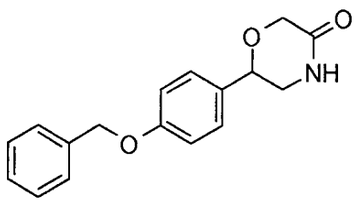
4-Benzyl-6-(4-hydroxy-2-trifluoromethyl-phenyl)-morpholin-3-one

4-Benzyl-6-(2-fluoro-4-hydroxy-phenyl)-morpholin-3-one

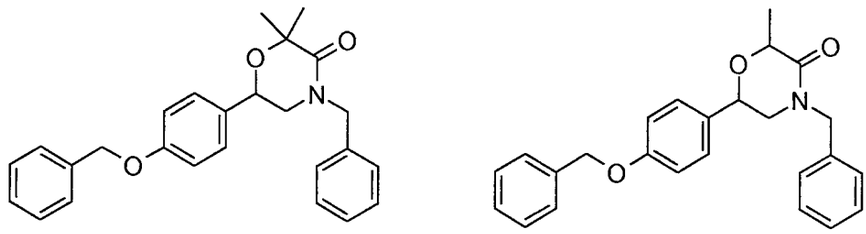
4-Benzyl-6-(3-chloro-4-hydroxy-phenyl)-morpholin-3-one



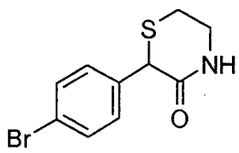
***N*-[2-(4-Benzyloxy-phenyl)-2-hydroxy-ethyl]-2-chloro-acetamide:** To a mixture of 2-amino-1-(4-benzyloxy-phenyl)-ethanol (20.10 g; 82.6 mmol), Et_3N (13.82 mL; 99.1 mmol), CH_2Cl_2 (200 mL) and MeOH (20 mL) was added dropwise chloroacetyl chloride (7.24 mL; 90.9 mmol) at -10°C. The resulting mixture was allowed to warm to RT and stirred overnight, and subsequently concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, EtOAc) to afford *N*-[2-(4-benzyloxy-phenyl)-2-hydroxy-ethyl]-2-chloro-acetamide (17.45 g).



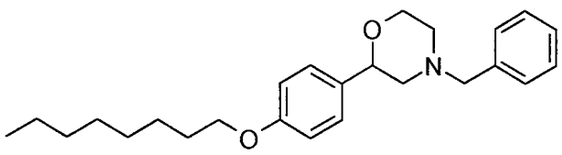
6-(4-Benzyloxy-phenyl)-morpholin-3-one: To a solution of KOtBu (6.68 g; 59.5 mmol) in 2-methyl-2-butanol (100 mL) was added dropwise a solution of *N*-[2-(4-benzyloxy-phenyl)-2-hydroxy-ethyl]-2-chloro-acetamide (17.30 g; 54.1 mmol) in THF (100 mL). The resulting mixture was stirred for 1 hour at RT and then concentrated in vacuo. The residue was dissolved in CH_2Cl_2 and treated with a 1M aqueous solution of HCl, at 0°C. The layers were separated and the aqueous layer extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo to afford 6-(4-benzyloxy-phenyl)-morpholin-3-one (14.10 g).



4-Benzyl-6-(4-benzyloxy-phenyl)-2,2-dimethyl-morpholin-3-one and **4-Benzyl-6-(4-benzyloxy-phenyl)-2-methyl-morpholin-3-one:** To a solution of 4-benzyl-6-(4-benzyloxy-phenyl)-morpholin-3-one (6.90 g; 18.5 mmol) in THF (100 mL) was added dropwise a solution of LiHMDS in THF (18.5 mL; 1.00 mol/l; 18.5 mmol), at -78°C. The resulting mixture was stirred at -78°C for 15 minutes, subsequently, MeI (1.15 mL; 18.5 mmol) was added, and the resulting mixture stirred for 1 hour at -78°C. The sequence of addition of LiHMDS and MeI, was repeated three times. After the last addition of MeI the mixture was allowed to warm to RT and stirred overnight. Then an 5% aqueous $NaHCO_3$ solution was added en the mixture extracted with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, Et_2O/hexanes 1:1) to afford two compounds. The least polar compound was 4-benzyl-6-(4-benzyloxy-phenyl)-2,2-dimethyl-morpholin-3-one (1.90 g), and the most polar compound was 4-benzyl-6-(4-benzyloxy-phenyl)-2-methyl-morpholin-3-one (3.81 g).



2-(4-Bromo-phenyl)-thiomorpholin-3-one: To a solution of 2-aminoethanethiol hydrochloride (6.93 g; 61 mmol) in EtOH (400 mL) was added K_2CO_3 (16.86 g; 122 mmol), at RT, followed after 15 minutes by bromo-(4-bromo-phenyl)-acetic acid ethyl ester (12 mL; 61 mmol). The resulting mixture was stirred at RT for two days, subsequently, water was added and the resulting mixture was extracted with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was recrystallized from EtOH to afford 2-(4-bromo-phenyl)-thiomorpholin-3-one (12.8 g).



4-Benzyl-2-(4-octyloxy-phenyl)-morpholine: To a solution of 4-benzyl-6-(4-octyloxy-phenyl)-morpholin-3-one (22.22 g; 56.2 mmol) in THF (400 mL) was added borane-THF complex (1M, 140.4 mL; 140.4 mmol) dropwise, at 0°C. After 1 hour the mixture was allowed to warm to RT and stirred for another 2 hours. To the reaction mixture was added MeOH (30 mL), at 0°C, and the resulting mixture was stirred at RT for 30 minutes, and subsequently concentrated in vacuo. The residue was suspended in MeOH (300 mL.) and 1 M aqueous NaOH (112 mL) was added and heated under reflux for 1 hour. The resulting mixture was concentrated in vacuo and the residue was partitioned between EtOAc and 5% aqueous $NaHCO_3$-solution. The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo to afford 4-benzyl-2-(4-octyloxy-phenyl)-morpholine (20.33 g), which was used as such in the next step.

The following compounds were obtained according to a similar manner:

4-Benzyl-6-(4-bromo-phenyl)-morpholine

4-Benzyl-2-(4-benzyloxy-phenyl)-morpholine

4-Benzyl-2-(4-benzyloxy-2-methyl-phenyl)-morpholine

4-Benzyl-2-(4-benzyloxy-3-methyl-phenyl)-morpholine

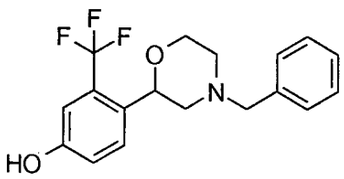
4-Benzyl-2-(4-benzyloxy-3-methoxy-phenyl)-morpholine

4-Benzyl-2-(4-benzyloxy-3-trifluoromethyl-phenyl)-morpholine

4-Benzyl-2-(4-benzyloxy-phenyl)-2-methyl-morpholine

4-Benzyl-6-(4-benzyloxy-phenyl)-2,2-dimethyl-morpholine

4-Benzhydryl-2-(5-bromo-pyridin-2-yl)-morpholine



4-(4-Benzyl-morpholin-2-yl)-3-trifluoromethyl-phenol: To a solution of 4-benzyl-6-(4-hydroxy-2-trifluoromethyl-phenyl)-morpholin-3-one (26.18 g; 67.3 mmol) in THF (600 mL) was added dropwise BH_3·THF in THF (235.4 mL; 1.00 mol/l; 235.4 mmol), at 0°C. The resulting mixture was stirred for 1 hour at 0°C and thereafter 18 hours at RT. Subsequently, 1M aqueous HCl (550 mL) was added and the mixture stirred overnight at RT. The resulting mixture was partitioned between EtOAc and 2M aqueous NaOH (350 mL), the organic layers was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH 98:2) to afford 4-(4-benzyl-morpholin-2-yl)-3-trifluoromethyl-phenol

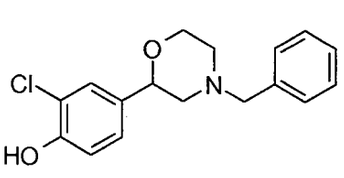
The following compounds were obtained according to a similar manner:

4-(4-Benzyl-morpholin-2-yl)-3-fluoro-phenol

4-Benzyl-2-(3-benzyloxy-phenyl)-morpholine

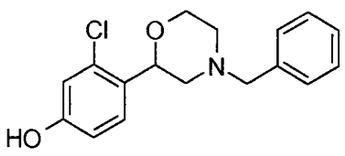
4-Benzyl-2-(2-chloro-4-methoxy-phenyl)-morpholine

2-(4-Bromo-phenyl)-thiomorpholine

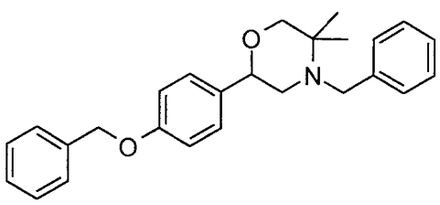


4-(4-Benzyl-morpholin-2-yl)-2-chloro-phenol: To a solution of 4-benzyl-6-(3-chloro-4-hydroxy-phenyl)-morpholin-3-one (13.05 g; 39.0 mmol) in THF (600 mL) was added portionwise $LiAlH_4$ (4.44 g; 117.04 mmol) at 0°C. The resulting mixtures was allowed to warm to RT and stirred overnight. Subsequently, the mixture was cooled to 0°C, and water (4.5 mL), a 2M aqueous NaOH-solution (9.0 mL) and water

(9.0 mL) were added consecutively.Thereafter the mixture was stirred for 1h. The formed precipitate was removed by filtration over kieselguhr, and washed with EtOAc. The organic solution was concentrated in vacuo, and the residue purified by column chromatography (SiO_2, CH_2Cl_2/MeOH 98:2) to afford 4-(4-benzyl-morpholin-2-yl)-2-chloro-phenol (9.10 g)



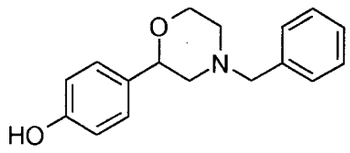
4-(4-Benzyl-morpholin-2-yl)-3-chloro-phenol: To a solution of 1 dodecanethiol (12.7 mL; 52.86 mmol) in dry DMF (50 mL), was added KOtBu (5.93 g; 52.86 mmol) at 0°C. After complete addition the mixture was allowed to slowly come to RT (~30 min), and then 4-benzyl-2-(2-chloro-4-methoxy-phenyl)-morpholine (5.60 g; 17.62 mmol) was added. The resulting mixture was stirred at 110°C for 6 hours. After cooling to RT, EtOAc was added and the resulting mixture was washed with 5% aqueous $NaHCO_3$, water and brine; dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, CH_2CL_2/MeOH 99:1) to afford 4-(4-benzyl-morpholin-2-yl)-3-chloro-phenol (4.56 g)



4-Benzyl-2-(4-benzyloxy-phenyl)-5,5-dimethyl-morpholine

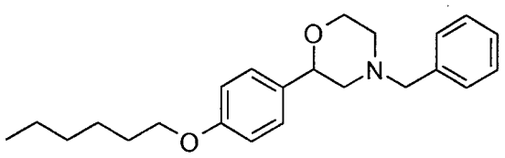
To a solution of 4-benzyl-6-(4-benzyloxy-phenyl)-morpholin-3-one (7.14 g; 19.1 mmol) in THF (100 mL) was added $ZrCl_4$ (4.46 g; 19.1 mmol), at -10°C. The resulting mixture was stirred for 30 min. at -10°C, subsequently, a solution of MeMgBr in Et_2O (38.2 mL; 3.00 mol/l; 114.6 mmol) was added dropwise, keeping the temperature below 10°C. After complete addition the resulting mixture was stirred at RT for 1 hour. After cooling the mixture to 0°C a 2M aqueous NaOH solution was added dropwise. The resulting suspension was filtered and the filtrate was extracted three times with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2,

Et_2O/hexanes 1:3) to afford 4-benzyl-2-(4-benzyloxy-phenyl)-5,5-dimethyl-morpholine (3.6 g).



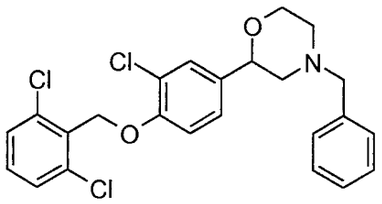
4-(4-Benzyl-morpholin-2-yl)-phenol: To a suspension of 4-benzyl-6-(4-bromo-phenyl)-morpholine (8.70 g; 26.19 mmol) in water (25 mL) and 1,4-dioxane (25 mL) was added KOH (3.23 g; 57.61 mmol), tris(dibenzylideneaceton)dipalladium(0) (479.6 mg; 0.52 mmol) and di-tert-butyl-(2',4',6'-triisopropyl-biphenyl-2-yl)-phosphane (444.8 mg; 1.05 mmol). The resulting mixture was heated under reflux for two hours. After cooling to RT the reaction mixture was concentrated *in vacuo*. The residue was partitioned between EtOAc and 5% aqueous $NaHCO_3$ solution. The organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, Et2O: hexanes 1:1) to afford 4-(4-benzyl-morpholin-2-yl)-phenol (3.67 g).

6-(4-Benzhydryl-morpholin-2-yl)-pyridin-3-ol was made by a similar method.



4-Benzyl-2-(4-hexyloxy-phenyl)-morpholine: To a mixture of 4-(4-benzyl-morpholin-2-yl)-phenol (1.33 g; 4.94 mmol) in water (10 mL) and 1,4-dioxane (10 mL) was added KOH (0.55 g; 9.88 mmol), 1-bromohexane (1.04 mL; 7.41 mmol) and tetrabutylammonium bromide (0.16 g; 0.49 mmol), the resulting mixture was heated under reflux overnight. After cooling to RT the mixture was concentrated in vacuo, and partitioned between EtOAc and 5% aqueous $NaHCO_3$ solution. The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, Et2O: hexanes 1:1) to afford 4-benzyl-2-(4-hexyloxy-phenyl)-morpholine (1.31 g).

4-Benzyl-2-(4-heptyloxy-phenyl)-morpholine was obtained according to a similar manner.

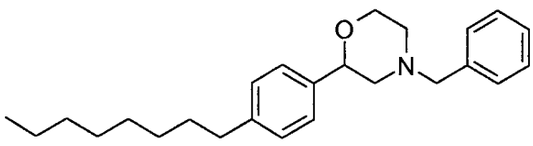


4-Benzyl-2-[3-chloro-4-(2,6-dichloro-benzyloxy)-phenyl]-morpholine: A mixture of 4-(4-benzyl-morpholin-2-yl)-2-chloro-phenol (0.50 g; 1.56 mmol), 2,6-dichlorobenzyl bromide (0.39 g; 1.64 mmol) and Cs_2CO_3 (2.55 g; 7.82 mmol) in CH_3CN (20 mL) was heated under reflux overnight. After cooling to RT the resulting mixture was partitioned between EtOAc and water. The layers were separated and the organic layer, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, CH_2Cl_2:MeOH 98:2) to afford 4-benzyl-2-[3-chloro-4-(2,6-dichloro-benzyloxy)-phenyl]-morpholine (0.74 g)

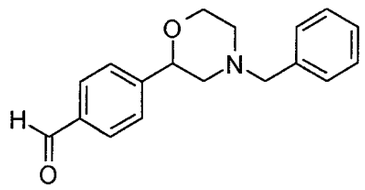
The following compounds were obtained according to a similar manner:

4-Benzyl-2-[3-chloro-4-(2-chloro-6-fluoro-benzyloxy)-phenyl]-morpholine

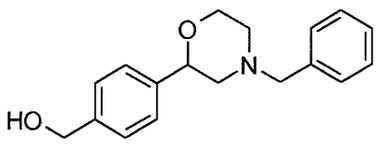
4-Benzyl-2-[3-chloro-4-(2-trifluoromethyl-benzyloxy)-phenyl]-morpholine



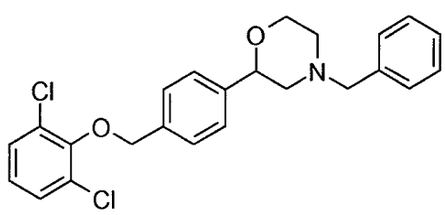
4-Benzyl-2-(4-octyl-phenyl)-morpholine: To a solution of 1-octene (2.12 mL, 13.5 mmol) in THF (50 mL) was added 9-BBN (4.3g, 17,6 mmol), at 0°C. The reaction mixture was allowed to warm to RT and stirred overnight. Subsequently, K_3PO_4 (7.6 g, 35.8 mmol) was added, followed, after 45 minutes, by 4-benzyl-6-(4-bromo-phenyl)-morpholine (3.0 g, 9 mmol), palladium(II) acetate (80mg; 4mol%), and dicyclohexyl-(2',6'-dimethoxy-biphenyl-2-yl)-phosphane (296mg; 8mol%). The resulting mixture was heated under reflux for 2 hours. After cooling to RT the mixture was concentrated in vacuo, the residue dissolved in EtOAc, and washed with 5% aqueous $NaHCO_3$ solution. The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, Et_2O: hexanes, 1:1) to afford 4-benzyl-2-(4-octyl-phenyl)-morpholine (2.58g).



4-(4-Benzyl-morpholin-2-yl)-benzaldehyde: To a solution of 4-benzyl-6-(4-bromo-phenyl)-morpholine (1.73 g; 5.21 mmol) in THF (25 mL) was added dropwise n-BuLi (2.08 mL; 2.50 mol/l; 5.21 mmol), at -78°C. The resulting mixture was stirred for one hour, and subsequently a solution of *N*-formylmorpholine (0.90 g; 7.81 mmol) in THF (5 mL) was added dropwise, at -78°C. The reaction was quenched by the addition of an 5% aqueous $NaHCO_3$ solution, at -70°C. The resulting mixture was extracted with Et_2O. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, Et2O: hexanes 1:1) to afford 4-(4-benzyl-morpholin-2-yl)-benzaldehyde (1.21 g).



[4-(4-Benzyl-morpholin-2-yl)-phenyl]-methanol: To a solution of 4-(4-benzyl-morpholin-2-yl)-benzaldehyde (1.19 g; 4.23 mmol) in MeOH (25 mL) was added $NaBH_4$ (0.16 g; 4.23 mmol), in small portions, at 0°C. After the addition was complete the mixture was allowed to warm to RT and stirred for one hour. Subsequently, the mixture was cooled to 0°C, water was added, and the MeOH evaporated in vacuo. To the aqueous solution was added a 5% aqueous $NaHCO_3$ solution and EtOAc. The layers were separated and the organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo to afford [4-(4-benzyl-morpholin-2-yl)-phenyl]-methanol (1.16 g) which was used as such.

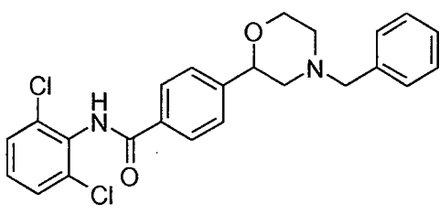


4-Benzyl-2-[4-(2,6-dichloro-phenoxymethyl)-phenyl]-morpholine: To a solution of 2,6-dichlorophenol (0.68 g; 4.19 mmol) in THF (20 mL) was added DIAD (1.13 mL; 5.72 mmol), and triphenylphosphine (1.50 g; 5.72 mmol), at RT, followed, after 30 minutes, by [4-(4-benzyl-morpholin-2-yl)-phenyl]-methanol (1.08 g; 3.81 mmol).

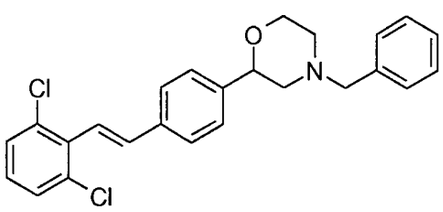
Subsequently, the resulting mixture was stirred at RT for 1 hour, and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, Et_2O: hexanes 1:1) to afford 4-benzyl-2-[4-(2,6-dichloro-phenoxymethyl)-phenyl]-morpholine (2.35 g) which was used as such in the next step.

The following compound was obtained according to a similar manner:

4-Benzyl-2-[2-chloro-4-(2,6-dichloro-benzyloxy)-phenyl]-morpholine

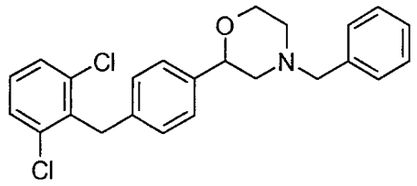


4-(4-Benzyl-morpholin-2-yl)-*N*-(2,6-dichloro-phenyl)-benzamide: To a solution of 4-benzyl-6-(4-bromo-phenyl)-morpholine (1.01 g; 3.04 mmol) in THF (25 mL) was added dropwise n-BuLi (1.2 mL; 2.5 mol/l in hexanes; 3.04 mmol), at -78°C. After 1 hour at -78°C, a solution of 2,6-dichlorophenyl isocyanate (0.63 g; 3.34 mmol) in THF (5 mL) was added dropwise. The mixture was allowed to warm to RT and then 5% aqueous $NaHCO_3$ was added. Subsequently, the mixture was extracted with Et_2O. The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography (Et_2O:hexanes 1:1) to afford 4-(4-benzyl-morpholin-2-yl)-*N*-(2,6-dichloro-phenyl)-benzamide (0.68 g).

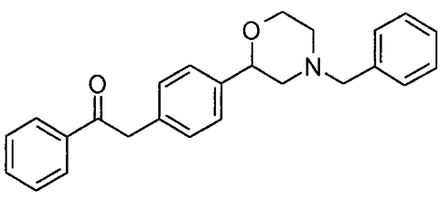


4-Benzyl-2-{4-[2-(2,6-dichloro-phenyl)-vinyl]-phenyl}-morpholine: To a suspension of (2,6-dichloro-benzyl)-triphenyl-phosphonium bromide (2.06 g; 4.1 mmol) (See: A. Schmidpeter, H. Noeth, G. Jochem, H.-P. Schroedel, K. Karaghiosoff; *Chem. Ber.*, **1995**, *128*, 379) in THF (25 mL) was added sodium hydride (60% dispersion in mineral oil) (215 mg; 4.5 mmol), at 0°C. After stirring for 1 hour, 4-(4-benzyl-morpholin-2-yl)-benzaldehyde (1.05 g; 3.7 mmol) was added, at 0 °C. Subsequently, the resulting mixture was heated under reflux for 1 hour. After cooling to RT, 5% aqueous $NaHCO_3$ was added and the mixture extracted with Et_2O. The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue

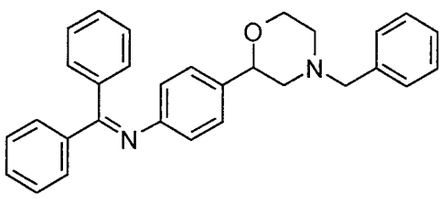
was purified by column chromatography (SiO_2, Et_2O: hexanes 1:1) to afford 4-benzyl-2-{4-[2-(2,6-dichloro-phenyl)-vinyl]-phenyl}-morpholine (1.15 g).



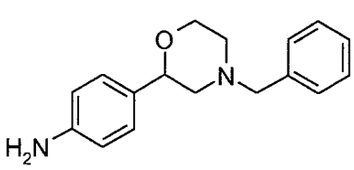
4-Benzyl-2-[4-(2,6-dichloro-benzyl)-phenyl]-morpholine: To a mixture of 2,6-dichlorobenzylzinc chloride (7.95 mL; 0.50 mol/l in THF; 3.97 mmol) and tetrakis(triphenylphosphine)palladium(0) (83.48 mg; 0.07 mmol) in THF (25 mL) was added 4-benzyl-6-(4-bromo-phenyl)-morpholine (1.20 g; 3.61 mmol) . The resulting mixture was stirred at RT for 2 hours, and subsequently heated under reflux, for 2 h. After cooling to RT the mixture was concentrated in vacuo. The residue was partitioned between 5% aqueous $NaHCO_3$ and EtOAc .The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, Et_2O: hexanes 1:1) to afford 4-benzyl-2-[4-(2,6-dichloro-benzyl)-phenyl]-morpholine (1.40 g).



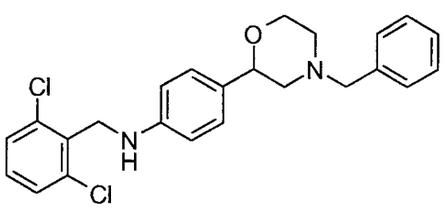
2-[4-(4-Benzyl-morpholin-2-yl)-phenyl]-1-phenyl-ethanone: To a degassed solution of 4-benzyl-2-(4-bromo-phenyl)-morpholine (205 mg; 0.62 mmol) and acetophenone (87 µL; 0.74 mmol) in toluene (4 mL) was added NaOtBu (148.3 mg; 1.54 mmol), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (38.4 mg; 0.06 mmol) and tris(dibenzylideneacetone)dipalladium(0) (28.3 mg; 0.03 mmol). The resulting mixture was heated to 110°C for 30 min. in a microwave. After cooling to room temperature 5% aqueous $NaHCO_3$ was added and the mixture extracted with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO2, Et2O / hexanes 1:1) to afford 2-[4-(4-Benzyl-morpholin-2-yl)-phenyl]-1-phenyl-ethanone (110.00 mg).



Benzhydrylidene-[4-(4-benzyl-morpholin-2-yl)-phenyl]-amine: To a degassed solution of 4-benzyl-6-(4-bromo-phenyl)-morpholine (4.00 g; 12.04 mmol) in toluene (50 mL) was added benzophenone imine (2.42 mL; 14.45 mmol), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.60 g; 0.96 mmol), tris-(dibenzylideneacetone)-dipalladium(0) (0.22 g; 0.24 mmol) and NaOtBu (1.62 g; 16.86 mmol). The resulting mixture was heated to 100°C for 16 hours. After cooling to RT a 5% aqueous $NaHCO_3$ solution was added, and the product was extracted with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, Et_2O: hexanes 1:1) to afford benzhydrylidene-[4-(4-benzyl-morpholin-2-yl)-phenyl]-amine (3.30 g).

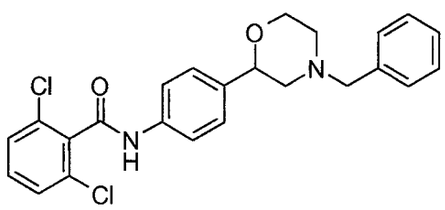


4-(4-Benzyl-morpholin-2-yl)-phenylamine: To a solution of benzhydrylidene-[4-(4-benzyl-morpholin-2-yl)-phenyl]-amine (3.30 g; 7.63 mmol) in THF (50 mL) was added hydrochloric acid (30.5 mL; 1.00 mol/L in water; 30.5 mmol). The resulting mixture was stirred overnight at RT. The reaction mixture was partitioned between 1M aqueous HCl and EtOAc. The aqueous layer was made basic with 1M aqueous NaOH (pH > 10) and extracted with EtOAc. The organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo to afford 4-(4-benzyl-morpholin-2-yl)-phenylamine (1.85 g).

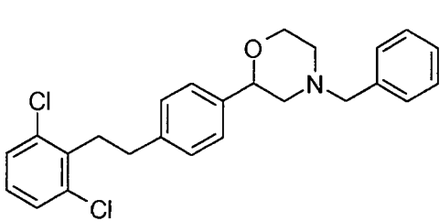


[4-(4-Benzyl-morpholin-2-yl)-phenyl]-(2,6-dichloro-benzyl)-amine: A mixture of 4-(4-benzyl-morpholin-2-yl)-phenylamine (0.82 g; 3.06 mmol), DIPEA (1.57 mL; 9.17

mmol) and 2,6-dichlorobenzyl bromide (0.88 g; 3.67 mmol) in MeOH (25 mL). was stirred at RT, overnight. The resulting mixture was partitioned between 5% aqueous $NaHCO_3$ and EtOAc. The organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo to afford [4-(4-benzyl-morpholin-2-yl)-phenyl]-(2,6-dichloro-benzyl)-amine (1.25 g).

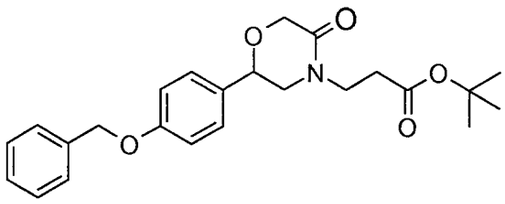


***N*-[4-(4-Benzyl-morpholin-2-yl)-phenyl]-2,6-dichloro-benzamide:** To a mixture of 4-(4-benzyl-morpholin-2-yl)-phenylamine (0.48 g; 1.8 mmol), and *N*-ethyldiisopropylamine (0.92 mL; 5.4 mmol) in CH_3CN (10 mL) was added 2,6-dichlorobenzoyl chloride (0.31 mL; 2.2 mmol), at 0°C. The resulting mixture was allowed to warm to RT, stirred for 1 h, and partitioned between Et_2O and 5% aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, Et_2O) to afford *N*-[4-(4-benzyl-morpholin-2-yl)-phenyl]-2,6-dichloro-benzamide (0.61 g).

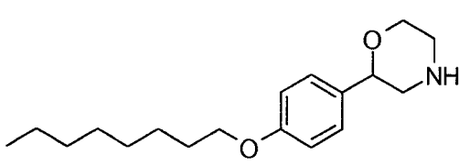


4-Benzyl-2-{4-[2-(2,6-dichloro-phenyl)-ethyl]-phenyl}-morpholine: To a degassed solution of potassium [2-(2,6-dichlorophenyl)ethyl]trifluoroborate (0.28 g; 1 mmol) and potassium phosphate tribasic (0.58 g; 2.7 mmol) in toluene (20 mL) and water (4 mL) was added 4-benzyl-6-(4-bromo-phenyl)-morpholine (0.30 g; 0.90 mmol), palladium(II) acetate (6.1 mg; 0.03 mmol), and 2-dicyclohexylphosphino-2',6'-diisopropoxy-1,1'-biphenyl (25.3 mg; 0.05 mmol). The resulting mixture was heated under reflux, overnight. After cooling to RT, the mixture was concentrated in vacuo and partitioned between EtOAc and 5% aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, Et_2O:hexanes 1:1) to afford 4-benzyl-2-{4-[2-(2,6-dichloro-phenyl)-ethyl]-phenyl}-morpholine (0.21 g).

The required **potassium [2-(2,6-dichlorophenyl)ethyl]trifluoroborate** was prepared as follows: To a solution of 2,6-dichlorostyrene (1.58 mL; 11.6 mmol) in THF (15 mL) was added chloro(1,5-cyclooctadiene)Iridium(I) dimer (38.8 mg; 0.06 mmol), 1,2-bis(diphenylphosphino)ethane (46.1 mg; 0.12 mmol) and pinacolborane (11.6 mL; 1M in THF; 11.6 mmol). The resulting mixture was stirred at RT, overnight, subsequently, concentrated in vacuo and purified by column chromatography (SiO2, Et_2O:hexanes 1:3). The obtained product was treated with MeOH (56 mL), water (14 mL), and potassium bifluoride (3.43 g; 43.9 mmol), and stirred at RT, overnight. Subsequently, the solvents were removed in vacuo and the residue treated with toluene and concentrated in vacuo. The latter steps were repeated three times to remove all the water. The obtained solid was treated with CH_3CN, and heated at 50°C. The precipitate was removed by filtration and washed with CH_3CN. The combined CH_3CN layers were concentrated in vacuo and the residue was treated with Et_2O. The formed precipitate was collected by filtration and dried in vacuo to afford potassium [2-(2,6-dichlorophenyl)ethyl]trifluoroborate (1.12 g), which was used as such.



3-[2-(4-Benzyloxy-phenyl)-5-oxo-morpholin-4-yl]-propionic acid tert-butyl ester: To a mixture of 6-(4-benzyloxy-phenyl)-morpholin-3-one (13.40 g; 47.3 mmol) and powdered NaOH (3.78 g; 94.6 mmol) in THF (250 mL) was added tert-butyl acrylate (13.7 mL; 94.6 mmol). The resulting mixture was stirred at RT for 2 hours and subsequently concentrated in vacuo. The residue was purified by column chromatography (SiO_2, Et_2O) to afford 3-[2-(4-benzyloxy-phenyl)-5-oxo-morpholin-4-yl]-propionic acid tert-butyl ester (14.20 g).



2-(4-octyloxy-phenyl)-morpholine: To a solution of 4-benzyl-2-(4-octyloxy-phenyl)-morpholine (20.22 g; 53 mmol) in MeOH (400 mL) was added palladium hydroxide (0.74 g; 5.30 mmol). The mixture was treated with H_2, at normal pressure, overnight.

The reaction mixture was filtered over Kieselguhr. The filter-cake was washed with a solution of ammonia in MeOH. Evaporation of the solvent afforded 2-(4-octyloxy-phenyl)-morpholine (14.80 g), which was used as such in the next step.

The following compounds were obtained according to a similar manner:

3-Methyl-4-morpholin-2-yl-phenol

4-Morpholin-2-yl-phenol

2-(4-Octyl-phenyl)-morpholine

2-(4-Hexyloxy-phenyl)-morpholine

2-(4-Heptyloxy-phenyl)-morpholine

4-Morpholin-2-yl-2-trifluoromethyl-phenol

4-(2-Methyl-morpholin-2-yl)-phenol

2-Methyl-4-morpholin-2-yl-phenol

2-Methoxy-4-morpholin-2-yl-phenol

4-(5,5-Dimethyl-morpholin-2-yl)-phenol

4-Morpholin-2-yl-3-trifluoromethyl-phenol

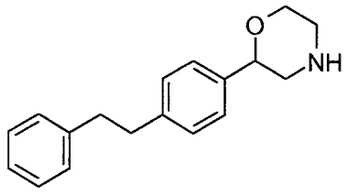
3-Fluoro-4-morpholin-2-yl-phenol

3-[2-(4-Hydroxy-phenyl)-5-oxo-morpholin-4-yl]-propionic acid tert-butyl ester:

4-(6,6-Dimethyl-morpholin-2-yl)-phenol

3-Morpholin-2-yl-phenol

6-Morpholin-2-yl-pyridin-3-ol



2-(4-Phenethyl-phenyl)-morpholine: A mixture of 4-benzyl-2-{4-[2-(2,6-dichloro-phenyl)-vinyl]-phenyl}-morpholine (0.54 g; 1.27 mmol) and palladium hydroxide (0.04 g; 0.25 mmol) in MeOH (25 mL) was treated with H_2, at normal pressure, overnight. The resulting mixture was filtered over Kieselguhr and the solvents evaporated to afford 2-(4-phenethyl-phenyl)-morpholine (0.34 g).

(+)-2-(4-octyloxy-phenyl)-morpholine and (-)-2-(4-octyloxy-phenyl)-morpholine: Racemic **2-(4-octyloxy-phenyl)-morpholine** was separated into both optical isomers by preparative chiral HPLC, at RT on a CHIRALPAK® IA 20 μm - 250 x 76

mm column, with as mobile phase 99.9% CH_3CN / 0.1% diethylamine (v/v) at a flow rate of 270 mL/min., and with UV-detection at 240 nm. This afforded after evaporation of the solvents **(+)-2-(4-octyloxy-phenyl)-morpholine** (e.e. 98.3%; $[\alpha]_D^{25}$ = +24 (*c* 1.0, MeOH)) and **(-)-2-(4-octyloxy-phenyl)-morpholine** (e.e. 99.0%, $[\alpha]_D^{25}$ = -28 (*c* 1.0, MeOH)).

2-[4-(2,6-Dichloro-phenoxymethyl)-phenyl]-morpholine: To a solution of 4-benzyl-2-[4-(2,6-dichloro-phenoxymethyl)-phenyl]-morpholine (2.25 g; 3.7 mmol) in 1,2-dichloroethane (10 mL), was added dropwise 1-chloroethyl chloroformate (0.44 mL; 4.0 mmol), at 0°C. After 15 minutes, the cooling was removed and subsequently the mixture was heated under reflux overnight. After cooling to RT the mixture was concentrated in vacuo. To the residue was added toluene and the mixture was concentrated in vacuo. This last step was repeated twice. To the final residue was added MeOH (10 mL), and this mixture was stirred overnight at RT. Once more the mixture was concentrated in vacuo. The residue was partitioned between EtOAc and 2 M Aqueous NaOH. The layers were separated, and the organic layer dried (Na_2SO_4), filtered, and concentrated in vacuo to afford 2-[4-(2,6-Dichloro-phenoxymethyl)-phenyl]-morpholine (0.98 g), which was used as such in the next step.

The following compounds were obtained according to a similar manner:

***N*-(2,6-Dichloro-phenyl)-4-morpholin-2-yl-benzamide**

2-{4-[2-(2,6-Dichloro-phenyl)-vinyl]-phenyl}-morpholine

(2,6-Dichloro-benzyl)-(4-morpholin-2-yl-phenyl)-amine

2,6-Dichloro-*N*-(4-morpholin-2-yl-phenyl)-benzamide

2-{4-[2-(2,6-Dichloro-phenyl)-ethyl]-phenyl}-morpholine

2-[4-(2,6-dichloro-benzyl)-phenyl]-morpholine

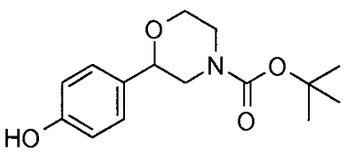
2-[3-Chloro-4-(2,6-dichloro-benzyloxy)-phenyl]-morpholine

2-[3-Chloro-4-(2-chloro-6-fluoro-benzyloxy)-phenyl]-morpholine

2-[3-Chloro-4-(2-trifluoromethyl-benzyloxy)-phenyl]-morpholine

2-[2-Chloro-4-(2,6-dichloro-benzyloxy)-phenyl]-morpholine

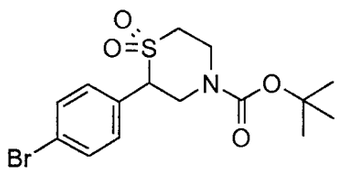
2-(4-Morpholin-2-yl-phenyl)-1-phenyl-ethanone



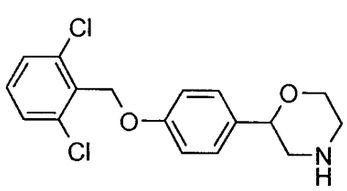
2-(4-Hydroxy-phenyl)-morpholine-4-carboxylic acid tert-butyl ester: A mixture of 4-morpholin-2-yl-phenol (0.99 g; 5.41 mmol) and di-tert-butyl dicarbonate (1.18 g; 5.41 mmol) in CH_3CN (50 mL) was stirred at RT for 3 days. Subsequently, the resulting mixture was concentrated in vacuo and the residue was purified by column chromatography (SiO_2, CH_2Cl_2:CH_3OH 97:3) to afford 2-(4-hydroxy-phenyl)-morpholine-4-carboxylic acid tert-butyl ester (1.15 g).

The following compound was obtained according to a similar manner:

2-(4-Bromo-phenyl)-thiomorpholine-4-carboxylic acid tert-butyl ester



2-(4-Bromo-phenyl)-1,1-dioxo-1λ^6-thiomorpholine-4-carboxylic acid tert-butyl ester: To a solution of 2-(4-bromo-phenyl)-thiomorpholine-4-carboxylic acid tert-butyl ester (3.60 g; 10.05 mmol) in CH_2Cl_2 (100 mL) was added 3-chloroperoxybenzoic acid (5.20 g; 30.14 mmol), at 0°C. The resulting mixture was stirred overnight at RT, and subsequently, a saturated aqueous sodium thiosulfate solution was added and the mixture stirred for another 30 min. The layers were separated and the aqueous layer was extracted twice with EtOAc. The combined EtOAc layers were washed twice with an aqueous Na_2CO_3 solution. The combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo to afford 2-(4-bromo-phenyl)-1,1-dioxo-1λ^6-thiomorpholine-4-carboxylic acid tert-butyl ester (4.06 g) which was used as such in the next step.

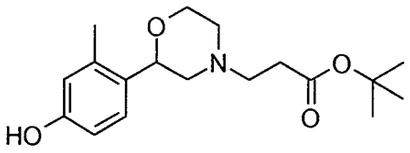


2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholine hydrochloride: Acetyl chloride (1.35 mL, 8.9 mmol) was added to ethanol (60 mL). The resulting solution was added to 2-[4-(2,6-dichloro-benzyloxy)-phenyl]-morpholine-4-carboxylic acid tert-butyl ester

(1.54 g; 3.4 mmol), at RT. The resulting mixture was stirred at 60°C for 3 hours, and subsequently, at RT for three days. The resulting suspension was concentrated in vacuo, and treated with iPr_2O. The formed precipitate was collected by filtration and dried in vacuo to afford 2-[4-(2,6-dichloro-benzyloxy)-phenyl]-morpholine hydrochloride (1.31 g).

The following compound was obtained according to a similar manner:

2-(4-Bromo-phenyl)-thiomorpholine 1,1-dioxide



3-[2-(4-Hydroxy-2-methyl-phenyl)-morpholin-4-yl]-propionic acid tert-butyl ester: A mixture of 3-methyl-4-morpholin-2-yl-phenol (14.26 g; 73.8 mmol) and tert-butyl acrylate (21.4 ml; 147.6 mmol) in CH_3CN (250 mL) was heated under reflux overnight. After cooling to RT the mixture was concentrated in vacuo, and the residue was partitioned between EtOAc and 5% aqueous $NaHCO_3$ solution. The organic layer was dried (Na_2SO_4), filtered, concentrated in vacuo, and purified by column chromatography (SiO_2, CH_2Cl_2 > Et_2O / hexanes 1:1 > Ether) to afford 3-[2-(4-hydroxy-2-methyl-phenyl)-morpholin-4-yl]-propionic acid tert-butyl ester (22.62 g).

The following compounds were obtained according to a similar manner:

3-[2-(4-Hydroxy-phenyl)-morpholin-4-yl]-propionic acid tert-butyl ester

Isomer 1 of 3-[2-(4-octyloxy-phenyl)-morpholin-4-yl]-propionic acid tert-butyl ester from (+)-2-(4-octyloxy-phenyl)-morpholine.

Isomer 2 of 3-[2-(4-octyloxy-phenyl)-morpholin-4-yl]-propionic acid tert-butyl ester from (-)-2-(4-octyloxy-phenyl)-morpholine.

3-[2-(4-Octyl-phenyl)-morpholin-4-yl]-propionic acid tert-butyl ester.

3-[2-(4-Hexyloxy-phenyl)-morpholin-4-yl]-propionic acid tert-butyl ester

3-[2-(4-Heptyloxy-phenyl)-morpholin-4yl]-propionic acid tert-butyl ester

3-[2-(4-Hydroxy-3-trifluoromethyl-phenyl)-morpholin-4-yl]-propionic acid tert-butyl ester

3-{2-[4-(2,6-Dichloro-phenylcarbamoyl)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(2,6-Dichloro-phenoxymethyl)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-(2-{4-[2-(2,6-Dichloro-phenyl)-vinyl]-phenyl}-morpholin-4-yl)-propionic acid tert-butyl ester

3-[2-(4-Phenethyl-phenyl)-morpholin-4-yl]-propionic acid tert-butyl ester

3-{2-[4-(2,6-Dichloro-benzylamino)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(2,6-Dichloro-benzoylamino)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-[2-(4-Hydroxy-phenyl)-2-methyl-morpholin-4-yl]-propionic acid tert-butyl ester.

3-(2-{4-[2-(2,6-Dichloro-phenyl)-ethyl]-phenyl}-morpholin-4-yl)-propionic acid tert-butyl ester.

3-[2-(4-Hydroxy-3-methyl-phenyl)-morpholin-4-yl]-propionic acid tert-butyl ester.

3-[2-(4-Hydroxy-3-methoxy-phenyl)-morpholin-4-yl]-propionic acid tert-butyl ester.

3-{2-[4-(2,6-Dichloro-benzyl)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester.

3-[2-(4-Hydroxy-phenyl)-5,5-dimethyl-morpholin-4-yl]-propionic acid tert-butyl ester.

3-[2-(4-Hydroxy-2-trifluoromethyl-phenyl)-morpholin-4-yl]-propionic acid tert-butyl ester

3-[2-(2-Fluoro-4-hydroxy-phenyl)-morpholin-4-yl]-propionic acid tert-butyl ester

3-[6-(4-Hydroxy-phenyl)-2,2-dimethyl-morpholin-4-yl]-propionic acid tert-butyl ester

3-{2-[3-Chloro-4-(2,6-dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[3-Chloro-4-(2-chloro-6-fluoro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[3-Chloro-4-(2-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-[2-(3-Hydroxy-phenyl)-morpholin-4-yl]-propionic acid tert-butyl ester

3-{2-[2-Chloro-4-(2,6-dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

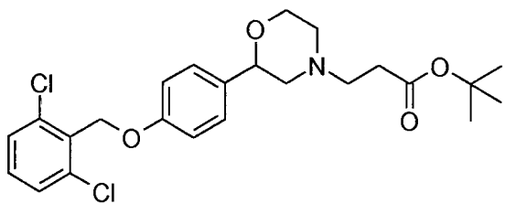
3-[2-(4-Bromo-phenyl)-thiomorpholin-4-yl]-propionic acid tert-butyl ester

3-[2-(4-Bromo-phenyl)-1,1-dioxo-1λ^6-thiomorpholin-4-yl]-propionic acid tert-butyl ester

3-[2-(5-Hydroxy-pyridin-2-yl)-morpholin-4-yl]-propionic acid tert-butyl ester

3-{2-[4-(2-Oxo-2-phenyl-ethyl)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionitrile using acrylonitrile instead of tert-butyl acrylate.



3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester: A mixture of 3-[2-(4-hydroxy-phenyl)-morpholin-4-yl]-propionic acid tert-butyl ester (5.00 g; 16.3 mmol) and K_2CO_3 (6.74 g; 48.8 mmol) in CH_3CN (100 mL) was stirred for one hour at RT. Subsequently 2,6-dichlorobenzyl bromide (4.29 g; 17.9 mmol) was added and the resulting mixture was stirred overnight at RT. The reaction mixture was partitioned between EtOAc (250 mL) and 5% aqueous $NaHCO_3$ solution (100 mL). The layers were separated and the organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO2, Et_2O /hexanes 1:1) to afford 3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester (7.40 g).

The following compounds were obtained according to a similar manner:

3-(2-(4-octyloxy-phenyl)-morpholin-4-yl)-propionic acid tert-butyl ester

3-{2-[4-(2-Chloro-6-fluorobenzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(2,6-Difluoro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(2-Trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(3-Trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(2,6-Dichloro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(2,6-Dichloro-benzyloxy)-3-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-methyl-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(2-Chloro-6-fluoro-benzyloxy)-phenyl]-2-methyl-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(2-Trifluoromethyl-benzyloxy)-phenyl]-2-methyl-morpholin-4-yl}-propionic acid tert-butyl ester

3-[2-Methyl-2-(4-octyloxy-phenyl)-morpholin-4-yl]-propionic acid tert-butyl ester

2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholine-4-carboxylic acid tert-butyl ester

3-{2-[3-Methoxy-4-(2-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(2-Chloro-6-fluoro-benzyloxy)-3-methoxy-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(2,6-Dichloro-benzyloxy)-3-methoxy-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[3-Methyl-4-(2-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(2-Chloro-6-fluoro-benzyloxy)-3-methyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(2,6-Dichloro-benzyloxy)-3-methyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester3-{2-[4-(2-Chloro-5-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(2-Chloro-3-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(2-Chloro-6-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(3-Phenyl-allyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-5-oxo-morpholin-4-yl}-propionic acid tert-butyl ester

3-[2-(4-Octyloxy-phenyl)-5-oxo-morpholin-4-yl]-propionic acid tert-butyl ester

3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-5,5-dimethyl-morpholin-4-yl}-propionic acid tert-butyl ester

3-[5,5-Dimethyl-2-(4-octyloxy-phenyl)-morpholin-4-yl]-propionic acid tert-butyl ester

3-{6-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2,2-dimethyl-morpholin-4-yl}-propionic acid tert-butyl ester

3-[2,2-Dimethyl-6-(4-octyloxy-phenyl)-morpholin-4-yl]-propionic acid tert-butyl ester

3-{2-[4-(2-Chloro-6-fluoro-benzyloxy)-2-fluoro-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[2-Fluoro-4-(2-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(2,6-Dichloro-benzyloxy)-2-fluoro-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

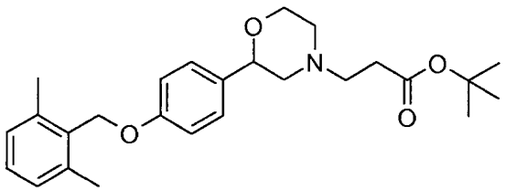
3-{2-[4-(2,6-Dichloro-benzyloxy)-2-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-[2-(4-Octyloxy-2-trifluoromethyl-phenyl)-morpholin-4-yl]-propionic acid tert-butyl ester

3-{2-[4-(2,6-Dichloro-3-ethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester. The required **2-bromomethyl-1,3-dichloro-4-ethyl-benzene** was prepared as follows: To a mixture of 2',4'-dichloroacetophenone (4.85 g; 25.66 mmol) suspended in diethylene glycol (20 mL) was added KOH (2.37 g; 35.92 mmol) and hydrazine hydrate (2.9 mL). The resulting mixture was heated at 100°C (for 1 hour) and subsequently overnight, at 200°C. After cooling to RT, the mixture was partitioned between Et_2O and water. The layers were separated and the organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, hexanes) to afford the product: 2,4-dichloro-1-ethylbenzene (2.24 g). To a solution 2,2,6,6-tetramethylpiperidine (2.36 mL; 14 mmol), dissolved in THF (40 ml) was added a solution of n-BuLi in hexanes (5.6 mL; 2.50 mol/l; 14 mmol), at -78°C. The reaction mixture was stirred for 90 minutes, allowing the temperature to reach 0°C. Subsequently, a solution of 2,4-dichloro-1-ethylbenzene (2.23 g; 12.74 mmol), dissolved in THF (5 mL) was added at -78°C. The resulting mixture was stirred for 2.5 hours. Subsequently, DMF (1.48 mL; 19.11 mmol) was added dropwise and the resulting mixture was stirred for 30 minutes. The reaction was quenched by the addition of a saturated aqueous NH_4Cl solution, at -50°C. The resulting mixture was extracted with Et_2O. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo to afford the crude 2,6-dichloro-3-ethylbenzaldehyde, which was redissolved in MeOH (100 mL). Subsequently, $NaBH_4$ (1.45 g; 38.22 mmol) was added, in small portions, at 0°C. After the addition was complete the mixture was allowed to warm to RT and stirred for one hour. Subsequently, the mixture was cooled to 0°C, water was added, and

the MeOH evaporated in vacuo. To the aqueous solution was added a 5% aqueous $NaHCO_3$ solution and Et_2O. The layers were separated and the organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, Et_2O:hexanes 1:7 followed by 1:1) to afford (2,6-dichloro-3-ethylphenyl)methanol (2.11 g). To a solution of (2,6-dichloro-3-ethylphenyl)methanol (0.79 g; 3.85 mmol) in Et_2O (25 mL) was added dropwise PBr_3 (0.47 ml; 5.01 mmol), at 0°C, and the resulting mixture was stirred overnight, at RT. Subsequently, water was added, at 0°C, followed by EtOAc en 5% aqueous $NaHCO_3$. The layers were separated and the organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo to afford 2-bromomethyl-1,3-dichloro-4-ethyl-benzene (0.57 g), which was used as such.

(+)-3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester and **(-)-3-{2-[4-(2,6-dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester**: Racemic 3-{2-[4-(2,6-dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester (7.1 gram) was separated into both optical isomers by preparative chiral HPLC, at 24°C on a CHIRALPAK® T304 20 µm - 270 x 110 mm column, with as mobile phase 60% n-heptane / 40% isopropanol (v/v) at a flow rate of 570 mL/min., and with UV-detection at 225 nm. This afforded after evaporation of the solvents **(+)-3-{2-[4-(2,6-dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester** (3.38 g; e.e. >99.5%, $[\alpha]_D^{25}$ = +13 (*c* 1.0, MeOH)). and **(-)-3-{2-[4-(2,6-dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester** (3.38 g; e.e. 99.0%, $[\alpha]_D^{25}$ = -12 (*c* 1.0, MeOH)).



3-{2-[4-(2,6-Dimethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester: To a solution of 3-[2-(4-hydroxy-phenyl)-morpholin-4-yl]-propionic acid tert-butyl ester (0.45 g; 1.5 mmol) in THF (10 mL) was added 2,6-dimethylbenzyl alcohol (0.22 g; 1.6 mmol), followed by DIAD (0.43 mL; 2.2 mmol) and triphenylphosphine (0.58 g; 2.2 mmol). The resulting mixture was stirred at RT for 3 days. Subsequently, the reaction mixture was concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, Et_2O: hexanes 2:1) to afford 3-{2-[4-

(2,6-dimethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester (0.38 g).

The following compounds were obtained according to a similar manner:

3-{2-[4-(3,5-Dichloro-pyridin-4-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-(2-{4-[1-(2,6-Dichloro-phenyl)-ethoxy]-phenyl}-morpholin-4-yl)-propionic acid tert-butyl ester.

3-{2-[4-(2,3-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester.

3-{2-[4-(2,3,6-Trichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester.

3-{2-[4-(2-Chloro-6-methyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester.

3-{2-[4-(2,4-Dichloro-pyridin-3-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester. The required **(2,4-dichloro-pyridin-3-yl)-methanol** was prepared as follows: To a solution of 2,4-dichloropyridine (3.00 mL; 27.8 mmol) in THF (25 mL) was added dropwise a solution of LDA (15.3 mL; 2.00 mol/l in THF/heptane/ethylbenzene; 30.6 mmol), at -78°C. The resulting mixture was stirred at -78°C for 1 h. Subsequently, a solution of ethyl chloroformate (3.2 mL; 33.33 mmol) in THF (5 mL), was added dropwise, at -78°C and the mixture was stirred for another 1 h at the same temperature. To the resulting mixture was added 5% aqueous $NaHCO_3$-solution, dropwise, at -78°C. The mixture was allowed to warm to RT and extracted with EtOAc. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, Et_2O: hexanes 1:3) to afford 2,4-dichloro-nicotinic acid ethyl ester (2.45 g). To a solution of 2,4-dichloro-nicotinic acid ethyl ester (2.35 g; 10.68 mmol) in THF (50 mL) was added dropwise diisobutylaluminum hydride (32.0 mL; 1.00 mol/l in THF, 32.0 mmol), at 4°C. After 15 minutes the ice-bath was removed and the reaction mixture was stirred at RT overnight. Subsequently, the resulting mixture was concentrated in vacuo and partitioned between 5% aqueous $NaHCO_3$ and EtOAc. The layers were separated and the organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography (Et_2O: hexanes 1:1) to afford (2,4-dichloro-pyridin-3-yl)-methanol (0.40 g).

3-{2-[4-(2-Chloro-5-methyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester. The required **(2-chloro-5-methylphenyl)methanol** was prepared as follows: To a solution of 2-chloro-5-methylbenzoic acid (2.05 g; 12.2 mmol) in THF

(20 mL) was added BH_3·THF complex in THF (1 mol/l, 24.0 mL; 24.0 mmol) dropwise and subsequently stirred for 2 hours at 60°C. To the reaction mixture was added 1 M aqueous HCl (30 mL), at 0°C, and the resulting mixture was stirred at RT for 10 minutes. The resulting mixture was concentrated in vacuo and the residue was partitioned between EtOAc and 5% aqueous $NaHCO_3$-solution. The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo to afford the product (1.8 g), which was used as such in the next step.

3-{2-[4-(2-Chloro-5-ethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester. The required (2-chloro-5-ethylphenyl)methanol was prepared as follows: To a nitrogen purged solution of ethyl 5-bromo-2-chlorobenzoate (4.3 mL, 25.1 mmol) in THF (100 mL) was added lithium chloride (2.12 g, 50.1 mmol) and $Pd(dppf)Cl_2$ (0.82 g, 1 mmol). Subsequently, the mixture was cooled to -78°C, and a solution of diethylzinc in heptane (37.6 mL; 1.00 mol/l; 37.6 mmol) was added dropwise. The reaction mixture was allowed to come to RT overnight. The resulting reaction mixture was cooled to -10°C and diluted with Et_2O (300 mL). Subsequently, a 1 M aqueous HCl solution (150 mL) was added carefully. The layers were separated, and the organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, Et_2O:hexanes 5:95) to afford ethyl 2-chloro-5-ethylbenzoate (4.61 g). To a nitrogen purged solution of ethyl 2-chloro-5-ethyl-benzoate (1 g, 4.70 mmol) in THF (25 mL), was added diisobutylaluminiumhydride (14.11 mL; 14.11 mmol) in toluene, at -5°C,. The reaction mixture was allowed to come to RT and stirred overnight. The resulting reaction mixture was cooled to -10°C and a 5% aqueous $NaHCO_3$-solution (10 mL) was added. The layers were separated, and the organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, Et_2O:hexanes 1:3 followed by Et_2O:hexanes 1:1) to afford (2-chloro-6-ethylphenyl)methanol (0.59 g) which was used as such.

3-{2-[4-(2-Chloro-5-propyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester. The required **(2-chloro-5-propylphenyl)methanol** was prepared in a similar way as described for (2-chloro-5-ethylphenyl)methanol using *N*-propylzinc bromide instead of diethylzinc.

3-{2-[4-(2-Chloro-5-isopropyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester. The required **(2-chloro-5-isopropylphenyl)methanol** was prepared in a similar way as described for (2-chloro-5-ethylphenyl)methanol using diisopropyl zinc instead of diethylzinc.

3-{2-[4-(2,4,6-Trichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester.

3-{2-[4-(2,6-Dichloro-4-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester. The required **[2,6-dichloro-4-(trifluoromethyl)-phenyl]methanol** was prepared as follows: To a solution of 1,3-dichloro-5-(trifluoromethyl)benzene (4.73 g; 22 mmol) in THF (40 mL) was added n-BuLi in hexanes (8 mL; 2.50 mol/l; 20 mmol), at -78°C. The resulting mixture was stirred for 15 minutes and poured onto dry ice in THF. The reaction mixture was acified to pH = 3 (with 5 M aqueous HCl solution) and extracted with EtOAc. The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH 8:2) to afford 2,6-dichloro-4-(trifluoromethyl)benzoic acid (1.2 g). To a solution of this 2,6-dichloro-4-(trifluoromethyl)benzoic acid (1.7 g; 6.6 mmol) in THF (20 mL) was added dropwise a solution of borane-THF complex in THF (1 mol/l, 13.3 mL; 13.3 mmol). Subsequently, the resulting mixture was stirred overnight at 60°C. To the reaction mixture was added 1 M aqueous HCl (30 mL), at 0°C, and the resulting mixture was stirred at RT for 10 minutes. The resulting mixture was concentrated in vacuo and the residue was partitioned between EtOAc and 5% aqueous $NaHCO_3$-solution. The layers were separated and the organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, Et_2O:hexanes 1:3 followed by Et_2O:hexanes 1:1) to afford [2,6-dichloro-4-(trifluoromethyl)phenyl]-methanol (1.3 g), which was used as such in the next step.

3-{2-[4-(2,6-Dichloro-4-iodo-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester. The required **(2,6-dichloro-4-iodophenyl)methanol** was prepared as follows: To a solution of 3,5-dichloroiodobenzene (2.72 g; 10 mmol) in THF (25 mL) was added a lithium diisopropylamide solution in THF/heptane/ethylbenzene (5.5 mL; 2.00 mol/l; 11 mmol), at -78°C. The resulting mixture was stirred for 4.5 hour, at -78°C, and subsequently a solution of DMF (1.2 mL, 15 mmol) in THF (5 mL) was added dropwise, at -78°C. The resulting reaction mixture was stirred for 2 hours at -40°C. Subsequently, the reaction was quenched by the addition of an 5% aqueous NH_4Cl solution, at -20°C. The resulting mixture was extracted with Et_2O. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, Et_2O:hexanes 1:3) to afford the 2,6-dichloro-4-benzaldehyde (0.7 g, 23%). To a solution of 2,6-dichloro-4-benzaldehyde (450 mg, 1.3 mmol) in MeOH (15 mL) was added $NaBH_4$ (72.14 mg; 1.9 mmol), in small portions, at 0°C. After the addition was complete the mixture was allowed to warm to RT and stirred for one hour. Subsequently, the mixture was cooled to 0°C, water was added, and the MeOH evaporated in vacuo. To the aqueous solution was added a 5% aqueous $NaHCO_3$ solution and EtOAc. The layers

were separated and the organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by column chromatography (CH_2Cl_2/acetone 95:5) to afford (2,6-dichloro-4-iodophenyl)methanol (0.42 g) which was used as such.

3-(2-{4-[3-(2-Fluoro-phenyl)-propoxy]-phenyl}-morpholin-4-yl)-propionic acid tert-butyl ester

3-(2-{4-[3-(2-Trifluoromethyl-phenyl)-propoxy]-phenyl}-morpholin-4-yl)-propionic acid tert-butyl ester

3-(2-{4-[3-(2-Chloro-6-fluoro-phenyl)-propoxy]-phenyl}-morpholin-4-yl)-propionic acid tert-butyl ester

3-(2-{4-[3-(2,6-Dichloro-phenyl)-propoxy]-phenyl}-morpholin-4-yl)-propionic acid tert-butyl ester

3-(2-{4-[3-(4-Chloro-phenyl)-propoxy]-phenyl}-morpholin-4-yl)-propionic acid tert-butyl ester

3-(2-{4-[3-(2-Chloro-phenyl)-propoxy]-phenyl}-morpholin-4-yl)-propionic acid tert-butyl ester

3-(2-{4-[3-(2,3-Difluoro-phenyl)-propoxy]-phenyl}-morpholin-4-yl)-propionic acid tert-butyl ester

3-(2-{4-[3-(4-Chloro-phenyl)-allyloxy]-phenyl}-morpholin-4-yl)-propionic acid tert-butyl ester

3-{2-[4-(3-Phenyl-prop-2-ynyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-(2-{4-[3-(4-Chloro-phenyl)-prop-2-ynyloxy]-phenyl}-morpholin-4-yl)-propionic acid tert-butyl ester

3-{2-[4-(Indan-1-yloxy)-phenyl]-morpholin-4-yl}-propionic acid

3-{2-[4-(7-Methyl-indan-1-yloxy)-phenyl]-morpholin-4-yl}-propionic acid. The required **7-methyl-indan-1-ol** was prepared as follows: To a solution of 7-methyl-1-Indanone (0.94 g; 6.43 mmol) in EtOH (50 mL) was added $NaBH_4$ (0.78 g; 20.6 mmol), at 0°C. The resulting mixture stirred at RT overnight, subsequently water (5 mL) was added and the resulting mixture stirred for 10 min. The mixture was concentrated in vacuo, the residue was dissolved in EtOAc and washed with water and brine, dried ($MgSO_4$) filtered, and concentrated in vacuo to afford .7-methyl-indan-1-ol (0.85 g), which was used as such.

3-{2-[4-(2,3-Dihydro-benzofuran-3-yloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester. The required **2,3-dihydro-benzofuran-3-ol** was prepared according to: Ghosh, S. et al *Tetrahedron*, **1989**, *45*, 1441 – 1446.

3-{2-[4-(2,6-Dichloro-4-methyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid. The required **(2,6-Dichloro-4-methyl-phenyl)-methanol** was prepared as

follows: To 1-bromo-3,5-dichlorobenzene (2.50 g; 11.1 mmol) was added a solution of LiCl in THF (44.3 mL; 0.50 mol/l; 22.2 mmol) and $Pd(dppf)Cl_2$ (0.32 g; 0.44 mmol). The resulting mixture was cooled to -78°C and a solution of methylzinc chloride in THF (11.1 mL; 2 mol/l; 22.2 mmol) was added dropwise, subsequently the mixture was slowly heated to 50°C for 4 hours. After cooling to RT, 1M aqueous HCl and Et_2O were added and the layers were separated. The organic layer was dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, hexanes/CH_2Cl_2 95:5) to afford 1,3-dichloro-5-methyl-benzene.

To a solution of 1,3-dichloro-5-methyl-benzene (0.95 g; 5.90 mmol) in THF (20 mL) was added dropwise a solution of n-BuLi in hexane (2.4 mL; 2.5 mol/l; 6 mmol) at -78°C. After 15 min at -78°C, the resulting mixture was poured onto dry ice in THF and allowed to come to RT overnight. Subsequently the reaction mixture was acidified with 1M aqueous HCl and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo to afford 2,6-dichloro-4-methyl-benzoic acid (1.35 g), which was used as such.

To a solution of 2,6-dichloro-4-methyl-benzoic acid (1.35 g; 6.58 mmol) in THF (13.5 mL) was added dropwise a solution of BH_3·THF in THF (19.8 mL; 1.00 mol/l; 19.8 mmol), at 0°C. After complete addition the resulting mixture was heated under reflux, overnight. Subsequently, the mixture was cooled to 0°C and 1M aqueous HCl (40 mL) was added followed after 10 min. by Et_2O (100 mL). The layers were separated; the aqueous layer extracted with Et_2O, and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, Et_2O/hexanes 1:2) to afford 2,6-dichloro-4-methyl-phenyl)-methanol (0.80 g).

3-{2-[4-(2-Chloro-6-ethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester; The required **(2-chloro-6-ethyl-phenyl)-methanol** was prepared as follows: To a solution of 2-chloro-6-ethylbenzaldehyde (1.8 g, 10.67 mmol), prepared according to US2007/197621, (see also WO2007/85556 and US6380387) in MeOH (50 mL) was added $NaBH_4$ (1.21 g; 32.02 mmol), in small portions, at 0°C. After the addition was complete the mixture was allowed to warm to RT and stirred for one hour. Subsequently, the mixture was cooled to 0°C, water was added, and the MeOH evaporated in vacuo. To the aqueous solution was added a 5% aqueous $NaHCO_3$ solution and EtOAc. The layers were separated and the organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, Et_2O:hexanes 1:7 followed by Et_2O:hexanes 3:1) to afford (2-chloro-6-ethylphenyl)methanol (1.2 g).

3-{2-[4-(2-Chloro-6-isopropyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester; The required **(2-chloro-6-isopropyl-phenyl)-methanol** was obtained from a $NaBH_4$ reduction of 2-chloro-6-isopropyl-benzaldehyde in MeOH, which was prepared in a similar manner as 2-chloro-6-ethylbenzaldehyde.

3-{2-[4-(2-Chloro-6-cyclopropyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester; The required **(2-chloro-6-cyclopropyl-phenyl)-methanol** was obtained from a $NaBH_4$ reduction of 2-chloro-6-cyclooropropyl-benzaldehyde in MeOH, which was prepared in a similar manner as 2-chloro-6-ethylbenzaldehyde.

3-{2-[4-(2-Chloro-6-isobutyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester; The required **(2-chloro-6-isobutyl-phenyl)-methanol** was obtained from a $NaBH_4$ reduction of 2-chloro-6-isobutyl-benzaldehyde in MeOH, which was prepared in a similar manner as 2-chloro-6-ethylbenzaldehyde.

3-[2-(3-Benzyloxy-phenyl)-morpholin-4-yl]-propionic acid tert-butyl ester

3-[2-(3-Octyloxy-phenyl)-morpholin-4-yl]-propionic acid tert-butyl ester

3-{2-[3-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[3-(2-Chloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(2,6-Dichloro-4-prop-1-ynyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester. The required **(2,6-dichloro-4-prop-1-ynyl-phenyl)-methanol** was prepared as follows: To a degassed solution of (2,6-dichloro-4-iodophenyl)methanol (3.00 g; 9.90 mmol) in Et_3N (80 ml), in a microwave pressure file, was added CuI (0.19 g; 0.99 mmol) and $PdCl_2(PPh_3)_2$ (0.35 g; 0.50 mmol). The pressure file was flushed with nitrogen-gas and charged with propyne to a pressure of 5 bar. Subsequently, the vessel was heated in a microwave at 50°C for 15 min. and thereafter at 80°C for 10 min. After cooling to room temperature the pressure was released and the volatiles removed in vacuo. The residue was dissolved in CH_2Cl_2 and washed with water. The organic layer was concentrated in vacuo, and the residue was purified by column chromatography to afford (2,6-dichloro-4-prop-1-ynyl-phenyl)-methanol (1.79 g).

3-{2-[4-(2,6-Dichloro-4-propyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester. The required **(2,6-dichloro-4-propyl-phenyl)-methanol** was prepared as follows: A mixture of (2,6-dichloro-4-prop-1-ynyl-phenyl)-methanol (800 mg; 3.72 mmol) and Raney Nickel (20 mg) in EtOH (15 mL) was treated with hydrogen gas (1 atm.) overnight, at RT. Subsequently, the catalyst was removed by filtration and the filtrate was concentrated in vacuo to afford (2,6-dichloro-4-propyl-phenyl)-methanol (790.0 mg).

3-{2-[4-(2,6-Dichloro-4-isopropyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester. The required **(2,6-dichloro-4-isopropyl-phenyl)-methanol** was prepared from (2,6-dichloro-4-isopropenyl-phenyl)-methanol in a similar way as described for (2,6-dichloro-4-propyl-phenyl)-methanol. **(2,6-Dichloro-4-isopropenyl-phenyl)-methanol** was prepared as follows: To a degassed mixture of (2,6-dichloro-4-iodophenyl)methanol (1.50 g; 4.95 mmol), Cs_2CO_3 (9.68 g; 29.71 mmol) and 2-isopropenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.85 ml; 9.90 mmol) in 1,2-dimethoxyethane (20 mL) and water (5 mL), was added $Pd(dppf)Cl_2$ (0.36 g; 0.50 mmol). The resulting mixture was stirred at RT for three days, and subsequently EtOAc and water were added. The layers were separated and the aqueous layer was extracted twice with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, CH_2Cl_2/hexanes 2:1) to afford (2,6-dichloro-4-isopropenyl-phenyl)-methanol (0.96 g)

3-{2-[4-(2-Chloro-6-trifluoromethoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester. The required **(2-chloro-6-trifluoromethoxy-phenyl)-methanol** was prepared as follows: To a solution of 2,2,6,6-tetramethylpiperidine (2.35 ml; 14. mmol) in THF (25 mL) was added dropwise a solution of n-BuLi in hexanes (5.60 ml; 2.50 mol/l; 14 mmol), at -78°C. The resulting mixture was stirred for 60 min. at -78°C, and subsequently a solution of 3-(trifluoromethoxy)chlorobenzene (2.50 g; 12.72 mmol) in THF (10 mL), was added dropwise, at -78°C. After 2.5 hours, at -78°C, DMF (1.48 mL, 19.11 mmol) was added dropwise, and stirring was contnued for another 30 min. after which time a saturated aqueous NH_4Cl solution was added followed by the addition of Et_2O.. After warming to RT the layers were separated, and the organic layer was washed with water, dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was dissolved in MeOH (25 mL) and $NaBH_4$ (1.44 g; 38.16 mmol) was added portion wise. After complete addition the mixture was allowed to warm to RT and stirred for 30 minutes. Subsequently, water (5 mL) was added and the volatiles were removed in vacuo. Et_2O and 5% aqueous $NaHCO_3$ solution were added, and the organic layer was separated, dried (Na_2SO_4), filtered and concentrated in vacuo to afford (2-chloro-6-trifluoromethoxy-phenyl)-methanol(2.10 g), which was used as such.

3-{2-[4-(2-Chloro-4-methyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester. The required **(2-chloro-4-methyl-phenyl)-methanol** was prepared as follows: To a solution of 2-chloro-4-methylbenzoic acid (2.18 g; 12.8 mmol) in THF (22 mL) was added dropwise a solution of BH_3·THF in THF (25.6 ml; 1.00 mol/l; 25.6 mmol), at 0°C. Upon complete addition the resulting mixture was heated under reflux,

for 3 hours. Subsequently, the mixture was cooled to 0°C, 1M aqueous HCl (30 mL) was added dropwise, and the mixture was stirred for 10 min. Et_2O (100 mL) was added and the layers were separated. The organic layer was washed with 1M aqueous HCl (2x), 5% aqueous $NaHCO_3$ (2x), and brine,dried (Na_2SO_4), filtered and concentrated in vacuo to afford (2-chloro-4-methyl-phenyl)-methanol (1.80 g), which was used as such.

3-{2-[4-(2-Chloro-3-methyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester. The required **(2-Chloro-3-methyl-phenyl)-methanol** was prepared in a similar manner as described for (2-Chloro-4-methyl-phenyl)-methanol

3-{2-[4-(2,4-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester.

3-{2-[4-(4-Methoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester.

3-{2-[4-(2-Methoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester.

3-{2-[4-(4,4-Dimethyl-cyclohexyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester.

3-{2-[4-(2-Difluoromethoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester.

3-{2-[4-(2,6-Diethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester. The required **(2,6-diethyl-phenyl)-methanol** was prepared as follows: To a mixture of 2,6-difluorobenzaldehyde (25.00 g; 175.93 mmol) and p-TsOH (0.67 g; 3.52 mmol) in toluene (150 mL) was added 1-aminobutane (16.5 mL; 167.1 mmol). The resulting mixture was stirred at RT for 24 hours, subsequently, washed with 5% aqueous $NaHCO_3$ solution, water and brine, dried (Na_2SO_4), filtered and concentrated in vacuo to afford butyl-(2,6-difluoro-benzylidene)-amine (35.36 g).

To a solution of butyl-(2,6-difluoro-benzylidene)-amine (1.10 g; 5.58 mmol) in THF (25 mL) was added dropwise a solution of ethylmagnesium bromide in Et_2O (4.1 ml; 3.00 mol/l; 12.3 mmol) at -10°C. After the addition was completed the reaction mixture was stirred at RT for 4 hours. The reaction mixture was quenched by dropwise addition of a 5% aqueous $NaHCO_3$-solution, and then extracted with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo to afford butyl-(2,6-diethyl-benzylidene)-amine (1.10 g).

To a solution of butyl-(2,6-diethyl-benzylidene)-amine (1.10 g; 5.06 mmol) in water (20 mL) was added H_2SO_4 (5.00 ml; 93.80 mmol), and the resulting mixture was heated under reflux for 2 hours. After cooling to RT the mixture was diluted with EtOAc, and washed with water, a 5% aqueous $NaHCO_3$-solution and brine. The

organic phase was dried (Na_2SO_4), filtered and concentrated in vacuo to afford 2,6-diethyl-benzaldehyde (0.72 g).

To a solution of 2,6-diethyl-benzaldehyde (0.68 g; 4.19 mmol) in THF (15 mL) was added dropwise a solution of BH_3·THF in THF (8.38 ml; 1.00 mol/l; 8.38 mmol), at 0°C. After complete addition the mixture was heated under reflux for 3 hours. Subsequently, the resulting mixture was cooled to 0°C and 1M aqueous HCl (10 ml) was added dropwise. The mixture was allowed to warm to room temperature (~10 min.), and treated with Et_2O. The layers were separated, the organic layer washed with 1M aqueous HCl (2x), 5% aqueous $NaHCO_3$ (2x), and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo to afford (2,6-diethyl-phenyl)-methanol (0.67 g), which was used as such.

3-{2-[4-(3-Trifluoromethyl-benzyloxy)-2-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(2-Chloro-6-ethyl-benzyloxy)-2-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(2-Chloro-6-trifluoromethoxy-benzyloxy)-2-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(2-Chloro-6-isopropyl-benzyloxy)-2-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(2-Chloro-6-fluoro-benzyloxy)-2-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(2-Chloro-6-trifluoromethyl-benzyloxy)-2-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

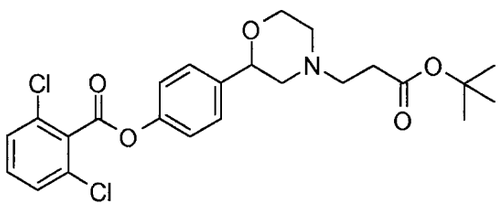
3-{2-[4-(2-Chloro-6-cyclopropyl-benzyloxy)-2-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[5-(2,6-Dichloro-benzyloxy)-pyridin-2-yl]-morpholin-4-yl}-propionic acid tert-butyl ester

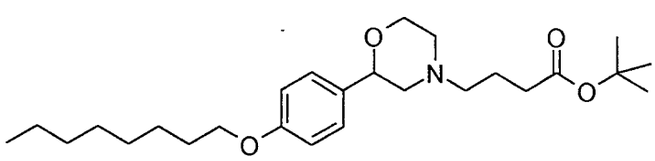
3-{2-[4-(2-Chloro-6-difluoromethoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester. The required **(2-chloro-6-difluoromethoxy-phenyl)-methanol** was prepared as follows: To a solution of 2-chloro-6-hydroxy-benzaldehyde (1.00 g; 6.39 mmol) and KOH (7.17 g; 127.7 mmol) in CH_3CN (20 mL) and water (20 mL) was added bromodifluoromethyl diethylphosphonate (1.25 ml; 7.03 mmol), at -15°C. After 30 minutes the mixture was allowed to warm to RT, stirred for another 30 min. and then treated with 1M aqueous HCl and extracted with Et_2O. The combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, Et_2O/hexanes 1:3), to afford 2-chloro-6-difluoromethoxy-benzaldehyde (0.68 g).

To a solution of 2-chloro-6-difluoromethoxy-benzaldehyde (0.65 g; 3.15 mmol) in MeOH (10 mL) was added $NaBH_4$ (357.13 mg; 9.44 mmol), at -15°C. After complete addition the mixture was allowed to warm to RT and stirred for 30 minutes. Subsequently, water (5 mL) was added and the volatiles were removed in vacuo. The residue was partitioned between Et_2O and 5% aqueous $NaHCO_3$. The layers were separated and the organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo to afford (2-chloro-6-difluoromethoxy-phenyl)-methanol (0.52 g), which was used as such.

3-{2-[4-(2-Chloro-6-difluoromethoxy-benzyloxy)-2-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester.



2,6-Dichloro-benzoic acid 4-[4-(2-tert-butoxycarbonyl-ethyl)-morpholin-2-yl]-phenyl ester : To a solution of 3-[2-(4-hydroxy-phenyl)-morpholin-4-yl]-propionic acid tert-butyl ester (0.39 g; 1.27 mmol) and *N*-ethyldiisopropylamine (0.65 mL, 3.81 mmol) in CH_3CN (5 mL) was added 2,6-dichlorobenzoyl chloride (0.44 ml; 3.0 mmol), at 0°C. Subsequently, the mixture was allowed to warm to RT and was stirred for 2 days at roomtemperature. The resulting mixture was partitioned between Et_2O and 5% aqueous $NaHCO_3$ solution. The layers were separated and the organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, Et_2O to afford 2,6-dichloro-benzoic acid 4-[4-(2-tert-butoxycarbonyl-ethyl)-morpholin-2-yl]-phenyl ester (0.51 g).



4-[2-(4-Octyloxy-phenyl)-morpholin-4-yl]-butyric acid tert-butyl ester: 2-(4-Octyloxy-phenyl)-morpholine (1.50 g; 5.2 mmol), 4-bromo-butyric acid tert-butyl ester (1.38 g; 6.2 mmol) (prepared according to C. Morin, M. Vidal *Tetrahedron*, **1992**,

48(42), 9277), potassium iodide (1.03 g; 6.2 mmol), K_2CO_3 (1.42 g; 10.29 mmol), and CH_3CN (15 mL) were mixed and heated under reflux for 2 hours. After cooling to RT the reaction mixture was concentrated in vacuo, dissolved in EtOAc, washed with 5% aqueous $NaHCO_3$ solution, dried (Na_2SO_4) concentrated in vacuo and purified by column chromatography (SiO_2, Et_2O: hexanes 1:1) to afford 4-[2-(4-octyloxy-phenyl)-morpholin-4-yl]-butyric acid tert-butyl ester (1.90 g), TLC (SiO_2 R_f 0.20 EtOAc:hexanes 1:1)

The following compounds were obtained according to a similar manner:

4-[2-(4-Octyl-phenyl)-morpholin-4-yl]-butyric acid tert-butyl ester

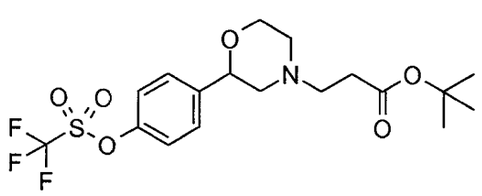
4-[2-(4-Hexyloxy-phenyl)-morpholin-4-yl]-butyric acid tert-butyl ester

4-[2-(4-Heptyloxy-phenyl)-morpholin-4-yl]-butyric acid tert-butyl ester

{3-[2-(4-Octyloxy-phenyl)-morpholin-4-yl]-propyl}-phosphonic acid diethyl ester

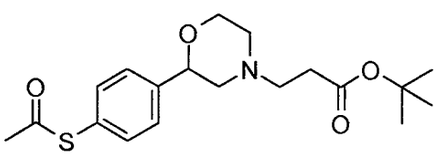
4-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-butyric acid tert-butyl ester

2,2-Dimethyl-3-(2-(4-octyloxy-phenyl)-morpholin-4-yl)-propionic acid tert-butyl ester The required **3-Chloro-2,2-dimethyl-propionic acid tert-butyl ester** was prepared as follows: To a solution of 3-chloro-2,2-dimethylpropionic acid (5.00 g; 36.6 mmol) in DMF (25 mL) was added *N,N'*-carbonyldiimidazole (5.94 g; 36.6 mmol) and the resulting mixture was stirred for 1 hour at 40°C. Subsequently, tert-butyl alcohol (7.1 mL; 73 mmol) and DBU (5.5 mL; 36.6 mmol) were added and the mixture stirred overnight at 40°C. After cooling to RT, 5% aqueous $NaHCO_3$ solution (50 mL) was added to the mixture and stirred for another 15 minutes. The reaction mixture was extracted with EtOAc. The organic layer was dried (Na_2SO_4), concentrated in vacuo and purified by column chromatography (SiO_2, Et_2O: hexanes 1:1) to afford 3-chloro-2,2-dimethyl-propionic acid tert-butyl ester (3.34 g).

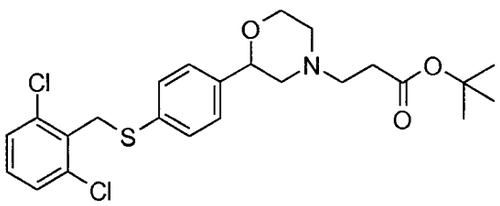


3-[2-(4-Trifluoromethanesulfonyloxy-phenyl)-morpholin-4-yl]-propionic acid tert-butyl ester: To a solution of -[2-(4-hydroxy-phenyl)-morpholin-4-yl]-propionic acid tert-butyl ester (2.07 g; 6.73 mmol) in $CHCl_3$ (50 mL) was added Et_3N (1.40 ml; 10.10 mmol), DMAP (82.3 mg; 0.67 mmol) and *N*-phenylbis(trifluoromethane-

sulfonimide) (2.89 g; 8.08 mmol). The resulting mixture was heated at 60°C for 3 hours. After cooling to RT the mixture was washed with 5% aqueous Na_2CO_3 and water. The organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, Et_2O) to afford 3-[2-(4-trifluoromethanesulfonyloxy-phenyl)-morpholin-4-yl]-propionic acid tert-butyl ester (2.30 g).



3-[2-(4-Acetylsulfanyl-phenyl)-morpholin-4-yl]-propionic acid tert-butyl ester: To a degassed solution of 3-[2-(4-trifluoromethanesulfonyloxy-phenyl)-morpholin-4-yl]-propionic acid tert-butyl ester (2.55 g; 5.80 mmol) in toluene (50 mL) was added Pd_2dba_3 (0.27 g; 0.29 mmol) and (2*R*)-1-[(1*R*)-1-[bis(1,1-dimethylethyl)phosphino]-ethyl]-2-(dicyclohexylphosphino)ferrocene (0.32 g; 0.58 mmol), followed, after 5 min. by ,potassium thioacetate (1.33 g; 11.6 mmol). The resulting mixture was heated under reflux overnight. After cooling to RT the mixture was diluted with CH_2Cl_2, filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, CH_2Cl_2/acetone 95:5) to afford 3-[2-(4-Acetylsulfanyl-phenyl)-morpholin-4-yl]-propionic acid tert-butyl ester (1.70 g)



3-{2-[4-(2,6-Dichloro-benzylsulfanyl)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester: A mixture of 3-[2-(4-Acetylsulfanyl-phenyl)-morpholin-4-yl]-propionic acid tert-butyl ester (0.31 g; 0.85 mmol) and NaOH (37 mg, 0.93 mmol) in EtOH (10 mL) and water (1 mL) was stirred for 30 min at 0°C. Subsequently, 2,6-dichlorobenzyl bromide (0.22 g; 0.93 mmol), dissolved in EtOH (2.5 mL), was added, and the mixture allowed to warm to RT. After 90 min. the mixture was partitioned between EtOAc and 5% aqueous $NaHCO_3$. The layers were separated, and the organic layer was washed with 5% aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2,

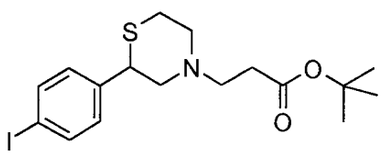
CH_2Cl_2/acetone 95:5) to afford 3-{2-[4-(2,6-dichloro-benzylsulfanyl)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester (0.20 g).

The following compounds were obtained according to a similar manner:

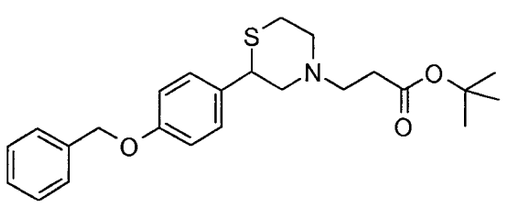
3-{2-[4-(2-Chloro-benzylsulfanyl)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester.

3-{2-[4-(2-Chloro-6-fluoro-benzylsulfanyl)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester.

3-[2-(4-Octylsulfanyl-phenyl)-morpholin-4-yl]-propionic acid tert-butyl ester.



3-[2-(4-Iodo-phenyl)-thiomorpholin-4-yl]-propionic acid tert-butyl ester: To a solution of 3-[2-(4-bromo-phenyl)-thiomorpholin-4-yl]-propionic acid tert-butyl ester (22.15 g; 57.33 mmol) 1,4-dioxane (250 mL) was added *N,N'*-dimethylethylene-diamine (3.05 mL; 28.67 mmol). Through the resulting mixture was bubled nitrogen gas for 1 hour, and subsequently CuI (1.09 g; 5.73 mmol), and NaI (21.48 g; 143.33 mmol) were added. The resulting mixture was heated at 130°C in a closed vessel for 4 days. After cooling to RT the mixture was concentrated in vacuo, and the residue purified by column chromatography (SiO_2, Et_2O/hexanes 2:3) to afford 3-[2-(4-iodo-phenyl)-thiomorpholin-4-yl]-propionic acid tert-butyl ester (19.30 g)



3-[2-(4-Benzyloxy-phenyl)-thiomorpholin-4-yl]-propionic acid tert-butyl ester: (All solutions were degassed) To a suspension of 1,10-phenanthroline (183.0 mg; 1.02 mmol) in toluene (15 mL) was added CuI (96.7 mg; 0.51 mmol), Cs_2CO_3 (3.31 g; 10.15 mmol), and a solution of 3-[2-(4-iodo-phenyl)-thiomorpholin-4-yl]-propionic acid tert-butyl ester (2.20 g; 5.08 mmol) and benzyl alcohol (1.05 mL; 10.15 mmol) in toluene (20 mL). The resulting mixture was heated for three days at 100°C. After cooling to RT EtOAc and water were added. The layers were separated and the

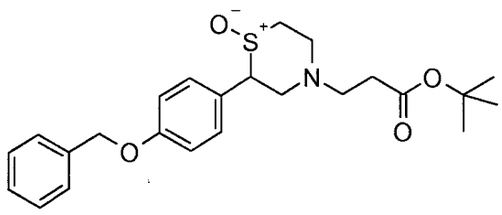
organic layer was dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, EtOAc/CH_2Cl_2 1:6) to afford 3-[2-(4-benzyloxy-phenyl)-thiomorpholin-4-yl]-propionic acid tert-butyl ester (1.85 g).

The following compounds were obtained according to a similar manner:

3-{2-[4-(2-Chloro-benzyloxy)-phenyl]-thiomorpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-thiomorpholin-4-yl}-propionic acid tert-butyl ester

3-[2-(4-Octyloxy-phenyl)-thiomorpholin-4-yl]-propionic acid tert-butyl ester



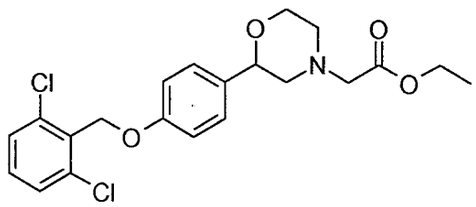
3-[2-(4-Benzyloxy-phenyl)-1-oxo-thiomorpholin-4-yl]-propionic acid tert-butyl ester: To a solution of 3-[2-(4-benzyloxy-phenyl)-thiomorpholin-4-yl]-propionic acid tert-butyl ester (0.85 g; 1.77 mmol) in MeOH (25 mL) was added dropwise a solution of oxone® (0.54 g; 0.89 mmol) in water (25 mL), at 0°C. The resulting mixture was stirred for 2 hours at 0°C, and subsequently, overnight at RT. The resulting mixture was treated with water and a 25% aqueous solution of NH_4OH, and extracted with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH 97.5:2.5) to afford 3-[2-(4-benzyloxy-phenyl)-1-oxo-thiomorpholin-4-yl]-propionic acid tert-butyl ester (0.65 g).

The following compounds were obtained according to a similar manner:

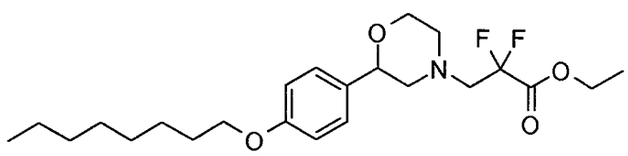
3-{2-[4-(2-Chloro-benzyloxy)-phenyl]-1-oxo-thiomorpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]- 1-oxo-thiomorpholin-4-yl}-propionic acid tert-butyl ester

3-[2-(4-Octyloxy-phenyl)- 1-oxo-thiomorpholin-4-yl]-propionic acid tert-butyl ester



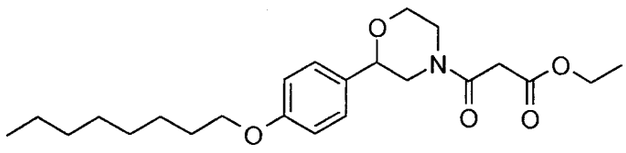
{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-acetic acid ethyl ester: A mixture of 2-[4-(2,6-dichloro-benzyloxy)-phenyl]-morpholine hydrochloride (0.65 g; 1.68 mmol), Et_3N (0.58 mL; 4.2 mmol), and ethyl bromoacetate (0.24 ml; 2.19 mmol) in CH_3CN (65 mL) was stirred at 85°C, overnight. After cooling to RT the mixture was concentrated in vacuo and the residue partitioned between water and CH_2Cl_2. The layers were separated and aqueous layer was extracted once more with CH_2Cl_2. The combined organic layers were concentrated in vacuo and the residue was purified by column chromatography (SiO_2, Et_2O: hexanes 2:1) to afford {2-[4-(2,6-dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-acetic acid ethyl ester (0.62 g).



2,2-Difluoro-3-(2-(4-octyloxy-phenyl)-morpholin-4-yl)-propionic acid ethyl ester. To a solution of 2-(4-octyloxy-phenyl)-morpholine (0.75 g; 2.6 mmol) in EtOH (10 mL) was added 1*H*-benzotriazole-1-methanol (0.38 g; 2.6 mmol), and the reaction mixture was heated at 50°C for 20 minutes. After cooling to RT, the solvent was removed in vacuo to afford 1-[2-(4-octyloxy-phenyl)-morpholin-4-ylmethyl]-1*H*-benzotriazole; which was used as such.

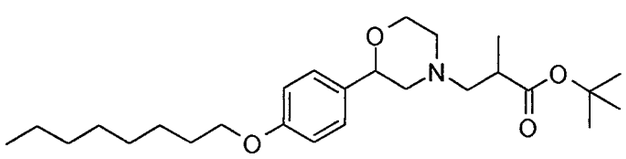
To a suspension of zinc dust (0.34 g; 5.2 mmol) in dry THF (10 mL) was added chlorotrimethylsilane (0.33 mL; 2.6 mmol) and ethyl bromodifluoroacetate (0.50 ml; 3.9 mmol), this mixture was heated under reflux for 10 min. and then cooled to RT. To the resulting mixture was added drop-wise a solution of 1-[2-(4-octyloxy-phenyl)-morpholin-4-ylmethyl]-1*H*-benzotriazole in THF (5 mL). After the addition is complete the resulting mixture is heated under efflux for 2 hours. After cooling to RT the reaction mixture was filtered over Kieselguhr and the filter-cake was washed with ethanol. The solvents were removed in vacuo and the residu was purified by column chromatography (SiO_2, Et_2O: hexanes 1:1) to afford 2,2-difluoro-3-(2-(4-octyloxy-phenyl)-morpholin-4-yl)-propionic acid ethyl ester (0.58 g).

3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-2,2-difluoro-propionic acid ethyl ester was obtained according to a similar manner.



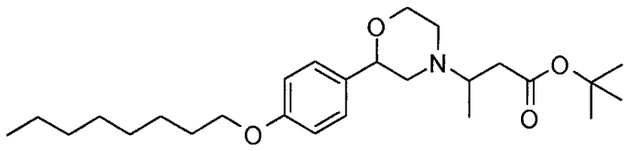
3-[2-(4-Octyloxy-phenyl)-morpholin-4-yl]-3-oxo-propionic acid ethyl ester: To a suspension of 2-(4-octyloxy-phenyl)-morpholine (0.97 g; 3.3 mmol) and *N*-ethyldiisopropylamine (1.14 ml; 6.7 mmol) in CH_3CN (10 mL) was added dropwise ethyl malonyl chloride (0.51 ml; 4.0 mmol). The resulting mixture was stirred for one hour at RT and subsequently partitioned between 5% aqueous $NaHCO_3$ solution and Et_2O. The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, Et_2O) to afford 3-[2-(4-octyloxy-phenyl)-morpholin-4-yl]-3-oxo-propionic acid ethyl ester (0.50 g).

3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-3-oxo-propionic acid ethyl ester was obtained according to a similar manner.



2-Methyl-3-[2-(4-octyloxy-phenyl)-morpholin-4-yl]-propionic acid tert-butyl ester To a suspension of 2-(4-octyloxy-phenyl)-morpholine hydrochloride (0.17 g; 0.5 mmol) in DMF (5.00 mL) was added tert-butyl methacrylate (0.17 mL; 1.0 mmol) and DBU (0.23 mL; 1.5 mmol) The resulting mixture was heated at 140°C in a sealed flask overnight. After cooling to RT the reaction mixture was partitioned between 5% aqueous $NaHCO_3$ solution and EtOAc. The layers were separated and the organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography (SiO_2, Et_2O: hexanes 1:1) to afford 2-methyl-3-[2-(4-octyloxy-phenyl)-morpholin-4-yl]-propionic acid tert-butyl ester (0.11 g).

3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-2-methyl-propionic acid tert-butyl ester was obtained according to a similar manner.



3-[2-(4-Octyloxy-phenyl)-morpholin-4-yl]-butyric acid tert-butyl ester: A mixture of 2-(4-octyloxy-phenyl)-morpholine (0.24 gram, 1.1 mmol), 3-bromobutyric acid tert-butyl ester (0.24 g; 1.1 mmol), sodium iodide (27.4 mg; 0.2 mmol), and DBU (0.4 mL; 2.7 mmol) in CH_3CN (10 mL) was heated in a closed vessel at 120°C. After cooling to RT the reaction mixture was partitioned between 5% aqueous $NaHCO_3$ solution and EtOAc. The layers were separated and the organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography (SiO_2, Et_2O) to afford 3-[2-(4-octyloxy-phenyl)-morpholin-4-yl]-butyric acid tert-butyl ester (0.15 g).

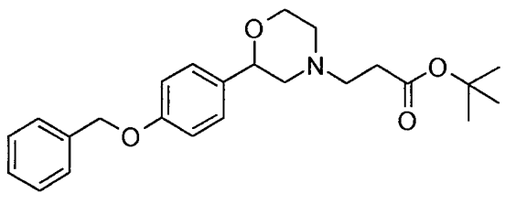
3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-butyric acid tert-butyl ester was obtained according to a similar manner. The required **3-bromobutyric acid tert-butyl ester** was prepared as follows: To a solution of 3-bromobutyric acid (5.0 mL; 47.0 mmol) in tetrahydrofuran (50 mL) was added dropwise trifluoroacetic anhydride (13.7 mL; 98.7 mmol) at -40°C. After 1 hour at -40°C tert-butyl alcohol (20 mL) was added. The resulting mixture was allowed to warm to RT and stirred overnight. Subsequently, the reaction mixture was concentrated in vacuo. The residue was treated with 2M aqueous NaOH solution and extracted with Et_2O. The organic layer was dried (Na_2SO_4), and concentrated in vacuo to afford 3-bromobutyric acid tert-butyl ester (6.05 g), which was used as such.

3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-2,2-dimethyl-propionic acid methyl ester: To a solution of 2,2-dimethyl-3-oxo-propionic acid methyl ester (WHSS0374-001) (0.90 g; 5.44 mmol) in 1,2-dichloroethane (20 mL) was added 2-[4-(2,6-dichloro-benzyloxy)-phenyl]-morpholine (0.91 g, 2.7 mmol) and NaBH(OAc)3 (1.62 g; 7.62 mmol). The resulting mixture was stirred overnight at RT, and subsequently treated with 5 % aqueous $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 X 30 ml). The combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, Et_2O/hexanes 1:1) to afford 3-{2-[4-(2,6-dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-2,2-dimethyl-propionic acid methyl ester (1.12 g) as a clear colourless oil. The required **2,2-dimethyl-3-oxo-propionic acid methyl ester** was prepared as follows: To a solution of 2,2-dimethyl-3-hydroxypropionic acid methyl ester (10.00 g; 75.7 mmol) in CH_2Cl_2 (200 mL) was added pyridinium chloroformate (28.54 g; 132.4

mmol) in small portions, at 0°C. The reaction mixture was allowed to slowly warm to RT and stirred overnight. Subsequently, the mixture was diluted with CH_2Cl_2, filtered over kieselguhr, and concentrated in vacuo. The remaining oil was purified by column chromatography (SiO_2, hexanes/Et_2O 7:3) to afford 2,2-dimethyl-3-oxo-propionic acid methyl ester (5.59 g)

The following compound was made according to a similar method:

3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-cyclobutanecarboxylic acid tert-butyl ester. The required **3-oxo-cyclobutanecarboxylic acid tert-butyl ester** was prepared as described in: R. P. Lemieux, G. B. Schuster, *J. Org. Chem.*, **1993**, *58*, 100.



3-{2-[4-(Benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester: A mixture of 3-[2-(4-hydroxy-phenyl)-morpholin-4-yl]-propionic acid tert-butyl ester) (76,8 mg; 0.25 mmol), Cs_2CO_3 (241 mg; 0.74 mmol), and NaI (3,7 mg, 25 µmol) in CH_3CN /THF (6:4; 2.5 mL) was stirred for three hours at RT. Subsequently, benzyl chloride (35 µL; 0.3 mmol) in CH_3CN (1 mL) was added and the resulting mixture was heated at 60°C, for 20h. After cooling to RT the solvents were removed in vacuo. The residue was partitioned between CH_2Cl_2 and 1M aqueous K_2CO_3. The layers were separated and the aqueous layer washed with CH_2Cl_2. The combined organic layers were concentrated in vacuo, and the residue dried under vacuum, at 40°C, overnight. The obtained product was used as such in the next step.

The following compounds were obtained according to a similar manner:

3-{2-[4-(6-Methyl-imidazo[1,2-a]pyridin-2-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-(2-{4-[3-(2-Propyl-thiazol-5-yloxy)-propoxy]-phenyl}-morpholin-4-yl)-propionic acid tert-butyl ester

3-{2-[4-(2-Benzyloxy-ethoxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(2-Phenoxy-ethoxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-[2-(4-Hex-5-ynyloxy-phenyl)-morpholin-4-yl]-propionic acid tert-butyl ester
3-{2-[4-(4-Acetoxy-butoxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester
3-(2-{4-[3-(4-Fluoro-phenoxy)-propoxy]-phenyl}-morpholin-4-yl)-propionic acid tert-butyl ester
3-(2-{4-[2-(Naphthalen-2-yloxy)-ethoxy]-phenyl}-morpholin-4-yl)-propionic acid tert-butyl ester
3-[2-(4-Phenylcarbamoylmethoxy-phenyl)-morpholin-4-yl]-propionic acid tert-butyl ester
3-{2-[4-(4-Pyrazol-1-yl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester
3-{2-[4-(1-Methyl-1H-pyrazol-3-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester
3-{2-[4-(4-Chloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester
3-{2-[4-(6-Cyano-hexyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester
3-[2-(4-Phenethyloxy-phenyl)-morpholin-4-yl]-propionic acid tert-butyl ester
3-{2-[4-(3-Phenyl-propoxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester
3-{2-[4-(3-Benzyloxy-propoxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester
3-{2-[4-(7-Methoxy-heptyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester
3-(2-{4-[3-(4-tert-Butyl-phenyl)-[1,2,4]oxadiazol-5-ylmethoxy]-phenyl}-morpholin-4-yl)-propionic acid tert-butyl ester
3-{2-[4-(5-Oxo-hexyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester
3-{2-[4-(4-Phenyl-butoxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester
3-{2-[4-(3-Methoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester
3-{2-[4-(2-Chloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester
3-[2-(4-Cyclohexylmethoxy-phenyl)-morpholin-4-yl]-propionic acid tert-butyl ester
3-{2-[4-(2-Benzenesulfonyl-ethoxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(3-Phenoxy-propoxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(4-[1,2,4]Triazol-1-yl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(2,3-Dihydro-benzofuran-2-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

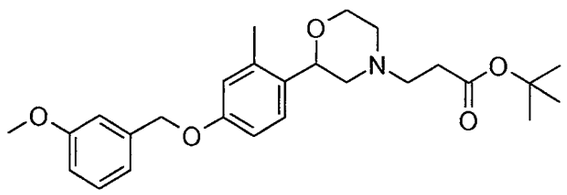
3-{2-[4-(2-Biphenyl-4-yl-2-oxo-ethoxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(4-Phenoxy-butoxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(2-Oxo-2-phenyl-ethoxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(3-Chloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-(2-{4-[2-(1H-Indol-3-yl)-ethoxy]-phenyl}-morpholin-4-yl)-propionic acid tert-butyl ester



3-{2-[4-(3-Methoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester: To a solution of (3-methoxybenzyl alcohol (0.25M, 450µl) in THF was added a solution of 3-[2-(4-hydroxy-2-methyl-phenyl)-morpholin-4-yl]-propionic acid tert-butyl ester (0.25M, 360 µl) in THF. To this mixture a solution of DIAD in THF (0.25M, 360 µl) was added. Finally, polystyrene supported triphenylphosphine (~190 mg, 1.2 mmol/g) was added followed by THF (1 mL). The reaction mixture was shaken with interval for 20 hours at 30 °C. Subsequently, more DIAD (360µl, 0.25M in THF) and polystyrene supported triphenylphosphine (95 mg, 1.2 mmol/g) were added. The mixture was shaken again with interval for 20 hours at 30 °C. To the resulting mixture was added macroporous carbonate resin (~90mg, 3.06 mmol/g, Argonaut Technologies) and the mixture was shaken again with interval for 20 hours at 50 °C.

The mixture was transferred to a Methanol and THF conditioned Strong Cationic Exchange cartridge (IST, 0.5g, 0.6 mmol/g), washed with THF (6ml) and CH_3CN (8ml) consecutively before being eluted with 1N NH_4OH in CH_3CN (6ml).

Concentration in vacuo afforded 3-{2-[4-(3-Methoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester (~15mg), which was used as such.

The following compounds were obtained according to a similar manner:

3-{2-[4-(5-Bromo-2-methoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(2,4-Dichloro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(2,3-Dimethoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-[2-(4-Cyclopentylmethoxy-2-methyl-phenyl)-morpholin-4-yl]-propionic acid tert-butyl ester

3-{2-[4-(2,5-Dichloro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[2-Methyl-4-(pyridin-3-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[2-Methyl-4-(naphthalen-2-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(Benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(2-Methoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[2-Methyl-4-(6-methyl-pyridin-2-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(2-Chloro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(2,5-Dimethoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(2-Bromo-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[2-Methyl-4-(2-methyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(6,6-Dimethyl-bicyclo[3.1.1]hept-2-ylmethoxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(2-Chloro-6-fluoro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(Biphenyl-2-ylmethoxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[2-Methyl-4-(2-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(3,5-Dichloro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[2-Methyl-4-(3-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(4-Chloro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(4-Isopropyl-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[2-Methyl-4-(3-phenoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(4-Methoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[2-Methyl-4-(2-phenethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(3,4-Dimethoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(3,5-Dimethyl-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(4-Benzyloxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[2-Methyl-4-(thiophen-2-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(3-Fluoro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(3-Benzyloxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(4-Fluoro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(Biphenyl-4-ylmethoxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[2-Methyl-4-(pyridin-2-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(4-Butoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-[2-(4-Cyclohexylmethoxy-2-methyl-phenyl)-morpholin-4-yl]-propionic acid tert-butyl ester

3-{2-[2-Methyl-4-(tetrahydro-furan-2-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[2-Methyl-4-(3-methyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(2,3-Difluoro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[2-Methyl-4-(4-trifluoromethoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(3-Chloro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[2-Methyl-4-(tetrahydro-pyran-2-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[2-Methyl-4-(4-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(3,4-Difluoro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[2-Methyl-4-(2,3,4-trimethoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(Cyclohex-3-enylmethoxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(4-Butyl-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[2-Methyl-4-(4-methyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(3-Dimethylamino-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[2-Methyl-4-(pyridin-4-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(2-Iodo-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(3,5-Dimethoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(2,4-Difluoro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[2-Methyl-4-(2,4,5-trimethoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

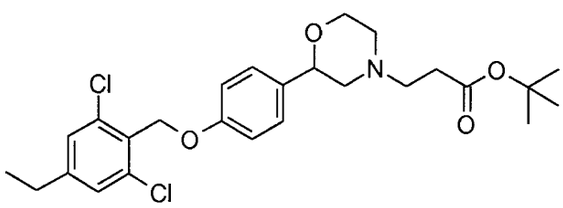
3-{2-[4-(3-Bromo-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(4-Bromo-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

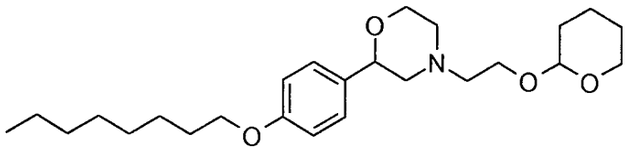
3-{2-[4-(4-tert-Butyl-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[4-(2,5-Difluoro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

3-{2-[2-Methyl-4-(tetrahydro-furan-3-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester

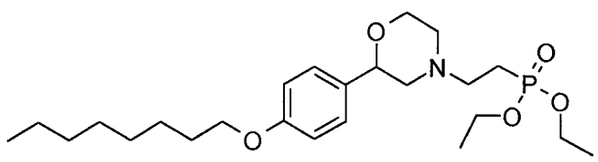


3-{2-[4-(2,6-Dichloro-4-ethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester: 3-{2-[4-(2,6-Dichloro-4-iodo-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester (0.34 g; 0.57 mmol), and $Pd(dppf)Cl_2$ (14.70 mg; 0.02 mmol) were added to a solution of lithium chloride (4.59 ml; 0.50 mol/l; 2.30 mmol) in THF; 0.04 eq.). The resulting mixture was cooled to 0°C and a solution of diethylzinc in n-heptane (1.15 ml; 1.00 mol/l; 1.15 mmol) was added dropwise. The mixture was heated to 60°C overnight. After cooling to RT saturated aqueous NH_4Cl was added. The mixture was extracted with EtOAc. The organic layer was dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO2, EtOAc:hexanes 1:1) to afford 3-{2-[4-(2,6-dichloro-4-ethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester (115.00 mg)

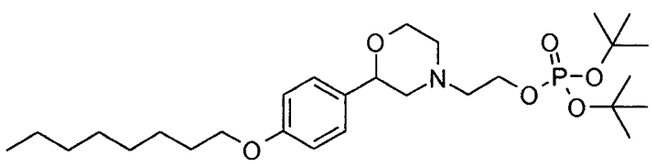


2-(4-Octyloxy-phenyl)-4-[2-(tetrahydro-pyran-2-yloxy)-ethyl]-morpholine: A mixture of 2-(4-octyloxy-phenyl)-morpholine (1.99 g; 6.8 mmol), 2-(2-chloroethoxy)-tetrahydro-2*H*-pyran (1.21 ml; 8.2 mmol), K_2CO_3 (1.89 g; 13.7 mmol) and NaI (0.20 g; 1.4 mmol) in DMF (15 mL) was heated to 100°C overnight. After cooling to RT the reaction mixture was partitioned between 5% aqueous $NaHCO_3$ solution and Et_2O. The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, EtOAc) to afford 2-(4-octyloxy-phenyl)-4-[2-(tetrahydro-pyran-2-yloxy)-ethyl]-morpholine (2.04 g).

2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-4-[2-(tetrahydro-pyran-2-yloxy)-ethyl]-morpholine was obtained according to a similar manner.

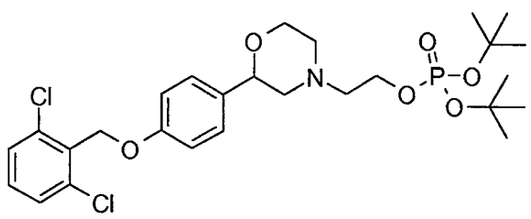


{2-[2-(4-Octyloxy-phenyl)-morpholin-4-yl]-ethyl}-phosphonic acid diethyl ester: A mixture of 2-(4-octyloxy-phenyl)-morpholine (0.83 g; 2.9 mmol) and diethyl vinylphosphonate (0.53 ml; 3.4 mmol) in CH_3CN (10 mL) was heated under reflux for 3 days. After cooling to RT the mixture was concentrated in vacuo and the residue was purified by column chromatography (SiO_2, EtOAc: MeOH 90:10) to afford {2-[2-(4-octyloxy-phenyl)-morpholin-4-yl]-ethyl}-phosphonic acid diethyl ester (0.42 g)

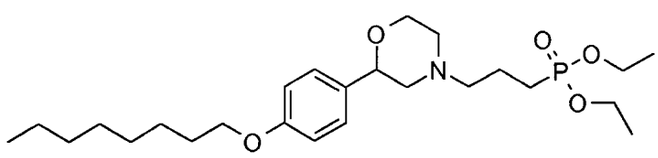


Phosphoric acid di-tert-butyl ester 2-[2-(4-octyloxy-phenyl)-morpholin-4-yl]-ethyl ester: To a solution of 2-[2-(4-octyloxy-phenyl)-morpholin-4-yl]-ethanol (1.33 g; 4.0 mmol) in a mixture of THF (15 mL) and CH_2Cl_2 (15 mL) was added a tetrazole solution in CH_3CN (17.6 mL; 0.45 mol/L; 7.9 mmol) at RT. The resulting mixture was stirred for 30 minutes and subsequently di-tert-butyl *N,N*-diisopropylphosphoramidite (2.00 ml; 6.3 mmol) was added and stirred overnight at RT. Subsequently, an

aqueous hydrogen peroxide solution (1.80 ml; 300 g/l; 15.9 mmol) was added and the mixture stirred at RT for another 15 min. The reaction was quenched by the addition of an 5% aqueous $NaHCO_3$ solution and extracted with EtOAc. The organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, Et_2O) to afford phosphoric acid di-tert-butyl ester 2-[2-(4-octyloxy-phenyl)-morpholin-4-yl]-ethyl ester (0.71 g).



Phosphoric acid di-tert-butyl ester 2-{2-[4-(2,6-dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-ethyl ester: To a solution of 2-{2-[4-(2,6-dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-ethanol (0.74 g; 1.94 mmol) in a mixture of THF (10 mL) and CH_2Cl_2 (10 mL) was added a tetrazole solution in CH_3CN ((8.60 ml; 0.45 mol/l; 3.87 mmol) at RT. The resulting mixture was stirred for 30 minutes and subsequently di-tert-butyl *N,N*-diisopropylphosphoramidite (0.98 ml; 3.10 mmol) was added and stirred overnight at RT. Subsequently, the mixture was cooled to 4°C, and a solution of tert-butyl hydroperoxide in nonane (0.31 ml; ~5.5 mol/L, 2.90 mmol) was added. Thereafter the mixture was stirred at RT for another 30 min. The reaction was quenched by the addition of an 5% aqueous $NaHCO_3$ solution and extracted with EtOAc. The organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, EtOAc) to afford phosphoric acid di-tert-butyl ester 2-{2-[4-(2,6-dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-ethyl ester (0.66 g).



{2-[2-(4-Octyloxy-phenyl)-morpholin-4-yl]-propyl}-phosphonic acid diethyl ester: A mixture of 2-(4-octyloxy-phenyl)-morpholine (1.04 g; 3.6 mmol), diethyl (3-bromopropyl)phosphonate (0.82 mL; 4.3 mmol), NaI (0.11 g; 0.7 mmol), and K_2CO_3 (0.99 g; 7.1 mmol) in CH_3CN (10 mL) was heated under reflux for 2 hours. After cooling to RT the mixture was partitioned between 5% aqueous $NaHCO_3$ solution and Et_2O. The organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo.

The residue was purified by column chromatography (SiO_2, EtOAc : MeOH 90:10) to afford {2-[2-(4-octyloxy-phenyl)-morpholin-4-yl]-propyl}-phosphonic acid diethyl ester (1.13 g).

(3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propyl)-phosphonic acid diethyl ester was obtained according to a similar manner.

§4. SYNTHESES OF SPECIFIC COMPOUNDS

(See Tables)

Method A:

Compound 1 (3-{2-[4-(benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid): The crude 3-{2-[4-(benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester (see §3) was treated with a mixture of TFA, water, and CH_2Cl_2 (30:3:67; 3 mL) and stirred at RT for 2h. Subsequently, the volatiles were removed in vacuo, and the crude product was purified by preparative HPLC to afford 3-{2-[4-(benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid trifluoroacetic acid salt; R_t = 1.86 min. (System A), $[M+H]^+$ Found: 342.19; Calc: 342.17. Conditions for the preparative LC-MS: Injection of the crude product dissolved in 600 L DMSO/CH_3CN 1:2; column Waters Sunfire 19x100mm 5 µm 45°C, mobile phase water/CH_3CN/TFA 0.1% 25 mL/min, run 20 min 10%-90% CH_3CN, detection with UV 210-260nm.

The following compounds were obtained similarly:

Compound 2; 3-{2-[4-(6-Methyl-imidazo[1,2-a]pyridin-2-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid trifluoroacetic acid salt R_t = 0.76 min. (System A), $[M+H]^+$ Found: 396.23; Calc: 396.19.

Compound 3; 3-(2-{4-[3-(2-Propyl-thiazol-5-yloxy)-propoxy]-phenyl}-morpholin-4-yl)-propionic acid trifluoroacetic acid salt R_t = 2.04 min. (System A), $[M+H]^+$ Found: 435.21; Calc: 435.20.

Compound 4; 3-{2-[4-(2-Benzyloxy-ethoxy)-phenyl]-morpholin-4-yl}-propionic acid trifluoroacetic acid salt R_t = 1.89 min. (System A), $[M+H]^+$ Found: 386.22; Calc: 386.20.

Compound 5; 3-{2-[4-(2-Phenoxy-ethoxy)-phenyl]-morpholin-4-yl}-propionic acid trifluoroacetic acid salt R_t = 1.91 min. (System A), $[M+H]^+$ Found: 372.21; Calc: 372.18.

Compound 6; 3-[2-(4-Hex-5-ynyloxy-phenyl)-morpholin-4-yl]-propionic acid trifluoroacetic acid salt R_t = 1.77 min. (System A), $[M+H]^+$ Found: 332.21; Calc: 332.19.

Compound 7; 3-{2-[4-(4-Acetoxy-butoxy)-phenyl]-morpholin-4-yl}-propionic acid trifluoroacetic acid salt R_t = 1.51 min. (System A), $[M+H]^+$ Found: 366.21; Calc: 366.19.

Compound 8; 3-(2-{4-[3-(4-Fluoro-phenoxy)-propoxy]-phenyl}-morpholin-4-yl)-propionic acid trifluoroacetic acid salt R_t = 2.16 min. (System A), $[M+H]^+$ Found: 404.22; Calc: 404.19.

Compound 9; 3-(2-{4-[2-(Naphthalen-2-yloxy)-ethoxy]-phenyl}-morpholin-4-yl)-propionic acid trifluoroacetic acid salt R_t = 2.35 min. (System A), $[M+H]^+$ Found: 422.24; Calc: 422.20.

Compound 10; 3-[2-(4-Phenylcarbamoylmethoxy-phenyl)-morpholin-4-yl]-propionic acid trifluoroacetic acid salt R_t = 1.48 min. (System A), $[M+H]^+$ Found: 385.20; Calc: 385.18.

Compound 11; 3-{2-[4-(4-Pyrazol-1-yl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid trifluoroacetic acid salt R_t = 1.83 min. (System A), $[M+H]^+$ Found: 408.22; Calc: 408.19.

Compound 12; 3-{2-[4-(1-Methyl-1H-pyrazol-3-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid trifluoroacetic acid salt R_t = 1.14 min. (System A), $[M+H]^+$ Found: 346.20; Calc: 346.18.

Compound 13; 3-{2-[4-(4-Chloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid trifluoroacetic acid salt R_t = 2.14 min. (System A), $[M+H]^+$ Found: 376.13; Calc: 376.13.

Compound 14; 3-{2-[4-(6-Cyano-hexyloxy)-phenyl]-morpholin-4-yl}-propionic acid trifluoroacetic acid salt R_t = 1.68 min. (System A), $[M+H]^+$ Found: 361.24; Calc: 361.21.

Compound 15; 3-[2-(4-Phenethyloxy-phenyl)-morpholin-4-yl]-propionic acid trifluoroacetic acid salt R_t = 1.93 min. (System A), $[M+H]^+$ Found: 356.23; Calc: 356.19.

Compound 16; 3-{2-[4-(3-Phenyl-propoxy)-phenyl]-morpholin-4-yl}-propionic acid trifluoroacetic acid salt R_t = 2.11 min. (System A), $[M+H]^+$ Found: 370.24; Calc: 370.20.

Compound 17; 3-{2-[4-(3-Benzyloxy-propoxy)-phenyl]-morpholin-4-yl}-propionic acid trifluoroacetic acid salt R_t = 1.97 min. (System A), $[M+H]^+$ Found: 400.26; Calc: 400.21.

Compound 18; 3-{2-[4-(7-Methoxy-heptyloxy)-phenyl]-morpholin-4-yl}-propionic acid trifluoroacetic acid salt R_t = 2.04 min. (System A), $[M+H]^+$ Found: 380.27; Calc: 380.24.

Compound 19; 3-(2-{4-[3-(4-tert-Butyl-phenyl)-[1,2,4]oxadiazol-5-ylmethoxy]-phenyl}-morpholin-4-yl)-propionic acid trifluoroacetic acid salt R_t = 2,67 min. (System A), $[M+H]^+$ Found: 466.27; Calc: 466.23.

Compound 20; 3-{2-[4-(5-Oxo-hexyloxy)-phenyl]-morpholin-4-yl}-propionic acid trifluoroacetic acid salt R_t = 1.35 min. (System A), $[M+H]^+$ Found: 350.22; Calc: 350.20.

Compound 21; 3-{2-[4-(4-Phenyl-butoxy)-phenyl]-morpholin-4-yl}-propionic acid trifluoroacetic acid salt R_t = 2.38 min. (System A) , $[M+H]^+$ Found: 384.25; Calc: 384.22.

Compound 22; 3-{2-[4-(3-Methoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid trifluoroacetic acid salt R_t = 1.75 min. (System A).

Compound 23; 3-{2-[4-(2-Chloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid trifluoroacetic acid salt R_t = 1.99 min. (System A), $[M+H]^+$ Found: 376.18; Calc: 376.13.

Compound 24; 3-[2-(4-Cyclohexylmethoxy-phenyl)-morpholin-4-yl]-propionic acid trifluoroacetic acid salt R_t = 2.26 min. (System A), $[M+H]^+$ Found: 348.27; Calc: 348.22.

Compound 25; 3-{2-[4-(2-Benzenesulfonyl-ethoxy)-phenyl]-morpholin-4-yl}-propionic acid trifluoroacetic acid salt R_t = 1.45 min. (System A), $[M+H]^+$ Found: 420.18; Calc: 420.15.

Compound 26; 3-{2-[4-(3-Phenoxy-propoxy)-phenyl]-morpholin-4-yl}-propionic acid trifluoroacetic acid salt R_t = 2.12 min. (System A), $[M+H]^+$ Found: 386.21; Calc: 386.20.

Compound 27; 3-{2-[4-(4-[1,2,4]Triazol-1-yl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid trifluoroacetic acid salt R_t = 1.46 min. (System A), $[M+H]^+$ Found: 409.22; Calc: 409.19.

Compound 28; 3-{2-[4-(2,3-Dihydro-benzofuran-2-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid trifluoroacetic acid salt R_t = 1.94 min. (System A), $[M+H]^+$ Found: 384.21; Calc: 384.18.

Compound 29; 3-{2-[4-(2-Biphenyl-4-yl-2-oxo-ethoxy)-phenyl]-morpholin-4-yl}-propionic acid trifluoroacetic acid salt R_t = 2.30 min. (System A), $[M+H]^+$ Found: 446.23; Calc: 446.20.

Compound 30; 3-{2-[4-(4-Phenoxy-butoxy)-phenyl]-morpholin-4-yl}-propionic acid trifluoroacetic acid salt R_t = 2.25 min. (System A), $[M+H]^+$ Found: 400.24; Calc: 400.21.

Compound 31; 3-{2-[4-(2-Oxo-2-phenyl-ethoxy)-phenyl]-morpholin-4-yl}-propionic acid trifluoroacetic acid salt R_t = 1.60 min. (System A), $[M+H]^+$ Found: 370.18; Calc: 370.17.

Compound 32; 3-{2-[4-(3-Chloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid trifluoroacetic acid salt R_t = 2.09 min. (System A), $[M+H]^+$ Found: 376.16; Calc: 376.13.

Compound 33; 3-(2-{4-[2-(1H-Indol-3-yl)-ethoxy]-phenyl}-morpholin-4-yl)-propionic acid trifluoroacetic acid salt R_t = 1.99 min. (System A), $[M+H]^+$ Found: 395.22; Calc: 395.20.

Method B:

Compound 34; 3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid. 3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester (0.59 g; 1.27 mmol) was dissolved in a 4M solution of HCl in 1,4-dioxane (6.33 mL, 25.30 mmol) and stirred overnight at RT. Subsequently, the solvent was removed in vacuo and the residue treated with iPr_2O, the precipitate was collected by filtration and dried overnight under reduced pressure to afford 3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride (0.50 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.88 - 2.97 (2 H, m) 3.11 (1 H, t, J=11.7 Hz) 3.15 - 3.23 (1 H,m) 3.30 - 3.43 (2 H, m) 3.49 (1 H, d, J=12.0 Hz) 3.55 - 3.64 (1 H, m) 4.01 - 4.20 (2 H, m) 4.88 (1 H, d,J=12.0 Hz) 5.24 (2 H, s) 7.04 - 7.12 (2 H, m) 7.35 (2 H, d, J=8.7 Hz) 7.40 - 7.49 (1 H, m) 7.49 - 7.56 (2H, m).

The following compounds were obtained according to a similar manner:

Compound 34a; (+)-3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride $([\alpha]_D^{25}$ = +7 (*c* 1.0, MeOH)). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.82 - 2.96 (m, 2 H) 3.09 (d, J=0.37 Hz, 2 H) 3.34 (br. s., 2 H) 3.43 - 3.52 (m, 1 H3.95 - 4.07 (m, 1 H) 4.09 - 4.20 (m, 1 H) 4.78 - 4.88 (m, 1 H) 5.24 (s, 2 H) 7.06 - 7.14 (m, 2 H) 7.30 - 7.39 (m, 2 H) 7.43 - 7.51 (m, 1 H) 7.54 - 7.62 (m, 2 H)

Compound 34b; (-)-3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride $([\alpha]_D^{25}$ = -7 (*c* 1.0, MeOH)). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.84 - 2.96 (m, 2 H) 3.09 (s, 2 H) 3.34 (br. s., 2 H) 3.43 - 3.52 (m, 1

H) 3.97 - 4.08 (m, 1 H) 4.09 - 4.18 (m, 1 H) 4.79 - 4.89 (m, 1 H) 5.24 (s, 2 H) 7.07 - 7.15 (m, 2 H) 7.31 - 7.38 (m, 2 H) 7.43 - 7.51 (m, 1 H) 7.54 - 7.60 (m, 2 H).

Compound 35; 3-(2-(4-Octyl-phenyl)-morpholin-4-yl)-propionic acid hydrochloride. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.55 - 0.71 (m, 3 H) 1.04 (br, 10 H) 1.25 - 1.43 (m, 2 H) 2.23 - 2.44 (m, 2 H) 2.55 - 2.73 (m, 2 H) 2.78 - 3.04 (m, 2 H) 3.08 - 3.53 (m, 4 H) 3.67 - 4.07 (m, 2 H) 4.48 - 4.69 (m, 1 H) 6.90 - 7.25 (m, 4 H).

Compound 36; 4-[2-(4-Octyl-phenyl)-morpholin-4-yl]-butyric acid hydrochloride. ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 0.86 (t, *J*=6.8 Hz, 3 H) 1.19 - 1.33 (m, 10 H) 1.52 - 1.60 (m, 2 H) 1.94 - 2.02 (m, 2 H) 2.36 (t, *J*=7.2 Hz, 2 H) 2.57 (t, *J*=7.7 Hz, 2 H) 3.03 - 3.18 (m, 4 H) 3.58 - 3.68 (m, 2 H) 4.10 - 4.19 (m, 2 H) 4.84 – 4.89 (m, 1 H) 7.22 (d, *J*=8.6 Hz, 2 H) 7.30 (d, *J*=8.6 Hz, 2 H).

Compound 37; 3-[2-(4-Hexyloxy-phenyl)-morpholin-4-yl]-propionic acid hydrochloride. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.84 - 0.91 (m, 3 H) 1.27 - 1.34 (m, 4 H) 1.36 - 1.46 (m, 2 H) 1.66 - 1.74 (m, 2 H) 2.84 - 2.91 (m, 2 H) 3.02 - 3.18 (m, 2 H) 3.30 - 3.40 (m, 2 H) 3.44 - 3.51 (m, 1 H) 3.52 - 3.61 (m, 1 H) 3.91 - 4.02 (m, 3 H) 4.09 - 4.17 (m, 1 H) 4.74 - 4.81 (m, 1 H) 6.95 (d, J=8.7 Hz, 2 H) 7.29 (d, J=8.7 Hz, 2 H) 11.10 -12.90 (m, 2H).

Compound 38; 4-[2-(4-Hexyloxy-phenyl)-morpholin-4-yl]-butyric acid hydrochloride. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.63 - 0.71 (m, 3 H) 1.05 - 1.15 (m, 4 H) 1.15 - 1.25 (m, 2 H) 1.44 - 1.53 (m, 2 H) 1.70 - 1.81 (m, 2 H) 2.14 (t, *J*=7.1 Hz, 2 H) 2.78 - 2.95 (m, 2 H) 3.11 - 3.39 (m, 4 H) 3.75 (t, *J*=6.4 Hz, 2 H) 3.78 - 3.84 (m, 1 H) 3.87 - 3.96 (m, 1 H) 4.56 - 4.64 (m, 1 H) 6.75 (d, *J*=8.7 Hz, 2 H) 7.09 (d, *J*=8.7 Hz, 2 H) 10.70-11.00 (bs, 1H).

Compound 39; 3-[2-(4-Heptyloxy-phenyl)-morpholin-4-yl]-propionic acid hydrochloride. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.59 - 0.68 (m, 3 H) 0.96 - 1.22 (m, 8 H) 1.40 - 1.52 (m, 2 H) 2.61 - 2.72 (m, 2 H) 2.78 - 2.96 (m, 2 H) 3.02 - 3.39 (m, 4 H) 3.67 - 3.81 (m, 3 H) 3.84 - 3.94 (m, 1 H) 4.57 (d, *J*=10.8 Hz, 1 H) 6.71 (d, *J*=8.7 Hz, 2 H) 7.05 (d, *J*=8.7 Hz, 2 H) 10.67 - 12.94 (m, 2 H).

Compound 40; 4-[2-(4-Heptyloxy-phenyl)-morpholin-4-yl]-butyric acid hydrochloride. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.87 (t, *J*=7.0 Hz, 3 H) 1.22 - 1.35 (m, 6 H) 1.36 - 1.44 (m, 2 H) 1.66 - 1.74 (m, 2 H) 1.94 - 2.05 (m, 2 H) 2.34 (t, *J*=7.4 Hz, 2 H) 2.99 - 3.17 (m, 4 H) 3.43 - 3.57 (m, 2 H) 3.95 (t, *J*=6.4 Hz, 2 H) 4.03 - 4.14 (m, 2 H) 4.87 (d, *J*=10.2 Hz, 1 H) 6.94 (d, *J*=8.7 Hz, 2 H) 7.29 (d, *J*=8.7 Hz, 2 H) 10.80 - 11.20 (bs, 1 H) 12.00 – 12.40 (bs, 1 H).

Compound 41; 3-(2-(4-Octyloxy-phenyl)-morpholin-4-yl)-propionic acid hydrochloride. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.22 - 1.36 (8 H, m) 1.37 - 1.46 (2 H,

m) 1.66 - 1.77 (2 H, m)2.85 - 2.92 (2 H, m) 3.08 (1 H, t, J=11.7 Hz) 3.13 - 3.21 (1 H, m) 3.29 - 3.41 (2 H, m) 3.48 (1 H, d)3.56 (1 H, d, J=12.3 Hz) 3.95 (2 H, t, J=6.5 Hz) 4.01 (1 H, t, J=12.2 Hz) 4.07 - 4.17 (1 H, m) 4.80 (1 H,d, J=10.8 Hz) 6.92 (2 H, dt, J=8.5, 0.7 Hz) 7.28 (2 H, d, J=9.0 Hz).

Compound 41a; (+)-3-[2-(4-Octyloxy-phenyl)-morpholin-4-yl]-propionic acid hydrochloride from Isomer 2 of 3-[2-(4-octyloxy-phenyl)-morpholin-4-yl]-propionic acid tert-butyl ester, $[\alpha]_D^{25}$ = +5 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.81 - 0.92 (m, 3 H) 1.19 - 1.47 (m, 10 H) 1.64 - 1.77 (m, 2 H) 2.83 - 2.96 (m, 2 H) 3.03 - 3.21 (m, 2 H) 3.29 - 3.40 (m, 2 H) 3.48 (d, *J*=12.34 Hz, 1 H) 3.56 (d, *J*=12.34 Hz, 1 H) 3.95 (t, *J*=6.47 Hz, 2 H) 3.98 - 4.08 (m, 1 H) 4.08 - 4.18 (m, 1 H) 4.75 - 4.87 (m, 1 H) 6.88 - 6.97 (m, 2 H) 7.28 (d, *J*=8.73 Hz, 2H)

Compound 41b; (-)-3-[2-(4-Octyloxy-phenyl)-morpholin-4-yl]-propionic acid hydrochloride from Isomer 1 of 3-[2-(4-octyloxy-phenyl)-morpholin-4-yl]-propionic acid tert-butyl ester, $[\alpha]_D^{25}$ = -5 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.57 - 0.76 (m, 3 H) 0.93 - 1.31 (m, 10 H) 1.40 - 1.58 (m, 2 H) 2.61 - 2.80 (m, 2 H) 2.80 - 3.01 (m, 2 H) 3.13 (t, *J*=7.83 Hz, 2 H) 3.20 - 3.45 (m, 2 H) 3.65 - 4.01 (m, 4 H) 4.63 (m, 1 H) 6.65 - 6.87 (m, 2 H) 7.09 (d, *J*=8.73 Hz, 2 H)

Compound 42; 4-[2-(4-Octyloxy-phenyl)-morpholin-4-yl]-butyric acid hydrochloride^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 0.86 (t, *J*=6.8 Hz, 3 H) 1.21 - 1.34 (m, 8 H) 1.36 - 1.44 (m, 2 H) 1.66 - 1.74 (m, 2 H) 1.95 - 2.05 (m, 2 H) 2.36 (t, *J*=7.2 Hz, 2 H) 3.03 - 3.19 (m, 4 H) 3.47 - 3.59 (m, 2 H) 3.95 (t, *J*=6.4 Hz, 2 H) 4.02 - 4.20 (m, 2 H) 4.86 (d, *J*=10.2 Hz, 1 H) 6.93 (d, *J*=8.7 Hz, 2 H) 7.30 (d, *J*=8.7 Hz, 2 H) 11.23 – 11.40 (bs, 1 H).

Compound 43; 2,2-Dimethyl-3-(2-(4-octyloxy-phenyl)-morpholin-4-yl)-propionic acid hydrochloride. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.64 (t, *J*=6.32 Hz, 3 H) 0.86 - 1.25 (m, 17 H) 1.42 - 1.53 (m, *J*=6.96, 6.96, 6.85, 6.62 Hz, 2 H) 3.68 - 3.99 (m, 4 H) 4.73 (d, *J*=10.53 Hz, 1 H) 6.72 (d, 2 H) 7.06 (d, *J*=7.83 Hz, 2 H).

Compound 44; 3-[2-(4-octyloxy-phenyl)-morpholin-4-yl]-butyric acid hydrochloride ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.79 - 0.86 (m, 4 H) 1.17 - 1.42 (m, 16 H) 1.63 - 1.72 (m, 2 H) 3.93 (t, J=6.47 Hz, 3 H) 4.11 - 4.19 (m, 1 H) 4.65 - 4.73 (m, 1 H) 6.91 (d, J=8.73 Hz, 2 H) 7.31 (d, J=8.43 Hz, 2 H).

Compound 45; 2-Methyl-3-[2-(4-octyloxy-phenyl)-morpholin-4-yl]-propionic acid hydrochloride ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.67 (t, *J*=6.47 Hz, 2 H) 1.05 (dd, *J*=7.22, 3.91 Hz, 4 H) 1.03 (br. s., 2 H) 1.09 (br. s., 3 H) 1.19 (d, *J*=7.52 Hz, 2 H) 1.50 (qd, *J*=6.92, 6.62 Hz, 1 H) 2.31 (br. s., 3 H) 2.85 - 2.93 (m, 2 H) 2.95 (br. s., 1 H)

3.18 (br. s., 7 H) 3.26 (br. s., 2 H) 3.29 (br. s., 1 H) 3.37 (s, 1 H) 3.76 (t, *J*=6.47 Hz, 1 H) 3.90 (br. s., 1 H) 6.75 (d, *J*=8.43 Hz, 1 H) 7.08 (dd, *J*=8.43, 6.32 Hz, 1 H).

Compound 46; 3-{2-[4-(2-Chloro-6-fluorobenzyloxy)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.42 (s, 1 H) 2.82 - 2.98 (m, 2 H) 3.02 - 3.20 (m, 2 H) 3.26 - 3.40 (m, 2 H) 3.47 (d, *J*=12.04 Hz, 1 H) 3.93 - 4.07 (m, 1 H) 4.08 - 4.21 (m, 1 H) 4.75 - 4.91 (m, 1 H) 5.16 (dd, *J*=1.35, 0.75 Hz, 2 H) 7.02 - 7.17 (m, 1 H) 7.28 - 7.39 (m, 2 H) 7.40 - 7.46 (m, 1 H) 7.48 - 7.57 (m, 1 H).

Compound 47; 3-{2-[4-(2-Trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.41 (s, 1 H) 2.81 - 2.96 (m, 2 H) 3.01 - 3.20 (m, 2 H) 3.24 - 3.39 (m, 2 H) 3.47 (d, *J*=12.64 Hz, 1 H) 3.53 - 3.64 (m, 1 H) 3.92 - 4.06 (m, 1 H) 4.08 - 4.19 (m, 1 H) 4.80 (d, *J*=11.14 Hz, 1 H) 5.24 (s, 2 H) 7.00 - 7.09 (m, 2 H) 7.28 - 7.38 (m, 2 H) 7.54 - 7.64 (m, 1 H) 7.68 - 7.84 (m, 2 H).

Compound 48; 3-{2-[4-(2,6-Difluoro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.41 (s, 1 H) 2.85 - 2.99 (m, 2 H) 3.03 - 3.22 (m, 2 H) 3.25 - 3.40 (m, 2 H) 3.47 (d, *J*=12.04 Hz, 1 H) 3.95 - 4.08 (m, 1 H) 4.10 - 4.19 (m, 1 H) 4.78 - 4.91 (m, 1 H) 5.13 (s, 2 H) 7.08 (d, *J*=8.73 Hz, 2 H) 7.15 - 7.25 (m, 2 H) 7.34 (d, *J*=8.73 Hz, 2 H) 7.48 - 7.60 (m, 1 H).

Compound 49; 3-{2-[4-(3-Trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.83 - 2.94 (1 H, m) 3.02 - 3.19 (1 H, m) 3.26 - 3.37 (1 H, m)3.47 (1 H, d, J=12.4 Hz) 3.57 (1 H, dd, J=12.4, 0.8 Hz) 3.93 - 4.05 (1 H, m, J=12.3, 12.3, 1.3, 1.0 Hz)4.07 - 4.18 (1 H, m) 4.80 (1 H, d) 5.23 (1 H, s) 7.07 (1 H, d) 7.33 (1 H, d) 7.64 (1 H, t) 7.68 - 7.74 (1H, m) 7.77 (1 H, d, J=7.6 Hz) 7.82 (1 H, s).

Compound 50; 3-{2-[4-(2,6-Dimethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.32 (s, 6 H) 2.83 - 2.94 (m, 2 H) 3.02 - 3.21 (m, 2 H) 3.26 - 3.40 (m, 3 H) 3.41 - 3.51 (m, 1 H) 3.51 - 3.61 (m, 1 H) 3.91 - 4.06 (m, 1 H) 4.06 - 4.19 (m, 1 H) 4.82 (dd, J=9.85, 1.01 Hz, 1 H) 5.05 (s, 2 H) 6.74 - 6.81 (m, 0 H) 7.04 - 7.11 (m, 2 H) 7.17 (dd, J=8.34, 6.06 Hz, 2 H) 7.29 - 7.37 (m, 2 H).

Compound 51; 3-{2-[4-(3,5-Dichloro-pyridin-4-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.81 - 2.98 (m, 2 H) 3.01 - 3.22 (m, 2 H) 3.24 - 3.42 (m, 2 H) 3.42 - 3.70 (m, 2 H) 3.92 - 4.19 (m, 2 H) 4.85 (dd, J=11.17, 1.13 Hz, 1 H) 5.25 (s, 2 H) 7.03 - 7.14 (m, 2 H) 7.26 - 7.41 (m, 2 H) 8.61 - 8.79 (m, 2 H)

Compound 52; 3-{2-[4-(2,4-Dichloro-pyridin-3-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.83 - 2.98 (2 H, m) 3.01 - 3.22 (2 H, m) 3.23 - 3.53 (3 H, m) 3.52 - 3.65 (1 H, m) 3.94 - 4.07 (1 H, m) 4.08 - 4.21 (1 H, m) 4.84 (1 H, dt, J=11.1, 0.7 Hz) 5.21 - 5.31(2 H, m) 7.04 - 7.18 (2 H, m) 7.29 - 7.44 (2 H, m) 7.74 (1 H, d, J=5.3 Hz) 8.45 (1 H, d, J=5.3 Hz).

Compound 53; 3-{2-[4-(2,6-Dichloro-phenylcarbamoyl)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.85 - 2.98 (1 H, m) 3.02 - 3.25 (1 H, m) 3.35 (1 H, t, J=8.1 Hz) 3.51 (1 H, d, J=12.6 Hz) 3.67 - 3.77 (1 H, m) 4.07 (1 H, t, J=12.4 Hz) 4.15 - 4.26 (1 H, m) 4.96 - 5.07 (1 H, m) 7.41 (1 H, t, J=8.1 Hz) 7.51 - 7.64 (2 H, m) 8.06 (1 H, d, J=8.3 Hz).

Compound 54; 3-{2-[4-(2,6-Dichloro-phenoxymethyl)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.86 - 2.99 (2 H, m) 3.00 - 3.25 (2 H, m) 3.24 - 3.42 (2 H, m) 3.50 (1 H, d, J=12.1 Hz) 3.65 (1 H, d, J=12.6 Hz) 4.00 - 4.12 (1 H, m) 4.12 - 4.24 (1 H, m) 4.89 - 4.99 (1 H, m) 5.03 (2 H, s) 7.22 (1 H, t, J=8.1 Hz) 7.36 - 7.49 (2 H, m) 7.49 - 7.63 (3 H, m).

Compound 55; 3-(2-{4-[2-(2,6-Dichloro-phenyl)-vinyl]-phenyl}-morpholin-4-yl)-propionic acid hydrochloride ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.85 - 2.95 (1 H, m) 3.07 (1 H, t, J=11.5 Hz) 3.12 - 3.21 (1 H, m) 3.35 (1 H, t, J=7.8 Hz) 3.43 - 3.55 (1 H, m) 3.60 - 3.70 (1 H, m) 3.97 - 4.07 (1 H, m) 4.14 - 4.22 (1 H, m) 4.90 (1 H, dd, J=11.0, 0.6 Hz) 7.07 - 7.14 (1 H, m) 7.16 - 7.24 (1 H, m) 7.34 (1 H, t, J=8.1 Hz) 7.43 (1 H, d, J=8.3 Hz) 7.55 (1 H, d, J=8.1 Hz) 7.68 (1 H, d, J=8.3 Hz).

Compound 56; 3-[2-(4-Phenethyl-phenyl)-morpholin-4-yl]-propionic acid hydrochloride ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.80 - 3.23 (7 H, m), 3.24 - 3.80 (4 H, m), 3.96 - 4.29 (2 H, m), 4.80 - 5.04 (1 H, m), 7.10 - 7.52 (9 H, m).

Compound 57; 3-{2-[4-(2,6-Dichloro-benzylamino)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.86 - 2.98 (2 H, m) 3.01 - 3.18 (2 H, m) 3.26 - 3.36 (2 H, m)3.40 - 3.53 (2 H, m) 3.94 - 4.05 (1 H, m) 4.05 - 4.14 (1 H, m) 4.35 - 4.43 (2 H, m) 4.72 (1 H, dt, J=10.9, 1.1 Hz) 6.72 (2 H, d, J=8.6 Hz) 7.07 - 7.20 (2 H, m) 7.12 (1 H, d, J=8.8 Hz) 7.35 - 7.45 (1 H, m) 7.51 (1 H, d, J=7.8 Hz).

Compound 58; 3-{2-[4-(2,6-Dichloro-benzoylamino)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.87 - 2.97 (2 H, m) 2.99 - 3.22 (2 H, m) 3.27 - 3.42 (3 H, m)3.49 (1 H, d, J=11.9 Hz) 3.60 (1 H, dd, J=11.9, 1.0 Hz) 3.98 - 4.10 (1 H, m) 4.10 - 4.23 (1 H, m) 4.88(1 H, dd, J=11.0, 0.6 Hz) 7.38 (2 H, d, J=8.6 Hz) 7.46 - 7.55 (1 H, m) 7.55 - 7.63 (1 H, m) 7.72 (1 H, d,J=8.6 Hz).

Compound 59; 3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-methyl-morpholin-4-yl}-propionic acid hydrochloride ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.21 – 1.84 (m, 3 H) 2.95 (m, 2 H) 3.02 - 3.42 (m, 6 H) 3.70 - 4.20 (m, 2 H) 5.24 (s, 2 H) 7.10 (d, *J*=7.6 Hz, 2 H) 7.43 - 7.52 (m, 3 H) 7.56 - 7.60 (m, 2 H) 11.41 (br. s., 1 H) 12.85 (br. s.,1 H).

Compound 60; 3-{2-[4-(2-Chloro-6-fluoro-benzyloxy)-phenyl]-2-methyl-morpholin-4-yl}-propionic acid hydrochloride ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.21 - 1.93 (m, 3 H) 2.86 - 3.01 (m, 2 H) 3.02 - 3.44 (m, 6 H) 3.60 - 4.20 (m, 2 H) 5.16 (s, 2 H) 7.09 (d, *J*=7.8 Hz, 2 H) 7.34 (t, *J*=8.8 Hz, 1 H) 7.41 - 7.49 (m, 3 H) 7.49 - 7.56 (m, 1 H) 11.36 (br. s., 1 H) 12.72 (br. s., 1 H).

Compound 61; 3-{2-[4-(2-Trifluoromethyl-benzyloxy)-phenyl]-2-methyl-morpholin-4-yl}-propionic acid hydrochloride ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.21 - 1.90 (m, 3 H) 2.86 - 3.00 (m, 2 H) 3.02 - 3.46 (m, 6 H) 3.52 - 4.22 (m, 2 H) 7.04 (d, *J*=7.3 Hz, 2 H) 7.44 (d, *J*=8.6 Hz, 2 H) 7.60 (t, *J*=7.3 Hz, 1 H) 7.69 - 7.85 (m, 3 H) 11.33 (m, 1 H) 12.71 (br. s., 1 H).

Compound 62; 3-[2-Methyl-2-(4-octyloxy-phenyl)-morpholin-4-yl]-propionic acid hydrochloride ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.80 - 0.92 (m, 3 H) 1.20 - 1.89 (m, 13 H) 1.71 (quin, *J*=6.9 Hz, 2 H) 2.85 - 2.99 (m, 2 H) 3.00 - 3.43 (m, 6 H) 3.53 - 4.16 (m, 2 H) 3.95 (t, *J*=6.4 Hz, 2 H) 6.94 (d, *J*=8.7 Hz, 2 H) 7.39 (d, *J*=8.7 Hz, 2 H) 11.23 (br. s., 1 H) 12.72 (br. s., 1 H).

Compound 63; 4-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-butyric acid hydrochloride ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.92 – 2.04 (m, 2 H) 2.35 (t, *J*=7.20 Hz, 2 H) 3.02 – 3.18 (m , 4 H) 3.45 – 3.64 (m, 2 H) 4.00 – 4.18 (m, 2 H) 4.83 – 4.91 (m, 1 H) 5.23 (s, 2 H) 7.07 – 7.13 (m, 2 H) 7.32 – 7.38 (m, 2 H) 7.45 – 7.51 (m, 1 H) 7.58 (d, *J*=7 Hz, 2 H) 11.3 (br. s, 1 H) 12.3 (br. s, 1 H).

Compound 64; 3-(2-{4-[1-(2,6-Dichloro-phenyl)-ethoxy]-phenyl}-morpholin-4-yl)-propionic acid hydrochloride ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.71 (d, *J*=6.6 Hz, 3 H) 2.82 - 2.91 (m, 2 H) 2.96 - 3.13 (m, 2 H) 3.21 - 3.35 (m, 2 H) 3.39 - 3.56 (m, 2 H) 3.96 (t, *J*=12.0 Hz, 1 H) 4.08 (d, *J*=11.1 Hz, 1 H) 4.74 (d, *J*=10.6 Hz, 1 H) 6.04 (q, *J*=6.6 Hz, 1 H) 6.84 (d, *J*=8.7 Hz, 2 H) 7.24 (d, *J*=8.7 Hz, 2 H) 7.31 (t, *J*=8.1 Hz, 1 H) 7.44 (d, *J*=8.1 Hz, 2 H) 11.51 (br. s., 1 H) 12.69 (br. s., 1 H).

Compound 65; 3-(2-{4-[2-(2,6-Dichloro-phenyl)-ethyl]-phenyl}-morpholin-4-yl)-propionic acid hydrochloride ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.76 - 2.83 (m, 2 H) 2.85 - 2.93 (m, 2 H) 3.01 - 3.20 (m, 4 H) 3.34 (t, *J*=8.0 2 H) 3.45 - 3.66 (m, 2 H) 3.95 - 4.05 (m, 1 H) 4.16 (d, *J*=11.6 Hz 1 H) 4.84 (d, *J*=10.1 Hz 1 H) 7.27 - 7.36 (m, 5 H) 7.48 (d, *J*=8.1 Hz, 2 H) 11.31 (br. s., 1 H) 12.67 (br. s., 1 H).

Compound 66; **3-{2-[3-Methoxy-4-(2-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride.** Mp 170–172°C.

Compound 67; **3-{2-[4-(2-Chloro-6-fluoro-benzyloxy)-3-methoxy-phenyl]-morpholin-4-yl}-propionic acid hydrochloride.** Mp 169–171°C.

Compound 68; **3-{2-[4-(2,6-Dichloro-benzyloxy)-3-methoxy-phenyl]-morpholin-4-yl}-propionic acid hydrochloride .** Mp 214–216°C.

Compound 139: **3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-2-methyl-propionic acid hydrochloride** ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.20 - 1.26 (m, 3 H) 3.01 - 3.22 (m, 4 H) 3.41 - 3.63 (m, 3 H) 3.97 - 4.08 (m, 1 H) 4.09 - 4.16 (m, 1 H) 4.81 - 4.90 (m, 1 H) 5.24 (s, 2 H) 7.10 (d, *J*=8.6 Hz, 2H) 7.31 - 7.37 (m, 2 H) 7.45 - 7.51 (m, 1 H) 7.57 (d, *J*=8.3 Hz, 2 H) 10.2 – 10.9 (bs, 1H) 12.5 – 13.1 (bs, 1H).

Compound 140: **3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-butyric acid hydrochloride** ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.34 (d, *J*=6.6 Hz, 3 H) 2.54 - 2.64 (m, 1 H) 3.03 - 3.24 (m, 2 H) 3.33 - 3.76 (m, 4H) 4.01 - 4.22 (m, 2 H) 4.86 - 4.94 (m, 1 H) 5.23 (s, 2 H) 7.10 (d, *J*=8.6 Hz, 2 H) 7.38 (d, *J*=8.6 Hz, 2 H) 7.45 – 7.51 (m, 1 H) 7.57 (d, *J*=8.3 Hz, 2 H) 10.9 – 11.4 (bs, 1H) 12.5 – 13.0 (bs, 1H).

Compound 142: Phosphoric acid mono-(2-{2-[4-(2,6-dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-ethyl) ester hydrochloride ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.03 - 3.19 (m, 2 H) 3.30 - 3.41 (m, 2 H) 3.43 - 3.51 (m, 1 H) 3.52 - 3.65 (m, 1 H) 3.94 - 4.05 (m, 1 H) 4.09 - 4.24 (m, 3 H) 4.82 (d, *J*=10.6 Hz, 1 H) 5.23 (s, 2 H) 7.10 (d, *J*=8.6 Hz, 2 H) 7.34 (d, *J*=8.6 Hz, 2 H) 7.44 - 7.51 (m, 1 H) 7.57 (d, *J*=8.3 Hz, 2 H) 10.1 – 11.5 (bs, 1H).

Compound 143: 3-{2-[3-Methyl-4-(2-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride Mp 191–194°C.

Compound 144: 3-{2-[4-(2-Chloro-6-fluoro-benzyloxy)-3-methyl-phenyl]-morpholin-4-yl}-propionic acid hydrochloride Mp 194–196°C.

Compound 145: 3-{2-[4-(2,6-Dichloro-benzyloxy)-3-methyl-phenyl]-morpholin-4-yl}-propionic acid hydrochloride Mp 198–200°C.

Compound 147: **3-{2-[4-(2,3-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride.** Mp222–227°C.

Compound 148: **3-{2-[4-(2-Chloro-5-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride** Mp 218.5–222°C.

Compound 152: **3-{2-[4-(2-Chloro-3-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride.** Mp 223 - 228°C.

Compound 153: **3-{2-[4-(2-Chloro-6-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride.** Mp 185.5 – 190.5°C.

Compound 154: **3-{2-[4-(2,3,6-Trichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride.** Mp 213 - 216°C.

Compound 155: **3-{2-[4-(2-Chloro-6-methyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride.** Mp 215 - 218°C.

Compound 156: **3-{2-[4-(2-Chloro-5-methyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride.** Mp 209 - 213°C.

Compound 157: **3-{2-[4-(2-Chloro-5-ethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride.** Mp 198 - 202°C.

Compound 158: **3-{2-[4-(2-Chloro-5-propyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride.** Mp 199 - 203°C.

Compound 159: **3-{2-[4-(2-Chloro-5-isopropyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride.** Mp 203 - 207°C.

Compound 160: **3-{2-[4-(2,4,6-Trichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride.** Mp 215 - 218°C.

Compound 161: **3-{2-[4-(2,6-Dichloro-4-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride.** Mp 221 - 226°C.

Compound 162: **3-{2-[4-(2,6-Dichloro-4-iodo-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride.** Mp 210 - 215°C.

Compound 163: **3-(2-{4-[3-(2-Fluoro-phenyl)-propoxy]-phenyl}-morpholin-4-yl)-propionic acid hydrochloride** ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.96 - 2.05 (m, 2 H) 2.76 - 2.81 (m, 2 H) 2.83 - 2.96 (m, 2 H) 3.04 - 3.17 (m, 2 H) 3.28 - 3.37 (m, 2 H) 3.47 (d, *J*=12.2 Hz, 1 H) 3.56 (d, *J*=12.2 Hz, 1 H) 3.94 - 4.04 (m, 3 H) 4.08 - 4.16 (m, 1 H) 4.78 (d, *J*=10.6 Hz 1 H) 6.95 (*J*=8.6 Hz, 2 H) 7.10 - 7.17 (m, 2 H) 7.22 - 7.34 (m, 4 H) 11.0-11.6 (bs, 1 H) 12.1-12.9 (bs, 1 H).

Compound 164: **3-{2-[4-(2,6-Dichloro-4-ethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride.** Mp 198 - 202°C.

Compound 165: **3-{2-[4-(2,6-Dichloro-4-methyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride.** Mp 197 - 204°C.

Compound 166: **3-[2-(4-Benzyloxy-phenyl)-5-oxo-morpholin-4-yl]-propionic acid.** ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.71 - 2.79 (m, 2 H) 3.41 - 3.49 (m, 1 H) 3.56 - 3.72 (m, 3 H) 4.28 - 4.45 (m, 2 H) 4.70 - 4.76 (m, 1 H) 5.07 (s, 2 H) 6.98 (d, *J*=8.8 Hz, 2 H) 7.27 - 7.45 (m, 7 H).

Compound 167: **3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-5-oxo-morpholin-4-yl}-propionic acid.** ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.67 - 2.83 (m, 2 H) 3.43 - 3.51

(m, 1 H) 3.57 - 3.66 (m, 1 H) 3.67 - 3.75 (m, 2 H) 4.29 - 4.47 (m, 2 H) 4.72 - 4.79 (m, 1 H) 5.27 (s, 2 H) 7.03 (d, J=8.8 Hz, 2 H) 7.22 - 7.29 (m, 1 H) 7.30 - 7.40 (m, 4 H)

Compound 168: 3-[2-(4-Octyloxy-phenyl)-5-oxo-morpholin-4-yl]-propionic acid ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.85 - 0.93 (m, 3 H) 1.22 - 1.39 (m, 8 H) 1.39 - 1.50 (m, 2 H) 1.72 - 1.82 (m, 2 H) 2.67 - 2.81 (m, 2 H) 3.41 - 3.48 (m, 1 H) 3.61 (t, *J*=12.3 Hz, 1 H) 3.69 (t, *J*=6.6 Hz, 2 H) 3.94 (t, *J*=6.6 Hz, 2 H) 4.27 - 4.45 (m, 2 H) 4.69 – 4.74 (m, 1H) 6.89 (d, *J*=8.8 Hz, 2 H) 7.28 (d, *J*=8.8 Hz, 2 H).

Compound 169: 3-(2-{4-[3-(2-Trifluoromethyl-phenyl)-propoxy]-phenyl}-morpholin-4-yl)-propionic acid hydrochloride ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.97 - 2.07 (m, 2 H) 2.84 - 2.95 (m, 4 H) 3.04 – 3.19 (m, 2 H) 3.29 - 3.38 (m, 2 H) 3.47 (d, *J*=11.9 Hz, 1 H) 3.53 - 3.60 (m, 1 H) 3.94 – 4.08 (m, 3 H) 4.09 - 4.17 (m, 1 H) 4.80 (d, *J*=9.3 Hz, 1 H) 6.96 (d, *J*=8.7 Hz, 2 H) 7.30 (d, *J*=8.7 Hz, 2 H) 7.39 - 7.46 (m, 1 H) 7.52 (d, *J*=7.8 Hz, 1 H) 7.58 - 7.65 (m, 1 H) 7.68 (d, *J*=7.8 Hz, 1 H) 11.2 (bs, 1 H) 12.8 (bs, 1 H).

Compound 170: 3-(2-{4-[3-(2-Chloro-6-fluoro-phenyl)-propoxy]-phenyl}-morpholin-4-yl)-propionic acid hydrochloride ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.90 - 2.02 (m, 2 H) 2.83 - 2.95 (m, 4 H) 3.04 – 3.18 (m, 2 H) 3.33 (t, *J*=7.9 Hz, 2 H) 3.47 (d, *J*=11.9 Hz, 1 H) 3.57 (d, *J*=11.9 Hz, 1 H) 3.95 - 4.05 (m, 3 H) 4.13 (d, *J*=11.9 Hz, 1 H) 4.78 (d, *J*=10.0 Hz, 1 H) 6.96 (*J*=8.6 Hz, 2 H) 7.16 - 7.23 (m, 1 H) 7.27 - 7.35 (m, 4 H) 10.9 - 11.4 (bs, 1 H) 12.1 - 12.9 (bs, 1 H).

Compound 171: 3-(2-{4-[3-(2,6-Dichloro-phenyl)-propoxy]-phenyl}-morpholin-4-yl)-propionic acid hydrochloride ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.92 - 2.01 (m, 2 H) 2.84 - 2.91 (m, 2 H) 3.01 - 3.16 (m, 3 H) 3.28 – 3.38 (m, 2 H) 3.47 (d, *J*=12.2 Hz, 2 H) 3.58 (d, *J*=12.2 Hz, 1 H) 3.93 - 4.01 (m, 1 H) 4.03 - 4.08 (m, 2 H) 4.13 (d, *J*=12.1 Hz, 1 H) 4.77 (d, *J*=10.4 Hz, 1 H) 6.95 (d, *J*=8.9 Hz, 2 H) 7.25 - 7.33 (m, 3 H) 7.46 (d, *J*=8.1 Hz, 2 H) 10.8 - 11.4 (bs, 1 H) 12.2 - 12.9 (bs, 1 H).

Compound 172: 3-(2-{4-[3-(4-Chloro-phenyl)-propoxy]-phenyl}-morpholin-4-yl)-propionic acid hydrochloride ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.95 - 2.05 (m, 2 H) 2.69 - 2.76 (m, 2 H) 2.84 - 2.94 (m, 2 H) 3.04 - 3.16 (m, 2 H) 3.28 - 3.37 (m, 2 H) 3.47 (d, *J*=12.3 Hz, 1 H) 3.56 (d, *J*=12.3, 1 H) 3.92 - 4.04 (m, 3 H) 4.15 (d, *J*=12.3 Hz, 1 H) 4.80 (d, *J*=9.6 Hz, 1 H) 6.95 (d, *J*=8.7 Hz, 2 H) 7.24 - 7.36 (m, 6 H) 10.9 - 11.9 (bs, 1 H) 12.2 - 12.9 (bs, 1 H).

Compound 173: 3-(2-{4-[3-(2-Chloro-phenyl)-propoxy]-phenyl}-morpholin-4-yl)-propionic acid hydrochloride ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.97 - 2.09 (m, 2 H) 2.83 - 2.95 (m, 4 H) 3.04 - 3.17 (m, 2 H) 3.33 (t, *J*=7.9 Hz, 2 H) 3.47 (d, *J*=12.1 Hz, 1 H) 3.56 (d, *J*=12.1 Hz, 1 H) 3.96 - 4.05 (m, 3 H) 4.13 (d, *J*=12.1 Hz, 1 H) 4.79

(d, *J*=10.0 Hz, 1 H) 6.96 (*J*=8.6 Hz, 2 H) 7.20 - 7.31 (m, 4 H) 7.33 - 7.37 (m, 1 H) 7.40 - 7.45 (m, 1 H) 11.0-11.4 (bs, 1 H) 12.1-12.9 (bs, 1 H).

Compound 174: 3-(2-{4-[3-(2,3-Difluoro-phenyl)-propoxy]-phenyl}-morpholin-4-yl)-propionic acid hydrochloride ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.98 - 2.08 (m, 2 H) 2.82 - 2.88 (m, 2 H) 2.88 - 2.94 (m, 2 H) 3.01 - 3.16 (m, 2 H) 3.28 – 3.38 (m, 2 H) 3.47 (d, *J*=12.2 Hz, 1 H) 3.58 (d, *J*=12.2 Hz, 1 H) 3.93 - 4.08 (m, 3 H) 4.13 (d, *J*=12.1 Hz, 1 H) 4.82 (d, *J*=10.4 Hz, 1 H) 6.95 (d, *J*=8.9 Hz, 2 H) 7.11 - 7.18 (m, 2 H) 7.22 - 7.32 (m, 3 H) 11.2- 11.9 (bs, 1 H) 12.2 - 12.9 (bs, 1 H).

Compound 175: 3-{2-[3-Chloro-4-(2,6-dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride Mp 179 - 181°C.

Compound 176: 3-{2-[3-Chloro-4-(2-chloro-6-fluoro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride Mp 178 - 180°C.

Compound 177; 3-{2-[3-Chloro-4-(2-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride. Mp 199 - 201°C.

Compound 178; 3-{2-[4-(2-Chloro-6-fluoro-benzyloxy)-2-fluoro-phenyl]-morpholin-4-yl}-propionic acid hydrochloride Mp 189 - 190°C.

Compound 179; 3-{2-[4-(2,6-Dichloro-benzyloxy)-2-fluoro-phenyl]-morpholin-4-yl}-propionic acid hydrochloride Mp 174.5 - 178°C.

Compound 180; 3-{2-[2-Fluoro-4-(2-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride Mp 201 – 201.5°C.

Compound 181; 3-{2-[4-(2,6-Dichloro-3-ethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.19 (t, *J*=7.5 Hz, 3 H) 2.75 (q, *J*=7.5 Hz, 2 H) 2.83 - 2.95 (m, 2 H) 2.99 - 3.18 (m, 2 H) 3.30 - 3.38 (m, 2 H) 3.48 (d, *J*=12.7 Hz, 1 H) 3.57 - 3.65 (m, 1 H) 3.95 – 4.04 (m, 1 H) 4.10 - 4.17 (m, 1 H) 4.81 (d, *J*=11.9 Hz, 1 H) 5.26 (s, 2 H) 7.11 (d, *J*=8.7 Hz, 2 H) 7.34 (d, *J*=8.7 Hz, 2 H) 7.46 (d, *J*=8.4 Hz, 1 H) 7.52 (d, *J*=8.4 Hz, 1 H) 10.9 - 11.9 (bs, 1 H) 12.2 - 12.9 (bs, 1 H).

Compound 182; 3-{2-[4-(2-Chloro-6-ethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.17 (t, *J*=7.5 Hz, 3 H) 2.72 (q, *J*=7.5 Hz, 2 H) 2.83 - 2.95 (m, 2 H) 3.05 - 3.18 (m, 2 H) 3.29 - 3.38 (m, 2 H) 3.48 (d, *J*=11.9 Hz, 1 H) 3.55 – 3.65 (m, 1 H) 3.96 - 4.04 (m, 1 H) 4.11 - 4.18 (m, 1 H) 4.82 (d, *J*=11.9 Hz, 1 H) 5.17 (s, 2 H) 7.10 (d, *J*=8.7 Hz, 2 H) 7.27 - 7.39 (m, 5 H) 11.1 - 11.9 (bs, 1 H) 12.2 - 12.9 (bs, 1 H).

Compound 183; 3-{2-[4-(2-Chloro-6-isopropyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.21 (d, *J*=6.8 Hz, 6 H) 2.84 - 2.96 (m, 2 H) 3.08 - 3.22 (m, 3 H) 3.29 - 3.38 (m, 2 H) 3.48 (d,

J=12.8 Hz, 1 H) 3.58 (d, *J*=12.8 Hz, 1 H) 3.95 - 4.02 (m, 1 H) 4.10 - 4.18 (m, 1 H) 4.82 (d, *J*=10.1 Hz, 1 H) 5.21 (s, 2 H) 7.10 (d, *J*=8.7 Hz, 2 H) 7.31 - 7.44 (m, 5 H) 11.0 - 11.8 (bs, 1 H) 12.2 - 12.9 (bs, 1 H).

Compound 184; 3-{2-[4-(2-Chloro-6-cyclopropyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.64 - 0.76 (m, 2 H) 0.87 - 0.96 (m, 2 H) 2.02 - 2.11 (m, 1 H) 2.85 - 2.97 (m, 2 H) 3.06 - 3.18 (m, 2 H) 3.32 - 3.41 (m, 2 H) 3.48 (d, *J*=12.4 Hz, 1 H) 3.55 – 3.61 (m, 1 H) 3.97 - 4.03 (m, 1 H) 4.10 - 4.14 (m, 1 H) 4.83 (d, *J*=10.6 Hz, 1 H) 5.33 (s, 2 H) 7.10 dd, *J*=6.9 1.6 Hz, 1 H) 7.12 (d, *J*=8.8 Hz, 2 H) 7.30 – 7.37 (m, 4 H) 11.1 – 11.8 (bs, 1 H) 12.4 – 13.0 (bs, 1 H).

Compound 185; 3-{2-[4-(2-Chloro-6-isobutyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.85 (d, *J*=6.6 Hz, 6 H) 1.78 - 1.90 (m, 1 H) 2.58 (d, *J*=7.2 Hz, 2 H) 2.84 - 2.92 (m, 2 H) 3.06 - 3.18 (m, 2 H) 3.32 - 3.41 (m, 2 H) 3.41 - 3.53 (m, 2 H) 3.97 - 4.07 (m, 1 H) 4.10 - 4.18 (m, 1 H) 4.83 (d, *J*=10.5 Hz, 1 H) 5.13 (s, 2 H) 7.06 (d, *J*=8.8 Hz, 2 H) 7.23 (dd, *J*=7.1, 1.8 Hz, 1 H) 7.30 - 7.41 (m, 4 H) 11.1 – 11.8 (bs, 1 H) 12.4 – 12.9 (bs, 1 H).

Compound 186; 3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-5,5-dimethyl-morpholin-4-yl}-propionic acid hydrochloride ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.37 - 1.47 (m, 6 H) 2.91 - 3.03 (m, 3 H) 3.12 - 3.23 (m, 1 H) 3.51 - 3.64 (m, 2 H) 3.79 - 3.88 (m, 1 H) 3.92 - 4.01 (m, 1 H) 4.93 (d, *J*=11.9 Hz, 1 H) 5.24 (s, 2 H) 7.11 (d, *J*=8.8 Hz, 2 H) 7.38 (d, *J*=8.8 Hz, 2 H) 7.45 - 7.52 (m, 1 H) 7.58 (d, *J*=7.8 Hz, 2 H) 10.9 - 11.3 (bs, 1 H) 12.6 – 13.1 (bs, 1 H).

Compound 187; 3-[5,5-Dimethyl-2-(4-octyloxy-phenyl)-morpholin-4-yl]-propionic acid hydrochloride ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.81 - 0.89 (m, 3 H) 1.17 - 1.47 (m, 16 H) 1.63 – 1.75 (m, 2 H) 2.91 - 3.04 (m, 3 H) 3.12 - 3.23 (m, 1 H) 3.47 - 3.64 (m, 2 H) 3.74 - 3.84 (m, 1 H) 3.91 - 4.03 (m, 3 H) 4.93 (d, *J*=11.9 Hz, 1 H) 6.95 (d, *J*=8.8 Hz, 2 H) 7.33 (d, *J*=8.8 Hz, 2 H) 11.1 (bs, 1 H) 12.8 (bs, 1 H).

Compound 188; 3-{2-[4-(2,6-Dichloro-benzyloxy)-2-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid hydrochloride Mp 195 -197°C.

Compound 189; 3-[2-(4-Octyloxy-2-trifluoromethyl-phenyl)-morpholin-4-yl]-propionic acid hydrochloride Mp 178.5 -180.5°C.

Compound 190; 3-{6-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2,2-dimethyl-morpholin-4-yl}-propionic acid hydrochloride ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.27 (s, 3 H) 1.53 (s, 3 H) 2.85 - 2.97 (m, 4 H) 3.29 - 3.35 (m, 2 H) 3.46 - 3.53 (m, 2 H) 4.93 (d, *J*=11.9 Hz, 1 H) 5.24 (s, 2 H) 7.10 (d, *J*=8.8 Hz, 2 H) 7.33 (d, *J*=8.8 Hz, 2 H)

7.44 - 7.52 (m, 1 H) 7.57 (d, *J*=7.8 Hz, 2 H) 10.5 – 10.9 (bs, 1 H) 12.5 – 13.0 (bs, 1 H).

Compound 191; 3-[2,2-Dimethyl-6-(4-octyloxy-phenyl)-morpholin-4-yl]-propionic acid hydrochloride ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.86 (t, *J*=6.8 Hz, 3 H) 1.19 - 1.45 (m, 13 H) 1.54 (s, 3 H) 1.64 - 1.75 (m, 2 H) 2.84 - 3.02 (m, 4 H) 3.24 - 3.36 (m, 2 H) 3.39 - 3.51 (m, 2 H) 3.95 (t, *J*=6.5 Hz, 2 H) 4.92 (d, *J*=10.6 Hz, 1 H) 6.94 (d, *J*=8.5 Hz, 2 H) 7.27 (d, *J*=8.5 Hz, 2 H) 10.9 – 11.4 (bs, 1 H) 12.5 – 13.0 (bs, 1 H).

Compound 192; 3-{2-[4-(2,6-Dichloro-4-propyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride. Mp 101 - 103°C.

Compound 193; 3-{2-[4-(2,6-Dichloro-4-isopropyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride. Mp 108 - 110°C.

Compound 194; 3-{2-[4-(2,6-Dichloro-4-prop-1-ynyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride. Mp 220 - 224°C.

Compound 195; 3-{2-[4-(2-Chloro-6-trifluoromethoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.85 - 2.97 (m, 2 H) 3.06 - 3.18 (m, 2 H) 3.29 - 3.38 (m, 1 H) 3.48 (d, *J*=11.9 Hz, 1 H) 3.59 (d, *J*=11.9, 1 H) 3.95 - 4.07 (m, 1 H) 4.09 - 4.18 (m, 1 H) 4.83 (d, *J*=10.6 Hz, 1 H) 5.16 (s, 2 H) 7.09 (d, *J*=8.8 Hz, 2 H) 7.35 (d, *J*=8.8 Hz, 2 H) 7.48 -7.52 (m, 2 H) 7.58 - 7.68 (m, 2 H) 11.2 – 11.9 (bs, 1 H) 12.4 – 13.0 (bs, 1 H).

Compound 196; 3-{2-[4-(2-Chloro-4-methyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.32 (s, 3 H) 2.83 - 2.92 (m, 2 H) 3.04 - 3.17 (m, 2 H) 3.28 - 3.40 (m, 2 H) 3.47 (d, *J*=10.6 Hz, 1 H) 3.57 (d, *J*=10.6 Hz, 1 H) 3.94 - 4.05 (m, 1 H) 4.08 - 4.16 (m, 1 H) 4.83 (d, *J*=10.2 Hz, 1 H) 5.12 (s, 2 H) 7.04 (d, *J*=8.8 Hz, 2 H) 7.18 (d, *J*=7.8 Hz, 1 H) 7.27 - 7.39 (m, 3 H) 7.46 (d, *J*=7.8 Hz, 1 H) 11.2 – 12.0 (bs, 1 H) 12.3 – 13.0 (bs, 1 H).

Compound 197; 3-{2-[4-(2-Chloro-3-methyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.38 (s, 3 H) 2.81 - 2.89 (m, 2 H) 3.04 – 3.18 (m, 2 H) 3.30 - 3.52 (m, 3 H) 3.55 - 3.61 (m, 1 H) 3.92 – 4.02 (m, 1 H) 4.13 (d, *J*=12.6 Hz, 1 H) 4.78 (d, *J*=10.2 Hz, 1 H) 5.17 (s, 2 H) 7.06 (d, *J*=8.8 Hz, 2 H) 7.27 - 7.43 (m, 5 H) 10.8 – 11.5 (bs, 1 H) 12.3 – 13.0 (bs, 1 H).

Compound 198; 3-{2-[4-(2,4-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.85 - 2.97 (m, 2 H) 3.04 - 3.17 (m, 2 H) 3.28 - 3.38 (m, 2 H) 3.42 - 3.51 (m, 1 H) 3.52 - 3.62 (m, 1 H) 3.96 - 4.06 (m, 1 H) 4.09 - 4.17 (m, 1 H) 4.83 (d, *J*=10.4 Hz, 1 H) 5.16 (s, 2 H) 7.06 (d,

J=8.8 Hz, 2 H) 7.32 (d, *J*=8.8 Hz, 2 H) 7.49 (dd, *J*=8.3, 2.1 Hz, 1 H) 7.61 (d, *J*=8.3 Hz, 1 H) 7.70 (d, *J*=2.1 Hz, 1 H) 11.2 – 12.0 (bs, 1 H) 12.3 – 12.9 (bs, 1 H).

Compound 199; 2,6-Dichloro-benzoic acid 4-[4-(2-carboxy-ethyl)-morpholin-2-yl]-phenyl ester hydrochloride. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.89 - 2.96 (m, 2 H) 3.09 - 3.22 (m, 2 H) 3.30 - 3.41 (m, 2 H) 3.51 (d, *J*=12.0 Hz, 1 H) 3.70 (d, *J*=12.0 Hz, 1 H) 4.01 - 4.11 (m, 1 H) 4.15 - 4.23 (m, 1 H) 4.96 (d, *J*=10.5 Hz, 1 H) 7.36 (d, *J*=8.7 Hz, 2 H) 7.55 (d, *J*=8.7 Hz, 2 H) 7.61 - 7.73 (m, 3 H)) 11.2 – 11.9 (bs, 1 H) 12.1 – 12.7 (bs, 1 H).

Compound 200; 3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-cyclobutanecarboxylic acid hydrochloride. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.40 - 2.53 (m, 2 H) 2.81 – 3.00 (m, H) 3.32 - 3.50 (m, 4 H) 3.54 - 3.66 (m, 1 H) 3.89 - 4.01 (m, 1 H) 4.10 - 4.20 (m, 1 H) 4.75 (d, *J*=10.8 Hz, 1 H) 5.20 (s, 2 H) 7.10 (d, *J*=8.8 Hz, 2 H) 7.37 (d, *J*=8.8 Hz, 2 H)7.45 - 7.50 (m, 1 H) 7.55 - 7.59 (m, 2 H) 11.1(bs, 1 H) 12.6 (bs, 1 H).

Compound 201; 3-{2-[4-(2,6-Dichloro-benzylsulfanyl)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.84 - 2.96 (m, 2 H) 3.05 - 3.09 (m, 1 H) 3.11 - 3.18 (m, 1 H) 3.33 (t, *J*=7.9 Hz, 1 H) 3.49 (d, *J*=11.0 Hz, 1 H) 3.64 (d, *J*=11.0 Hz, 1 H) 3.97 - 4.06 (m, 1 H) 4.12 - 4.20 (m, 1 H) 4.41 (s, 2 H) 4.87 (1 H) 4.86 (d, *J*=10.4 Hz, 1 H) 7.31 - 7.39 (m, 3 H) 7.42 - 7.52 (m, 4 H) 11.0 – 12.0 (bs, 1 H) 12.3 – 13.0 (bs, 1 H).

Compound 202; 3-{2-[4-(2-Chloro-benzylsulfanyl)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.84 - 2.96 (m, 2 H) 3.00 - 3.18 (m, 2 H) 3.28 - 3.37 (m, 2 H) 3.47 (d, *J*=12.0 Hz, 1 H) 3.61 (d, *J*=12.0 Hz, 1 H) 3.96 - 4.07 (m, 1 H) 4.10 - 4.18 (m, 1 H) 4.32 (s, 2 H) 4.86 (d, *J*=11.4 Hz, 1 H) 7.23 - 7.35 (m, 4 H) 7.37 - 7.43 (m, 3 H) 7.43 - 7.48 (m, 1 H) 11.2 – 11.9 (bs, 1 H) 12.3 – 12.9 (bs, 1 H).

Compound 203; 3-{2-[4-(2-Chloro-6-fluoro-benzylsulfanyl)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.84 - 2.91 (m, 2 H) 3.01 – 3.18 (m, 2 H) 3.30 - 3.38 (m, 2 H) 3.48 (d, *J*=12.0 Hz, 1 H) 3.63 (d, *J*=12.0 Hz, 1 H) 3.93 – 4.05 (m, 1 H) 4.12 – 4.19 (m, 1 H) 4.29 (s, 2 H) 4.80 – 4.88 (m, 1 H) 7.17 - 7.24 (m, 1 H) 7.32 - 7.45 (m, 6 H)) 11.0 – 11.6 (bs, 1 H) 12.1 – 12.7 (bs, 1 H).

Compound 204; 3-[2-(4-Octylsulfanyl-phenyl)-morpholin-4-yl]-propionic acid hydrochloride. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.81 - 0.89 (m, 3 H) 1.19 - 1.31 (m, 8 H) 1.32 - 1.43 (m, 2 H) 1.51 - 1.61 (m, 2 H) 2.86 - 2.92 (m, 2 H) 2.94 - 2.99 (m, 2 H) 3.01 - 3.18 (m, 2 H) 3.27 - 3.37 (m, 2 H) 3.46 (d, *J*=12.1 Hz, 1 H) 3.60 (d, *J*=12.1

Hz, 1 H) 3.96 - 4.06 (m, 1 H) 4.10 - 4.18 (m, 1 H) 4.84 (d, *J*=10.4 Hz, 1 H) 7.28 - 7.36 (m, 4 H) 11.0 –12.9 (bs, 2 H).

Compound 205; 3-{2-[4-(4,4-Dimethyl-cyclohexyloxy)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.93 (d, *J*=3.3 Hz, 6 H) 1.22 – 1.32 (m., 2 H) 1.39 – 1.47 (m., 2 H) 1.50 – 1.61 (m., 2 H) 1.75 – 1.84 (m., 2 H) 2.82 - 2.90 (m, 2 H) 3.02 - 3.16 (m, 2 H) 3.26 - 3.59 (m, 4 H) 3.94 (t, *J*=11.4, 1 H) 4.12 (d, *J*=11.4 Hz, 1 H) 4.30 – 4.39 (m, 1 H) 4.73 (d, *J*=11.4 Hz, 1 H) 6.95 (d, *J*=8.7 Hz, 2 H) 7.27 (d, *J*=8.7 Hz, 2 H) 10.9 (bs, 1 H) 12.9 (bs, 1 H).

Compound 206; 3-{2-[4-(2-Difluoromethoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.84 - 2.92 (m, 2 H) 3.04 - 3.16 (m, 2 H) 3.28 – 3.38 (m, 2 H) 3.43 - 3.51 (m, 1 H) 3.53 - 3.61 (m, 1 H) 3.97 (t, *J*=11.4, 1 H) 4.13 (dd, *J*=11.4, 2.4 Hz, 1 H) 4.78 (d, *J*=11.4 Hz, 1 H) 5.12 (s, 2 H) 7.02 - 7.09 (m, 2 H) 7.25 (t, *J*=75 Hz, 1 H) 7.24 - 7.35 (m, 4 H) 7.42 - 7.48 (m, 1 H) 7.57 (dd, *J*=7.6, 1.9 Hz, 1 H) 11.1 (bs, 1 H) 12.9 (bs, 1 H).

Compound 207; 3-{2-[4-(3-Trifluoromethyl-benzyloxy)-2-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid hydrochloride Mp 209 - 211°C.

Compound 208; 3-{2-[4-(2-Chloro-6-ethyl-benzyloxy)-2-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid hydrochloride Mp 214 - 215°C.

Compound 209; 3-{2-[4-(2-Chloro-6-trifluoromethoxy-benzyloxy)-2-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid hydrochloride Mp 179 - 182°C.

Compound 210; 3-{2-[4-(2-Chloro-6-isopropyl-benzyloxy)-2-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid hydrochloride Mp 206 - 210°C.

Compound 211; 3-{2-[4-(2-Chloro-6-fluoro-benzyloxy)-2-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid hydrochloride Mp 171.5 – 172.5°C.

Compound 212; 3-{2-[4-(2-Chloro-6-trifluoromethyl-benzyloxy)-2-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid hydrochloride Mp 200 - 201°C.

Compound 213; 3-{2-[4-(2-Chloro-6-cyclopropyl-benzyloxy)-2-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid hydrochloride Mp 203 - 204°C.

Compound 214; 3-{2-[4-(2,6-Diethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.15 (t, *J*=7.5 Hz, 6 H) 1.88 (d, *J*=11.3 Hz, 1 H) 2.01 – 2.10 (m., 3 H) 2.45 – 2.55 (m., 2 H) 2.66 (q, *J*=7.4 Hz, 4 H) 2.71 – 2.75 (m., 1 H) 2.80 – 2.85 (m., 1 H) 3.58 – 3.67 (m., 1 H) 3.87 – 3.92 (m., 1 H) 4.37 – 4.42 (m., 1 H) 5.01 (s, 2 H) 7.01 (d, *J*=8.7 Hz, 2 H) 7.11 (d, *J*=7.8 Hz, 2 H) 7.23 - 7.31 (m, 3 H).

Compound 215; 3-{2-[2-Chloro-4-(2,6-dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.87 – 2.93 (m, 2 H) 3.04 – 3.20 (m, 2 H) 3.30 – 3.38 (m, 2 H) 3.46 – 3.55 (m, 2 H) 4.02 – 4.11 (m, 1 H) 4.12 – 4.20 (m, 1 H) 5.19 – 5.25 (m, 1 H) 5.27 (s, 2 H) 7.15 (dd, *J*=8.8, 2.6 Hz, 1 H) 7.28 (d, *J*=2.6 Hz, 1 H) 7.46 - 7.53 (m, 2 H) 7.59 (d, *J*=8.8 Hz, 2 H) 11.8 – 12.9 (bs, 2 H).

Compound 216: 3-{2-[4-(2,6-Dichloro-benzyl)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.83 - 2.93 (m, 2 H) 2.97 - 3.20 (m, 2 H) 3.22 - 3.39 (m, 2 H) 3.47 (d, *J*=12.38 Hz, 1 H) 3.55 - 3.66 (m, 1 H) 3.94 - 4.06 (m, 1 H) 4.08 - 4.19 (m, 1 H) 4.28 (s, 2 H) 4.78 - 4.89 (m, 1 H) 7.15 (d, *J*=8.34 Hz, 2 H) 7.26 - 7.40 (m, 3 H) 7.53 (d, *J*=8.08 Hz, 2 H).

Compound 217: 3-{2-[4-(2-Chloro-6-difluoromethoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.88 - 2.95 (m, 2 H) 3.05 - 3.18 (m, 2 H) 3.28 – 3.39 (m, 2 H) 3.42 - 3.51 (m, 1 H) 3.53 - 3.62 (m, 1 H) 3.97 (t, *J*=11.4, 1 H) 4.13 (d, *J*=11.4 Hz, 1 H) 4.84 (d, *J*=11.4 Hz, 1 H) 5.13 (s, 2 H) 7.08 (d, *J*=8.7 Hz 2 H) 7.33 (t, *J*=85 Hz, 1 H) 7.26 - 7.37 (m, 3 H) 7.47 (d, *J*=7.6 Hz, 1 H) 7.56 (d, *J*=7.6, 1.9 Hz, 1 H) 11.8 (bs, 1 H) 12.8 (bs, 1 H).

Compound 218: 3-{2-[4-(2-Chloro-6-difluoromethoxy-benzyloxy)-2-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid hydrochloride: Mp 192 – 193°C.

Compound 230; 3-[2-(3-Benzyloxy-phenyl)-morpholin-4-yl]-propionic acid hydrochloride Mp 222 - 225°C.

Compound 231; 3-[2-(3-Octyloxy-phenyl)-morpholin-4-yl]-propionic acid hydrochloride Mp 218 - 220°C.

Compound 232; 3-{2-[3-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride Mp 229 - 230°C.

Compound 233; 3-{2-[3-(2-Chloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride Mp 233 - 234°C.

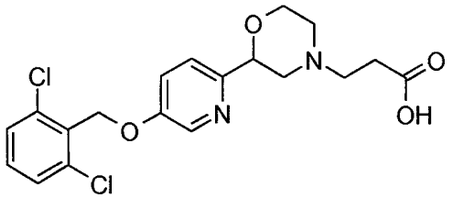
Compound 234; 3-[2-(4-Benzyloxy-phenyl)-thiomorpholin-4-yl]-propionic acid ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.91 – 1.99 (m, 2 H) 2.11 - 2.19 (m, 1 H) 2.25 - 2.33 (m, 1 H) 2.47 - 2.54 (m, 3 H) 2.72 - 2.83 (m, 1 H) 2.91 - 3.04 (m, 2 H) 3.81 - 3.88 (m, 1 H) 5.01 (s, 2 H) 6.88 (d, *J*=8.8 Hz, 2 H) 7.18 - 7.39 (m, 7 H).

Compound 235; 3-{2-[4-(2-Chloro-benzyloxy)-phenyl]-thiomorpholin-4-yl}-propionic acid hydrochloride Mp 178 – 182°C

Compound 236; 3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-thiomorpholin-4-yl}-propionic acid hydrochloride ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.89 - 2.99 (m, 3 H) 3.10 – 3.20 (m, 1 H) 3.33 - 3.54 (m, 4 H) 3.71 – 3.83 (m, 2 H) 4.54 – 4.60

(m, 1 H) 5.23 (s, 2 H) 7.11 (d, *J*=8.7 Hz, 2 H) 7.32 (d, *J*=8.7 Hz, 2 H) 7.46 - 7.52 (m, 1 H) 7.55 - 7.59 (m, 2 H) 11.4 (bs, 1 H) 12.8 (bs, 1 H).

Compound 237; 3-[2-(4-Octyloxy-phenyl)-thiomorpholin-4-yl]-propionic acid ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.84 - 0.90 (m, 3 H) 1.23 - 1.34 (m, 8 H) 1.35 - 1.42 (m, 2 H) 1.64 - 1.73 (m, 2 H) 2.26 - 2.34 (m, 1 H) 2.35 - 2.41 (m, 2 H) 2.41 – 2.48 (m, 1 H) 2.57 – 2.63 (m, 1 H) 2.64 – 2.70 (m, 2 H) 2.81 – 2.89 (m, 1 H) 3.02 – 3.14 (m, 2 H) 3.89 – 3.96 (m, 3 H) 6.86 (d, *J*=8.8 Hz, 2 H) 7.26 (d, *J*=8.8 Hz, 2 H).



Compound 238; 3-{2-[5-(2,6-Dichloro-benzyloxy)-pyridin-2-yl]-morpholin-4-yl}-propionic acid hydrochloride ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.88 - 2.97 (m, 2 H) 3.11 - 3.26 (m, 2 H) 3.32 - 3.44 (m, 2 H) 3.52 (d, *J*=11.9 Hz, 1 H) 3.74 (d, *J*=11.9 Hz, 1 H) 4.06 - 4.21 (m, 2 H) 5.01 (d, *J*=11.9 Hz, 1 H) 5.34 (s, 2 H) 7.38 (bs, 1 H) 7.47 - 7.55 (m, 2 H) 7.56 - 7.61 (m, 2 H) 7.69 (dd, *J*=8.7, 3.0 Hz, 1 H) 8.40 (d, *J*=3.0 Hz, 1 H) 11.8 (bs, 1 H).

Compound 239; 3-{2-[4-(2-Oxo-2-phenyl-ethyl)-phenyl]-morpholin-4-yl}-propionic acid hydrochloride ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.84 – 2.92 (m, 2 H) 3.00 – 3.18 (m, 2 H) 3.28 – 3.38 (m, 2 H) 3.42 – 3.51 (m, 1 H) 3.58 – 3.66 (m, 1 H) 3.94 – 4.04 (m, 1 H)) 4.11 – 4.19 (m, 1 H) 4.42 (s, 2 H) 4.79 – 4.87 (m, 1 H) 7.28 – 7.37 (m., 4 H) 7.54 (t, *J*=7.6 Hz, 2 H) 7.65 (t, *J*=7.0 Hz, 1 H) 8.05 (t, *J*=7.6 Hz, 2 H) 11.2 (bs, 1 H) 12.8 (bs, 1 H)

Method C:

Compound 69; 3-{2-[4-(3-Methoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid: 3-{2-[4-(3-Methoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester was dissolved in a 4M solution of HCl in 1,4-dioxane (1 mL, 4 mmol) and stirred overnight at RT. Subsequently, the solvent was removed in vacuo. The residue was purified by preparative HPLC to afford 3-{2-[4-(3-Methoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid R_t = 1.00 min. (System B). Conditions for the preparative LC-MS: Injection of the crude product dissolved in 2700µL DMSO/CH_3CN 1:2; column Waters SunFire Prep OBD C18 Column 5 µm 30 x 100 mm, mobile phase water/CH_3CN/HCOOH 0.1% 40 mL/min, run 8.5 min 5%-100% CH_3CN, detection with UV 225nm.

The following compounds were obtained according to a similar manner:

Compound 70; 3-{2-[4-(5-Bromo-2-methoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid R_t = 1.26 min. (System B).

Compound 71; 3-{2-[4-(2,4-Dichloro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid R_t = 1.61 min. (System B).

Compound 72; 3-{2-[4-(2,3-Dimethoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid R_t = 0.99 min. (System B).

Compound 73; 3-[2-(4-Cyclopentylmethoxy-2-methyl-phenyl)-morpholin-4-yl]-propionic acid R_t = 1.05 min. (System B).

Compound 74; 3-{2-[4-(2,5-Dichloro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid R_t = 1.10 min. (System B).

Compound 75; 3-{2-[2-Methyl-4-(pyridin-3-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid R_t = 0.68 min. (System B).

Compound 76; 3-{2-[2-Methyl-4-(naphthalen-2-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid R_t = 1.10 min. (System B).

Compound 77; 3-{2-[4-(Benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid R_t = 1.01 min. (System B).

Compound 78; 3-{2-[4-(2-Methoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid R_t = 0.92 min. (System B).

Compound 79; 3-{2-[2-Methyl-4-(6-methyl-pyridin-2-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid R_t = 0.71 min. (System B).

Compound 80; 3-{2-[4-(2-Chloro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid R_t = 1.04 min. (System B).

Compound 81; 3-{2-[4-(2,5-Dimethoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid R_t = 0.93 min. (System B).

Compound 82; 3-{2-[4-(2-Bromo-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid R_t = 1.05 min. (System B).

Compound 83; 3-{2-[2-Methyl-4-(2-methyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid R_t = 1.04 min. (System B).

Compound 84; 3-{2-[4-(6,6-Dimethyl-bicyclo[3.1.1]hept-2-ylmethoxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid R_t = 1.21 min. (System B).

Compound 85; 3-{2-[4-(2-Chloro-6-fluoro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid R_t = 1.03 min. (System B).

Compound 86; 3-{2-[4-(Biphenyl-2-ylmethoxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid R_t = 1.13 min. (System B).

Compound 87; **3-{2-[2-Methyl-4-(2-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid** R_t = 1.06 min. (System B).

Compound 88; **3-{2-[4-(3,5-Dichloro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid** R_t = 1.13 min. (System B).

Compound 89; **3-{2-[2-Methyl-4-(3-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid** R_t = 1.09 min. (System B).

Compound 90; **3-{2-[4-(4-Chloro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid** R_t = 1.06 min. (System B).

Compound 91; **3-{2-[4-(4-Isopropyl-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid** R_t = 1.14 min. (System B).

Compound 92; **3-{2-[2-Methyl-4-(3-phenoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid** R_t = 1.15 min. (System B).

Compound 93; **3-{2-[4-(4-Methoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid** R_t = 0.92 min. (System B).

Compound 94; **3-{2-[2-Methyl-4-(2-phenethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid** R_t = 1.19 min. (System B).

Compound 95; **3-{2-[4-(3,4-Dimethoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid** R_t = 0.86 min. (System B).

Compound 96; **3-{2-[4-(3,5-Dimethyl-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid** R_t = 1.08 min. (System B).

Compound 97; **3-{2-[4-(4-Benzyloxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid** R_t = 1.05 min. (System B).

Compound 98; **3-{2-[2-Methyl-4-(thiophen-2-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid** R_t = 0.90 min. (System B).

Compound 99; **3-{2-[4-(3-Fluoro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid** R_t = 1.03 min. (System B).

Compound 100; **3-{2-[4-(3-Benzyloxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid** R_t = 1.15 min. (System B).

Compound 101; **3-{2-[4-(4-Fluoro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid** R_t = 1.01 min. (System B).

Compound 102; **3-{2-[4-(Biphenyl-4-ylmethoxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid** R_t = 1.14 min. (System B).

Compound 103; **3-{2-[4-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid** R_t = 1.03 min. (System B).

Compound 104; **3-{2-[2-Methyl-4-(pyridin-2-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid** R_t = 0.75 min. (System B).

Compound 105; **3-{2-[4-(4-Butoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid** R_t = 1.05 min. (System B).

Compound 106; **3-[2-(4-Cyclohexylmethoxy-2-methyl-phenyl)-morpholin-4-yl]-propionic acid** R_t = 1.10 min. (System B).

Compound 107; **3-{2-[2-Methyl-4-(tetrahydro-furan-2-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid** R_t = 0.83 min. (System B).

Compound 108; **3-{2-[2-Methyl-4-(3-methyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid** R_t = 1.05 min. (System B).

Compound 109; **3-{2-[4-(2,3-Difluoro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid** R_t = 1.03 min. (System B).

Compound 110; **3-{2-[2-Methyl-4-(4-trifluoromethoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid** R_t = 1.12 min. (System B).

Compound 111; **3-{2-[4-(3-Chloro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid** R_t = 1.05 min. (System B).

Compound 112; **3-{2-[2-Methyl-4-(tetrahydro-pyran-2-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid** R_t = 0.91 min. (System B).

Compound 113; **3-{2-[2-Methyl-4-(4-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid** R_t = 1.08 min. (System B).

Compound 114; **3-{2-[4-(3,4-Difluoro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid** R_t = 1.05 min. (System B).

Compound 115; **3-{2-[2-Methyl-4-(2,3,4-trimethoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid** R_t = 0.91 min. (System B).

Compound 116; **3-{2-[4-(Cyclohex-3-enylmethoxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid** R_t = 1.07 min. (System B).

Compound 117; **3-{2-[4-(4-Butyl-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid** R_t = 1.22 min. (System B).

Compound 118; **3-{2-[2-Methyl-4-(4-methyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid** R_t = 1.05 min. (System B).

Compound 119; **3-{2-[4-(3-Dimethylamino-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid** R_t = 0.86 min. (System B).

Compound 120; **3-{2-[2-Methyl-4-(pyridin-4-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid** R_t = 0.66 min. (System B).

Compound 121; **3-{2-[4-(2-Iodo-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid** R_t = 1.07 min. (System B).

Compound 122; **3-{2-[4-(3,5-Dimethoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid** R_t = 1.00 min. (System B).

Compound 123; 3-{2-[4-(2,4-Difluoro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid R_t = 1.03 min. (System B).

Compound 124; 3-{2-[2-Methyl-4-(2,4,5-trimethoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid R_t = 0.88 min. (System B).

Compound 125; 3-{2-[4-(3-Bromo-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid R_t = 1.08 min. (System B).

Compound 126; 3-{2-[4-(4-Bromo-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid R_t = 1.07 min. (System B).

Compound 127; 3-{2-[4-(4-tert-Butyl-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid R_t = 1.18 min. (System B).

Compound 128; 3-{2-[4-(2,5-Difluoro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid R_t = 1.02 min. (System B).

Compound 129; 3-{2-[2-Methyl-4-(tetrahydro-furan-3-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid R_t = 0.83 min. (System B).

Method D:

Compound 130; 3-{2-[4-(2,6-Dichloro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid trifluoroacetic acid salt: 3-{2-[4-(2,6-Dichloro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid tert-butyl ester (1.23 g; 2.6 mmol) was dissolved in CH_2Cl_2 (15 mL). TFA (5 mL) was added and the resulting mixture was stirred overnight at RT. The reaction mixture was concentrated *in vacuo*, and the residue was treated with iPr_2O. The precipitate was collected by filtration to afford 3-{2-[4-(2,6-dichloro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid trifluoroacetic acid salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.27 - 2.38 (2 H, m), 2.83 (2 H, t, J=7.6 Hz), 3.07 (1 H, t, J=11.7Hz), 3.13 - 3.28 (1 H, m), 3.39 (2 H, t, J=7.7 Hz), 3.48 - 3.69 (2 H, m), 3.83 - 3.98 (1 H, m), 4.18 (1 H, d), 4.90 (1 H, d, J=10.6 Hz), 5.22 (2 H, d), 6.88 - 7.01 (2 H, m), 7.34 (1 H, d, J=8.3 Hz), 7.43 - 7.52 (1 H, m), 7.58 (2 H, d).

The following compound was obtained according to a similar manner:

Compound 131; 3-{2-[4-(2,6-Dichloro-benzyloxy)-3-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid trifluoroacetic acid salt . ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.73 - 2.90 (m, 2 H) 3.07 - 3.26 (m, 2 H) 3.28 - 3.45 (m, 2 H) 3.51 (d, *J*=12.1 Hz, 1 H) 3.71 (d, *J*=12.1 Hz, 1 H) 3.90 (t, *J*=12.1 Hz, 1 H) 4.20 (d, *J*=10.7 Hz,

1 H) 4.81 (d, *J*=10.7 Hz, 1 H) 5.38 (s, 2 H) 7.47 - 7.53 (m, 1 H) 7.56 - 7.63 (m, 3 H) 7.65 - 7.75 (m, 2 H) 10.84 (br. s., 1 H) 12.42 (br. s., 1 H).

Method E:

Compound 132; {2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-acetic acid: A mixture of {2-[4-(2,6-dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-acetic acid ethyl ester (0.62 g; 1.5 mmol), 2M aqueous NaOH (5 mL) and ethanol (25 mL) was stirred for 3 hours at RT. Subsequently, 1M aqueous HCl (9.8 mL) was added and the mixture concentrated in vacuo. The residue was treated with saturated NH_4Cl and CH_2Cl_2. The formed precipitate was collected by filtration, washed with small amounts of water and ethanol, and dried in vacuo to yield {2-[4-(2,6-dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-acetic acid (0.41 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.23 (t, *J*= 10 Hz, 1 H) 2.40 (dt, *J*=10 Hz *J*=3 Hz, 1 H) 2.76 – 2.83 (m , 1 H) 2.86 – 2.93 (m, 1 H) 3.13 – 3.25 (m, 2 H) 3.67 (dt, *J*= 11 Hz *J*=2 Hz, 1 H) 3.87 – 3.95 (m, 1 H) 4.46 (dd, *J*=10 Hz *J*=2 Hz, 1H) 5.21 (s, 2 H) 6.99 – 7.06 (m, 2 H) 7.26 – 7.32 (m, 2 H) 7.44 – 7.50 (m, 1 H) 7.57 (d, *J*=7 Hz, 2 H) 12.3 (br. s, 1 H).

The following compounds were obtained according to a similar manner:

Compound 219; 3-{2-[4-(Indan-1-yloxy)-phenyl]-morpholin-4-yl}-propionic acid Mp 124 – 129.5°C.

Compound 220; 3-{2-[4-(7-Methyl-indan-1-yloxy)-phenyl]-morpholin-4-yl}-propionic acid Mp 134 – 139°C.

Compound 221; 3-{2-[4-(2,3-Dihydro-benzofuran-3-yloxy)-phenyl]-morpholin-4-yl}-propionic acid. Mp 141.5 – 144.5°C.

Compound 222; 3-(2-{4-[3-(4-Chloro-phenyl)-allyloxy]-phenyl}-morpholin-4-yl)-propionic acid ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.33 (t, *J*=11.7 Hz, 1 H) 2.47 - 2.59 (m, 3 H) 2.74 - 2.86 (m, 2 H) 2.98 - 3.10 (m, 2 H) 3.87 (td, *J*=11.9, 2.4 Hz, 1 H) 4.13 (dd, *J*=11.9, 2.4 Hz, 1 H) 4.55 (dd, *J*=10.5, 2.5 Hz, 1 H) 4.69 (dd, *J*=5.7, 1.6 Hz, 2 H) 6.32 - 6.42 (m, 1 H) 6.68 (d , *J*=16.0 1 H) 6.95 (d, *J*=8.8 Hz, 2 H) 7.23 - 7.36 (m, 6 H).

Compound 223; 3-{2-[4-(3-Phenyl-prop-2-ynyloxy)-phenyl]-morpholin-4-yl}-propionic acid ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.33 (t, *J*=11.7 Hz, 1 H) 2.47 - 2.60 (m, 3 H) 2.74 - 2.86 (m, 2 H) 2.98 - 3.11 (m, 2 H) 3.87 (td, *J*=11.9, 2.5 Hz, 1 H) 4.13 (dd, *J*=11.9, 2.4 Hz, 1 H) 4.55 (dd, *J*=10.5, 2.5 Hz, 1 H) 4.91 (s, 2 H) 7.03 (d, *J*=8.8 Hz, 2 H) 7.25 - 7.36 (m, 5 H) 7.40 - 7.46 (m, 2 H).

Compound 224; 3-(2-{4-[3-phenyl-allyloxy]-phenyl}-morpholin-4-yl)-propionic acid ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.32 (t, *J*=11.7 Hz, 1 H) 2.47 - 2.59 (m, 3 H) 2.75 - 2.87 (m, 2 H) 2.98 - 3.11 (m, 2 H) 3.87 (td, *J*=11.9, 2.5 Hz, 1 H) 4.14 (dd, *J*=10.5, 2.4 Hz, 1 H) 4.55 (dd, *J*=10.5, 2.4 Hz, 1 H) 4.70 (dd, *J*=5.7, 1.6 Hz, 2 H) 6.36 - 6.44 (m, 1 H) 6.69 (d , *J*=15.9 1 H) 6.95 (d, *J*=8.8 Hz, 2 H) 7.22 - 7.43 (m, 7 H).

Compound 225; 3-(2-{4-[3-(4-Chloro-phenyl)-prop-2-ynyloxy]-phenyl}-morpholin-4-yl)-propionic acid ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.28 - 2.36 (m, 1 H) 2.47 - 2.59 (m, 3 H) 2.73 - 2.86 (m, 2 H) 3.01 (d, *J*=11.5 Hz, 1 H) 3.08 (d, *J*=11.5 Hz, 1 H) 3.86 - 3.91 (m, 1 H) 4.11 – 4.16 (m, 1 H) 4.53 - 4.58 (m, 1 H) 4.89 (s, 2 H) 7.03 (d, *J*=8.7 Hz, 2 H) 7.25 - 7.37 (m, 6 H).

Compound 226; 3-{2-[4-(4-Methoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.03 - 2.12 (m, 1 H) 2.20 – 2.28 (m, 1 H) 2.41 – 2.48 (m, 2 H) 2.63 - 2.71 (m, 2 H) 2.82 - 2.87 (m, 1 H) 2.88 - 2.96 (m, 1 H) 3.58 - 3.71 (m, 1 H) 3.75 (s, 3 H) 3.89 - 3.96 (m, 1 H) 4.35 - 4.44 (m, 1 H) 5.00 (s, 2 H) 6.88 - 6.99 (m, 4 H) 7.25 (d, *J*=8.7 Hz, 2 H) 7.37(d, *J*=8.7 Hz, 2 H) 12.3 (bs, 1 H).

Compound 227; 3-{2-[4-(2-Methoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.90 - 1.98 (m, 1 H) 2.08 - 2.17 (m, 1 H) 2.36 - 2.44 (m, 2 H) 2.54 - 2.61 (m, 2 H) 2.73 - 2.79 (m, 1 H) 2.82 - 2.88 (m, 1 H) 3.55 - 3.65 (m, 1 H) 3.82 (s, 3 H) 3.87 - 3.93 (m, 1 H) 4.35 - 4.40 (m, 1 H) 5.03 (s, 2 H) 6.91 - 6.99 (m, 3 H) 7.05 (d, *J*=7.8 Hz, 1 H) 7.27 (d, *J*=8.7 Hz, 2 H) 7.30 - 7.40 (m, 2 H) 12.1 –12.6 (bs, 1 H).

Method F:

Compound 133; 3-[2-(4-Octyloxy-phenyl)-morpholin-4-yl]-3-oxo-propionic acid: To a solution of 3-[2-(4-octyloxy-phenyl)-morpholin-4-yl]-3-oxo-propionic acid ethyl ester (0.46 g; 1.1 mmol) in tetrahydrofuran (4 mL) and water (1 mL) was added lithium hydroxide (54.3 mg; 2.3 mmol) and the mixture was stirred at 70°C for 3 hours. After cooling to RT the resulting mixture was loaded onto a PE-AX column [ISOLUTE (Biotage AB); 0.58 mmol/g, 10g]. The column was washed with CH_3CN and than the required compound was eluted with 20 v/v% TFA in CH_3CN. The compound containing fractions were concentrated in vacuo to afford 3-[2-(4-octyloxy-phenyl)-morpholin-4-yl]-3-oxo-propionic acid (0.40 g) ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.83 - 0.89 (m, 3 H) 1.22 - 1.34 (m, 8 H) 1.39 (d, *J*=7.52 Hz, 2 H) 1.65 - 1.73 (m, 2 H) 3.75 (d, *J*=1.20 Hz, 1 H) 3.91 - 3.99 (m, 3 H) 4.27 (br. s., 1 H) 6.89 (dd, *J*=8.58, 3.16 Hz, 2 H) 7.28 (dd, *J*=8.43, 3.91 Hz, 2 H)

Compound 151: 3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-3-oxo-propionic acid was obtained according to a similar manner. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 2.71 - 2.79 (m, 2 H) 3.41 - 3.49 (m, 1 H) 3.56 - 3.72 (m, 3 H) 4.28 - 4.45 (m, 2 H) 4.70 - 4.76 (m, 1 H) 5.07 (s, 2 H) 6.98 (d, *J*=8.8 Hz, 2 H) 7.27 - 7.45 (m, 7 H).

Method G:

Compound 134; 2,2-Difluoro-3-[2-(4-octyloxy-phenyl)-morpholin-4-yl]-propionic acid triethylammonium salt: To a solution of 2,2-difluoro-3-[2-(4-octyloxy-phenyl)-morpholin-4-yl]-propionic acid ethyl ester (0.55 g; 1.3 mmol) in THF (5 mL) and water (1 mL) was added Lithium hydroxide (0.06 g; 2.6 mmol) and stirred at 70°C for 3 hours. After cooling to RT the reaction mixture was loaded onto a SCX-3 column [ISOLUTE (Biotage AB); 0.61 mmol/g, 15g]. The column was washed with CH_3CN (4 x 15 mL) and subsequently the required compound was eluted with CH_3CN + 10% Et_3N (2 x 15 mL). The compound containing fractions were concentrated in vacuo to afford 2,2-Difluoro-3-[2-(4-octyloxy-phenyl)-morpholin-4-yl]-propionic acid as the triethylammonium salt (0.45 g). ^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm 0.85 - 0.92 (m, 1 H) 0.88 (s, 1 H) 1.13 (d, J=6.32 Hz, 5 H) 1.30 (t, J=7.37 Hz, 10 H) 1.43 (qd, J=7.22, 6.92 Hz, 1 H) 1.72 - 1.79 (m, J=7.30, 7.30, 7.07, 6.62 Hz, 1 H) 2.99 - 3.04 (m, 1 H) 3.06 (s, 1 H) 3.09 (br. s., 1 H) 3.09 - 3.15 (m, 2 H) 3.11 (d, J=7.52 Hz, 2 H) 3.77 - 3.85 (m, 1 H) 3.92 (t, J=6.62 Hz, 2 H) 6.84 (d, J=8.73 Hz, 1 H) 7.24 (d, J=8.73 Hz, 1 H).

Compound 150; 3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-2,2-difluoro-propionic acid triethylammonium salt: was obtained according to a similar manner. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.18 (t, *J*=10.8 Hz, 1 H) 2.32 - 2.42 (m, 1 H) 2.77 - 2.94 (m, 4 H) 3.56 - 3.65 (m, 1 H) 3.82 - 3.90 (m, 1 H) 4.34 - 4.41 (m, 1 H) 5.21 (s, 2 H) 7.02 (d, *J*=8.6 Hz, 2 H) 7.27 (d, *J*=8.6 Hz, 2 H) 7.44 - 7.50 (m, 1 H) 7.56 (d, *J*=8.3 Hz, 2 H) 10.4 (bs, 1 H).

Method H:

Compound 135; 2-[2-(4-Octyloxy-phenyl)-morpholin-4-yl]-ethanol: To a solution of 2-(4-octyloxy-phenyl)-4-[2-(tetrahydro-pyran-2-yloxy)-ethyl]-morpholine (1.85 g; 4.4

mmol) in MeOH (10 mL) was added p-toluenesulfonic acid monohydrate (0.84 g; 4.4 mmol) and the resulting mixture was stirred at RT for 3 hours. The reaction mixture was partitioned between 5% aqueous $NaHCO_3$ solution and EtOAc. The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo to afford 2-[2-(4-octyloxy-phenyl)-morpholin-4-yl]-ethanol (1.44 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.85 - 0.92 (m, 3 H) 1.23 - 1.37 (m, 7 H) 1.39 - 1.48 (m, 2 H) 1.71 - 1.81 (m, 2 H) 2.05 (s, 1 H) 2.15 - 2.24 (m, 1 H) 2.36 (td, *J*=11.44, 3.31 Hz, 1 H) 2.53 - 2.62 (m, 2 H) 2.79 (dd, *J*=11.44, 1.50 Hz, 1 H) 3.32 (d, *J*=1.50 Hz, 1 H) 3.61 - 3.68 (m, 2 H) 3.76 - 3.88 (m, 1 H) 3.94 (t, *J*=6.62 Hz, 2 H) 4.03 (dd, *J*=11.44, 1.81 Hz, 1 H) 4.48 (dd, *J*=10.23, 2.11 Hz, 1 H) 6.84 - 6.89 (m, 2 H) 7.24 - 7.30 (m, 2 H)

Compound 141; 2-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-ethanol was obtained according to a similar manner. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.06 - 3.28 (m, 4 H) 3.48 - 3.66 (m, 2 H) 3.81 (t, *J*=4.6 Hz, 2 H) 3.98 - 4.09 (m, 1 H) 4.10 - 4.19 (m, 1 H) 4.86 (d, *J*=10.6 Hz, 1 H) 5.24 (s, 2 H) 5.42 (bs., 1 H) 7.11 (d, *J*=8.6 Hz, 2 H) 7.34 (d, *J*=8.6 Hz, 2 H) 7.45 - 7.51 (m, 1 H) 7.57 (d, *J*=8.3 Hz, 2 H) 10.9 (s, 1H)

Method I:

Compound 136; {3-[2-(4-Octyloxy-phenyl)-morpholin-4-yl]-propyl}-phosphonic acid: To a solution of {3-[2-(4-Octyloxy-phenyl)-morpholin-4-yl]-propyl}-phosphonic acid diethyl ester (1.06 g; 2.26 mmol) in CH_2Cl_2 (10 mL) was added bromotrimethylsilane (2.38 ml; 18.06 mmol) and the reaction mixture was stirred at RT overnight. Subsequently the mixture was concentrated in vacuo, redissolved in MeOH (10 mL), and stirred for 2 hours at RT. The resulting mixture was concentrated *in vacuo* and treated with iPr_2O. The precipitate was collected by filtration and dried under vacuum to give {3-[2-(4-Octyloxy-phenyl)-morpholin-4-yl]-propyl}-phosphonic acid (0.82 g; 69.8%) ^{1}H NMR (400 MHz, DMSO-*d*6) δ ppm 0.75 (t, 3 H) 1.06 - 1.25 (m, 8 H) 1.24 - 1.35 (m, 2 H) 1.42 - 1.68 (m, 4 H) 1.73 - 1.94 (m, 2 H) 2.83 - 3.04 (m, 2 H) 3.10 (t, 2 H) 3.37 (d, *J*=12.04 Hz, 1 H) 3.43 (d, *J*=12.04 Hz, 1 H) 3.72 - 3.91 (m, 3 H) 4.04 (d, *J*=12.34 Hz, 1 H) 4.64 (d, *J*=10.83 Hz, 1 H) 6.83 (d, *J*=8.43 Hz, 2 H) 7.20 (d, *J*=8.43 Hz, 2 H).

The following compounds were obtained according to a similar manner:

Compound 137; {2-[2-(4-Octyloxy-phenyl)-morpholin-4-yl]-ethyl}-phosphonic acid ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.79 - 0.90 (m, 3 H) 1.15 - 1.45 (m, 9 H) 1.62 - 1.74 (m, 2 H) 2.04 - 2.20 (m, 2 H) 3.03 - 3.23 (m, 2 H) 3.25 - 3.39 (m, 2 H) 3.57 (d, *J*=11.74 Hz, 1 H) 3.67 (d, *J*=12.04 Hz, 1 H) 3.84 - 3.99 (m, 3 H) 4.09 - 4.22 (m, 1 H) 4.72 (d, *J*=10.53 Hz, 1 H) 6.94 (d, *J*=8.43 Hz, 2 H) 7.29 (d, *J*=8.73 Hz, 2 H).

Compound 146; (3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propyl)-phosphonic acid; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.57 – 1.69 (m, 2 H) 1.86 – 2.00 (m, 2H) 3.05 - 3.27 (m, 4 H) 3.47 - 3.65 (m, 2 H) 3.90 (d, J=12.8 Hz, 1 H) 4.18 (d, J=12.8 Hz 1 H) 4.72 (d, J=10.9 Hz, 1 H) 5.24 (s, 2H) 7.11 (d, J=8.6 Hz, 2 H) 7.37 (d, J=8.6 Hz, 2 H) 7.45 – 7.52 (m, 1H) 7.58 (d, J=8.3 Hz, 2H) 9.80 -10.20 (bs, 1H).

Method J:

Compound 138; Phosphoric acid mono-{2-[2-(4-octyloxy-phenyl)-morpholin-4-yl]-ethyl} ester : A solution of phosphoric acid di-tert-butyl ester 2-[2-(4-octyloxy-phenyl)-morpholin-4-yl]-ethyl ester (0.69 g; 1.31 mmol) in TFA (3 mL) and CH_2Cl_2 (3 mL) was stirred at RT for 1 hour. Subsequently, the reaction mixture was concentrated in vacuo and the residue treated with iPr_2O. The precipitate was collected by filtration and dried in vacuo overnight to afford phosphoric acid mono-{2-[2-(4-octyloxy-phenyl)-morpholin-4-yl]-ethyl} ester trifluoroacetic acid salt (0.42 g) 1H NMR (400 MHz, DMSO-d_6) δ ppm 0.63 - 0.79 (m, 3 H) 0.98 - 1.32 (m, 9 H) 1.45 - 1.58 (m, 2 H) 2.86 - 3.07 (m, 2 H) 3.13 - 3.28 (m, 2 H) 3.29 - 3.47 (m, 2 H) 3.68 - 3.83 (m, 3 H) 3.89 - 4.06 (m, 3 H) 4.57 (d, *J*=10.53 Hz, 1 H) 6.77 (d, *J*=8.43 Hz, 2 H) 7.10 (d, *J*=8.43 Hz, 2 H).

Method K:

Compound 149; 2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-4-(1(2)H-tetrazol-5-ylmethyl)-morpholine hydrochloride: To 2-[4-(2,6-dichloro-benzyloxy)-phenyl]-morpholine hydrochloride (0.30 g; 0.80 mmol) was added 2 M aqueous NaOH and EtOAc. The layers were separated and the organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The obtained 2-[4-(2,6-dichloro-benzyloxy)-phenyl]-morpholine was mixed with NaI (24.0 mg; 0.16 mmol), 5-chloromethyl-1(2)H-tetrazole (0.11 g; 0.96 mmol), K_2CO_3 (0.33 g; 2.40 mmol), and CH_3CN (10 mL) in a closed pyrex bottle. The resulting mixture was heated at 100°C, overnight. After cooling to

RT the mixture was concentrated in vacuo, and the residue was purified by column chromatography (SiO_2, EtOAc:MeOH 1:1) to afford 2-[4-(2,6-dichloro-benzyloxy)-phenyl]-4-(1(2)H-tetrazol-5-ylmethyl)-morpholine The free base was dissolved in a 4M solution of HCl in 1,4-dioxane (4 mL, 16 mmol) and stirred at RT, for one hour. Subsequently the mixture was concentrated in vacuo and the residue treated with iPr_2O. The precipitate was collected by filtration and dried under vacuum to afford 2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-4-(1(2)H-tetrazol-5-ylmethyl)-morpholine hydrochloride (0.13 g). 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.96 (t, *J*=10.9 Hz, 1 H) 2.13 - 2.21 (m, 1 H) 2.73 - 2.79 (m, 1 H) 2.84 - 2.90 (m, 1 H) 3.55 - 3.64 (m, 3 H) 3.84 - 3.91 (m, 1 H) 4.34 - 4.39 (m, 1 H) 5.21 (s, 2 H) 7.00 (d, *J*=8.6 Hz, 2 H) 7.24 (d, *J*=8.6 Hz, 2 H) 7.44 - 7.50 (m, 1 H) 7.56 (d, *J*=8.3 Hz, 2 H).

Method L:

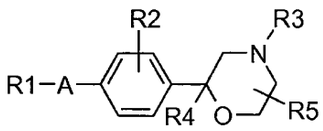
Compound 228; 2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-4-[2-(2H-tetrazol-5-yl)-ethyl]-morpholine hydrochloride: To a solution of 3-{2-[4-(2,6-dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionitrile (0.30 g; 0.77 mmol) in xylene (10 mL) was added tributyltin chloride (0.46 mL; 1.7 mmol) and NaN_3 (110 mg; 1.7 mmol). The resulting mixture was heated at 120°C for two days. After cooling to RT the mixture was treated with methanol (10 mL) and concentrated in vacuo. The residue was purified by column chromatography (EtOAc:methanol 90:10 to 50:50) to afford 2-[4-(2,6-dichloro-benzyloxy)-phenyl]-4-[2-(2H-tetrazol-5-yl)-ethyl]-morpholine as the free base (0.30 g), The free base was treated with a solution of HCl in 1,4-dioxane, after stirring at RT for 4 hours, the salt precipitated. The salt was collected by filtration, washed with Et_2O and dried in vacuo to afford 2-[4-(2,6-dichloro-benzyloxy)-phenyl]-4-[2-(2H-tetrazol-5-yl)-ethyl]-morpholine hydrochloride (0.30 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.15 - 3.29 (m, 2 H) 3.53 - 3.75 (m, 6 H) 4.06 - 4.22 (m, 2 H) 4.94 (d, *J*=11.0 Hz, 1 H) 5.24 (s, 2 H) 7.11 (d, *J*=8.6 Hz, 2 H) 7.36 (d, *J*=8.6 Hz, 2 H) 7.45 - 7.52 (m, 1 H) 7.58 (d, *J*=8.3 Hz, 2 H) 12.31 (bs, 1 H).

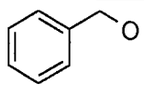
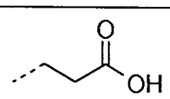
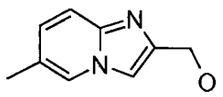
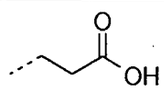
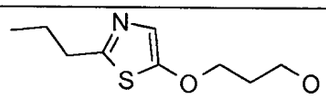
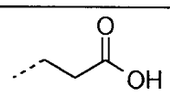
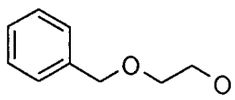
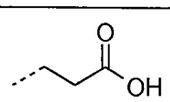
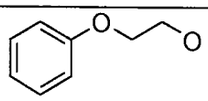
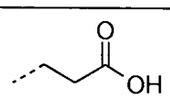
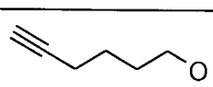
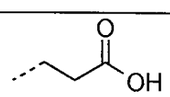
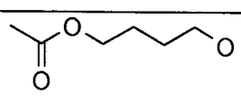
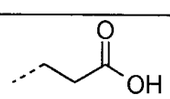
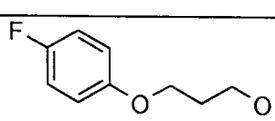
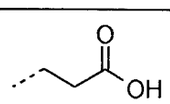
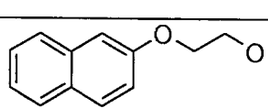
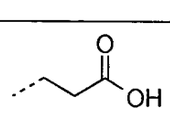
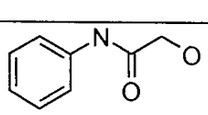
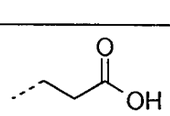
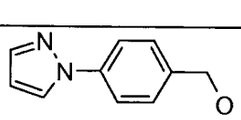
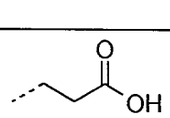
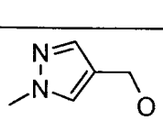
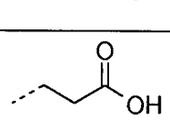
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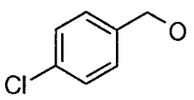
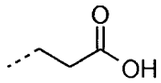
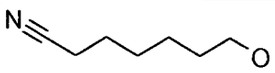
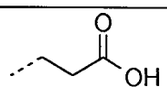
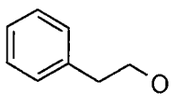
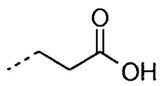
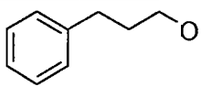
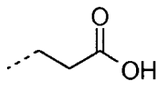
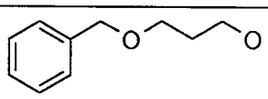
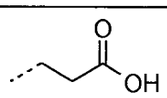
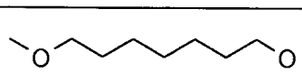
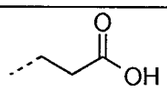
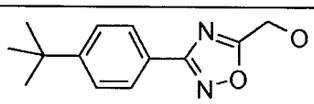
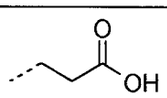
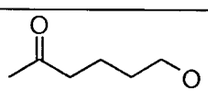
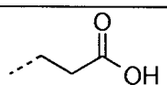
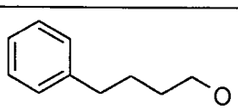
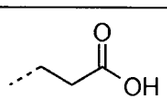
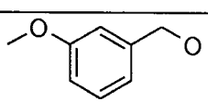
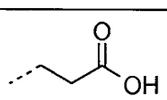
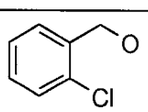
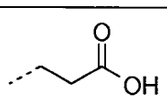
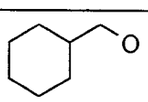
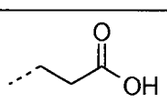
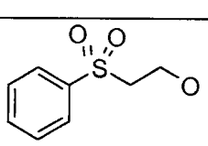
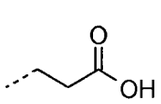
Compound 229; 3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-2,2-dimethyl-propionic acid: To a suspension of 3-{2-[4-(2,6-dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-2,2-dimethyl-propionic acid methyl ester (1.05 g; 2.32 mmol) in THF (21 mL) and water (5.25 ml) was added LiOH (111.2 mg; 4.64 mmol).The resulting

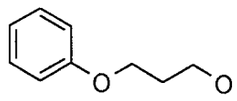
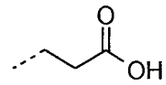
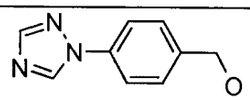
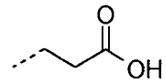
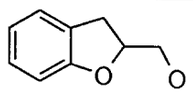
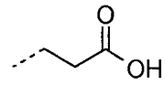
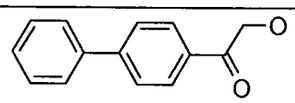
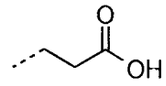
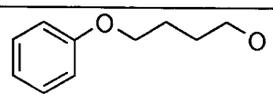
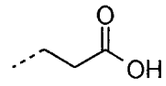
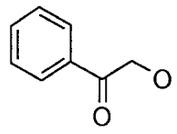
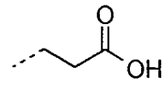
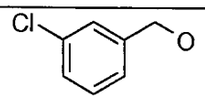
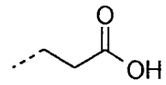
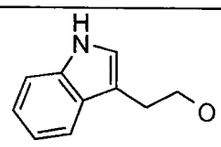
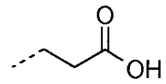
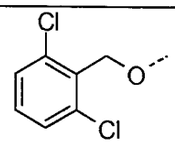
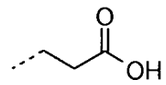
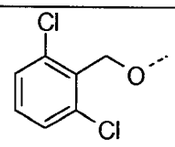
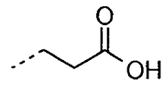
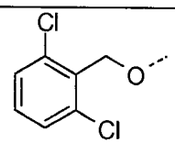
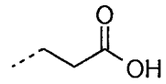
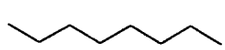
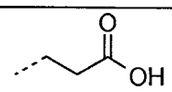
mixture was stirred for two days at 50°C. After cooling to RT the reaction mixture was neutralized (pH 7) with 1M aqueous HCl (4.64 mL), diluted with water (50 mL) and extracted with CH_2Cl_2 (3 X 50 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. The solid residue was triturated with $^iPr_2O$ (10 mL) and collected by filtration to afford 3-{2-[4-(2,6-dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-2,2-dimethyl-propionic acid (0.72 g) as a white powder.

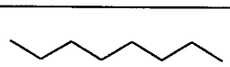
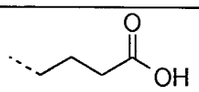
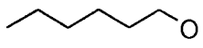
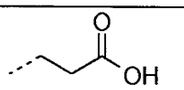
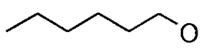
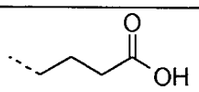
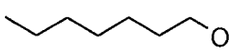
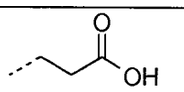
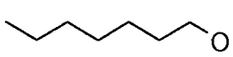
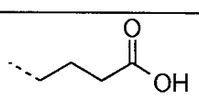
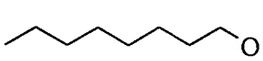
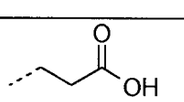
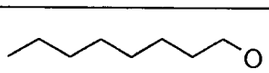
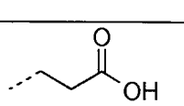
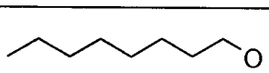
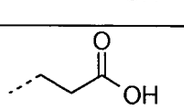
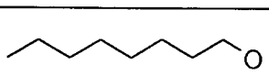
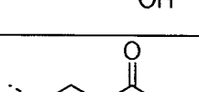
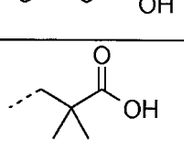
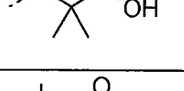
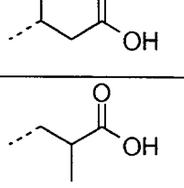
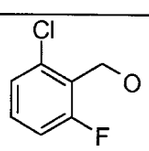
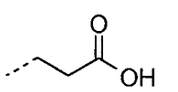
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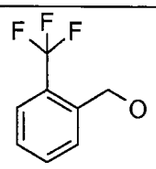
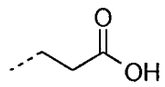
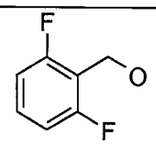
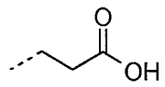
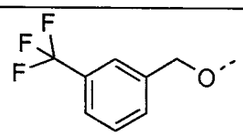
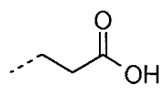
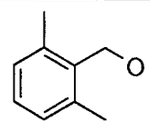
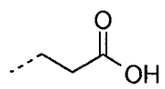
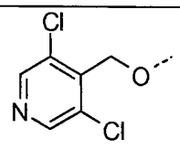
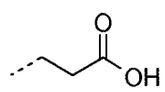
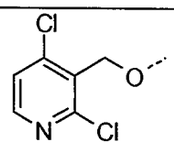
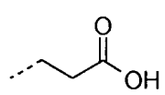
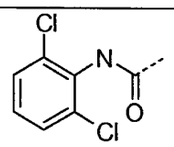
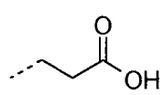
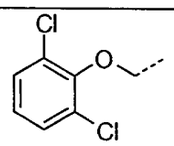
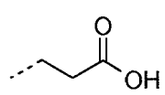
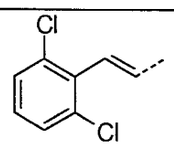
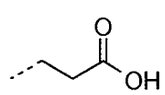
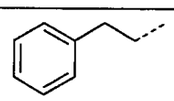
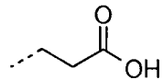


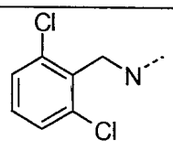
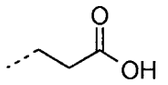
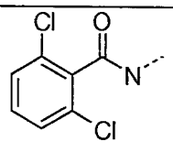
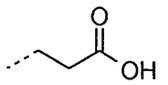
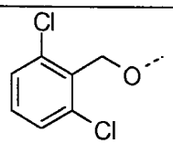
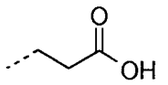
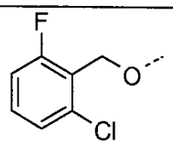
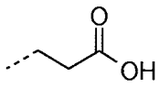
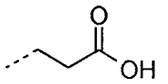
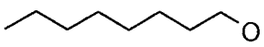
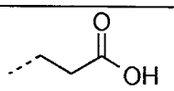
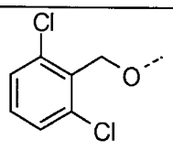
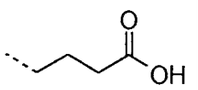
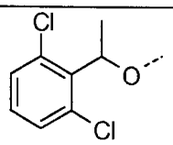
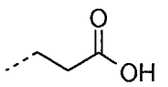
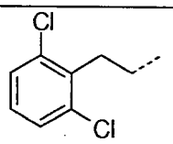
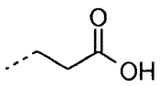
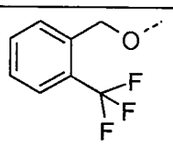
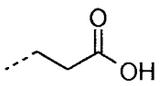
Comp no.	R1-A	R2	R3	R4	R5	Meth.
1		H		H	H	A
2		H		H	H	A
3		H		H	H	A
4		H		H	H	A
5		H		H	H	A
6		H		H	H	A
7		H		H	H	A
8		H		H	H	A
9		H		H	H	A
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11		H		H	H	A
12		H		H	H	A

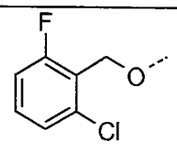
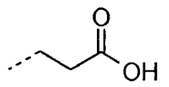
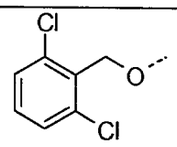
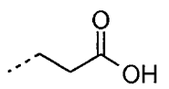
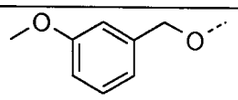
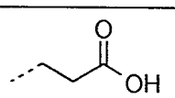
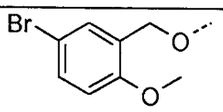
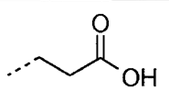
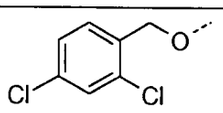
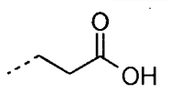
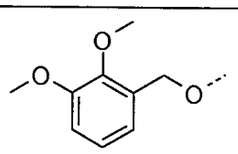
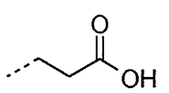
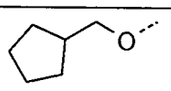
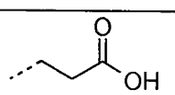
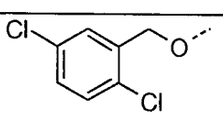
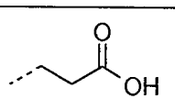
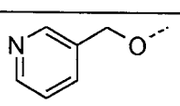
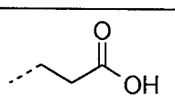
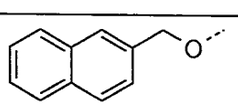
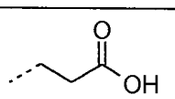
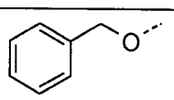
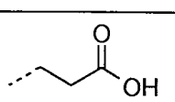
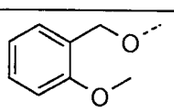
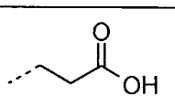
Comp no.	R1-A	R2	R3	R4	R5	Meth.
13		H		H	H	A
14		H		H	H	A
15		H		H	H	A
16		H		H	H	A
17		H		H	H	A
18		H		H	H	A
19		H		H	H	A
20		H		H	H	A
21		H		H	H	A
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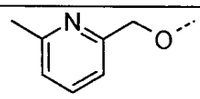
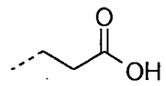
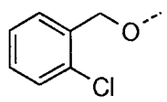
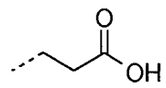
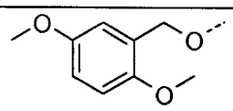
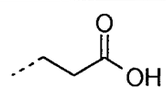
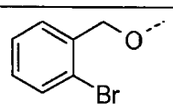
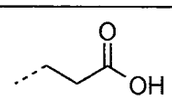
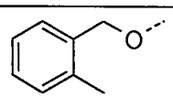
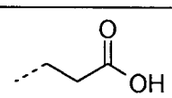
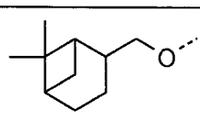
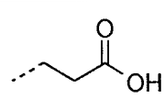
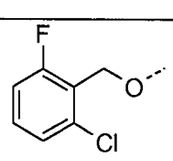
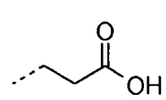
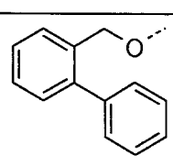
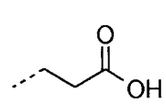
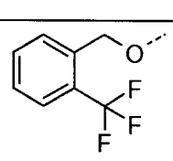
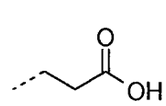
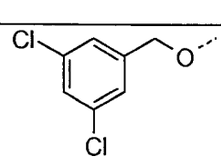
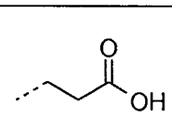
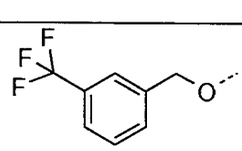
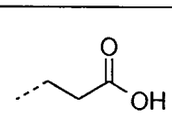
Comp no.	R1-A	R2	R3	R4	R5	Meth.
26		H		H	H	A
27		H		H	H	A
28		H		H	H	A
29		H		H	H	A
30		H		H	H	A
31		H		H	H	A
32		H		H	H	A
33		H		H	H	A
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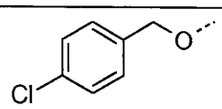
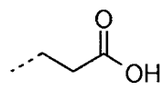
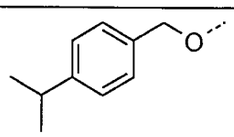
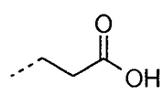
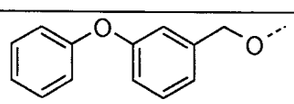
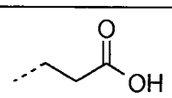
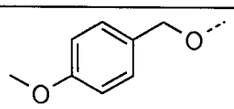
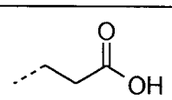
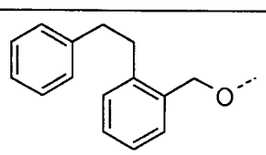
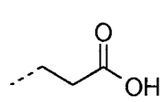
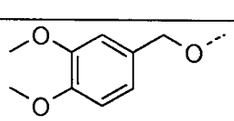
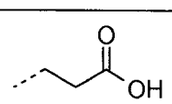
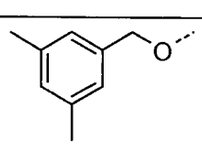
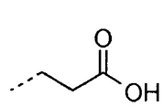
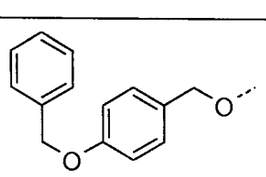
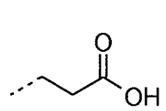
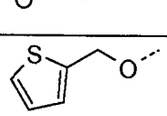
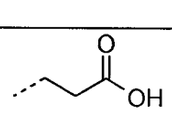
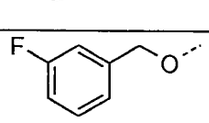
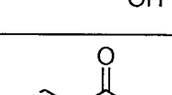
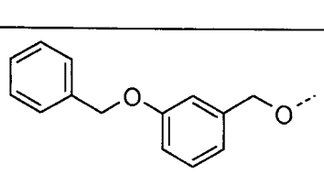
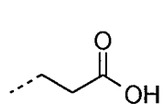
Comp no.	R1-A	R2	R3	R4	R5	Meth.
36		H		H	H	B
37		H		H	H	B
38		H		H	H	B
39		H		H	H	B
40		H		H	H	B
41		H		H	H	B
41a		H		H	H	B
41b		H		H	H	B
42		H		H	H	B
43		H		H	H	B
44		H		H	H	B
45		H		H	H	B
46		H		H	H	B

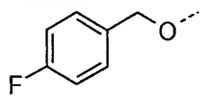
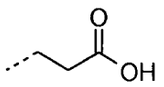
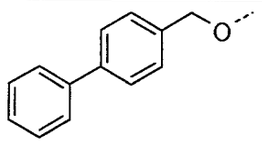
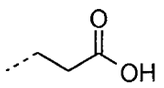
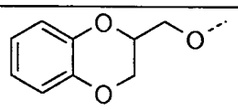
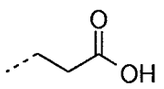
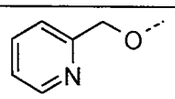
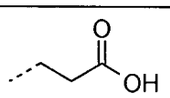
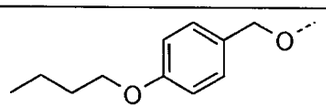
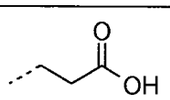
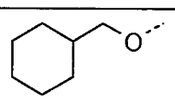
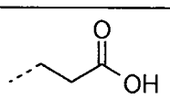
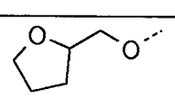
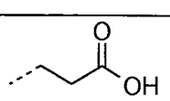
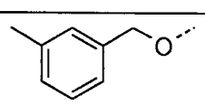
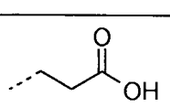
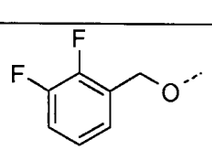
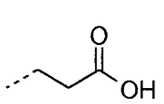
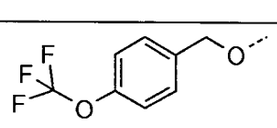
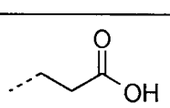
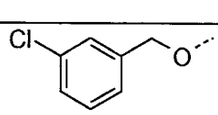
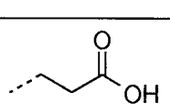
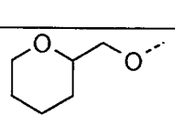
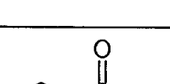
Comp no.	R1-A	R2	R3	R4	R5	Meth.
47		H		H	H	B
48		H		H	H	B
49		H		H	H	B
50		H		H	H	B
51		H		H	H	B
52		H		H	H	B
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54		H		H	H	B
55		H		H	H	B
56		H		H	H	B

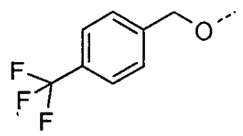
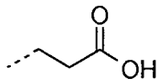
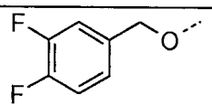
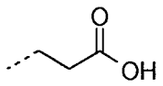
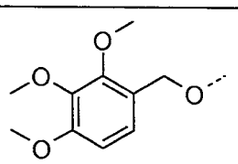
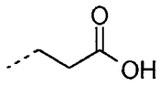
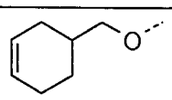
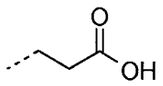
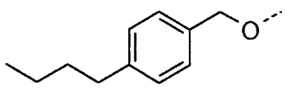
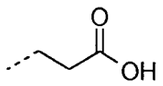
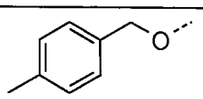
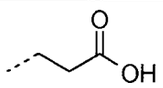
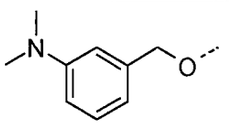
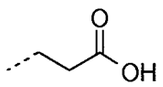
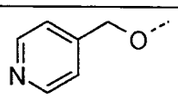
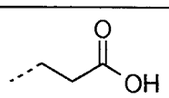
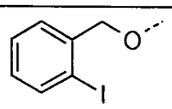
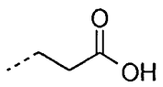
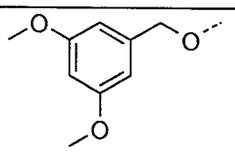
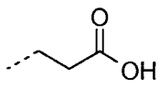
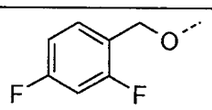
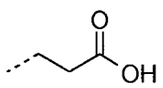
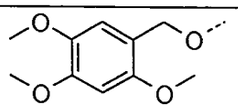
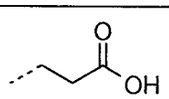
Comp no.	R1-A	R2	R3	R4	R5	Meth.
57		H		H	H	B
58		H		H	H	B
59		H		Me	H	B
60		H		Me	H	B
61		H		Me	H	B
62		H		Me	H	B
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66		3-OMe		H	H	B

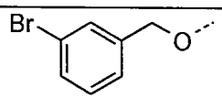
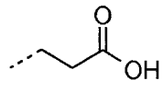
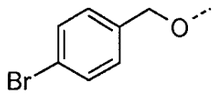
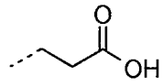
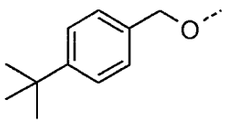
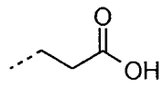
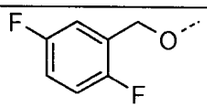
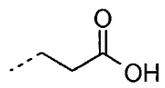
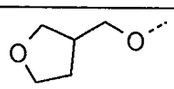
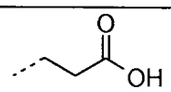
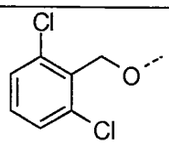
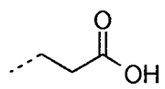
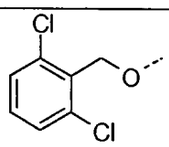
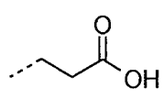
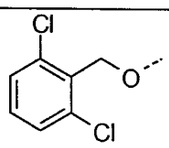
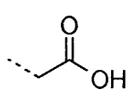
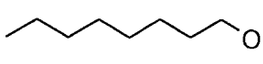
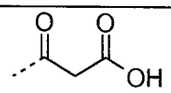
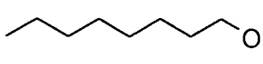
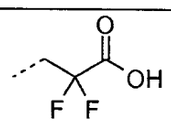
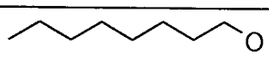
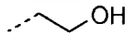
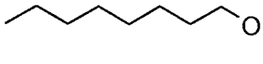
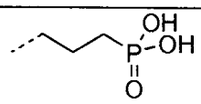
Comp no.	R1-A	R2	R3	R4	R5	Meth.
67		3-OMe		H	H	B
68		3-OMe		H	H	B
69		2-Me		H	H	C
70		2-Me		H	H	C
71		2-Me		H	H	C
72		2-Me		H	H	C
73		2-Me		H	H	C
74		2-Me		H	H	C
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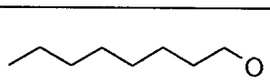
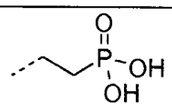
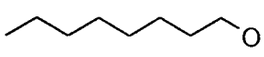
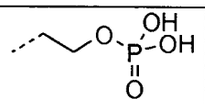
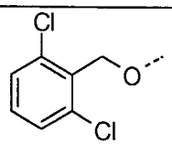
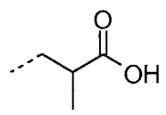
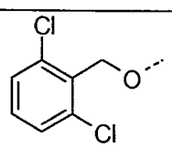
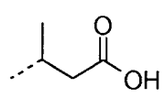
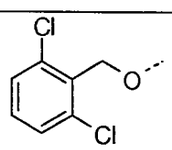
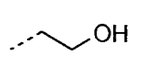
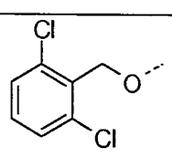
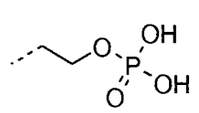
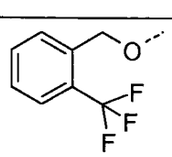
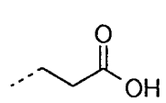
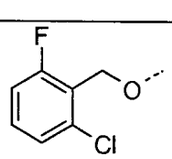
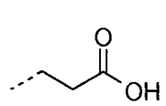
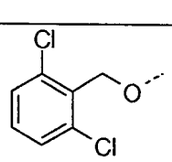
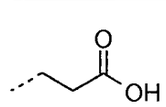
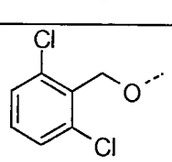
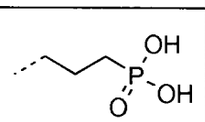
Comp no.	R1-A	R2	R3	R4	R5	Meth.
79		2-Me		H	H	C
80		2-Me		H	H	C
81		2-Me		H	H	C
82		2-Me		H	H	C
83		2-Me		H	H	C
84		2-Me		H	H	C
85		2-Me		H	H	C
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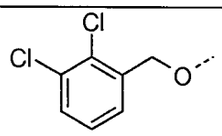
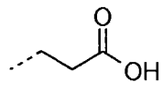
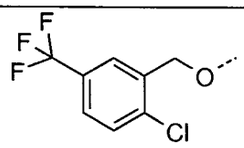
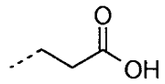
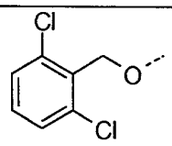
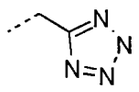
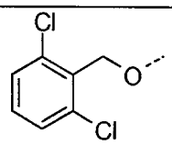
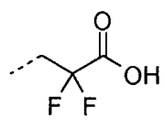
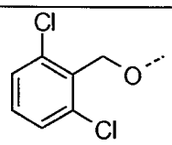
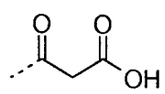
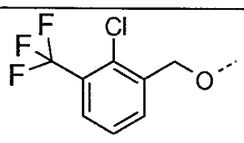
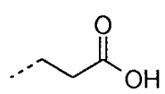
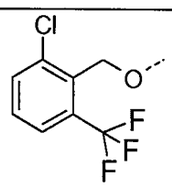
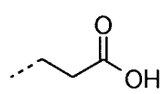
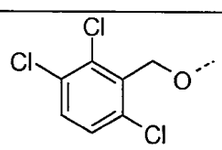
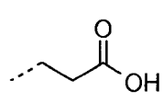
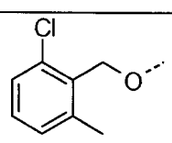
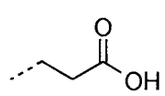
Comp no.	R1-A	R2	R3	R4	R5	Meth.
90		2-Me		H	H	C
91		2-Me		H	H	C
92		2-Me		H	H	C
93		2-Me		H	H	C
94		2-Me		H	H	C
95		2-Me		H	H	C
96		2-Me		H	H	C
97		2-Me		H	H	C
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100		2-Me		H	H	C

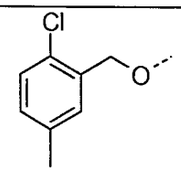
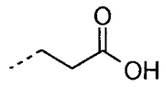
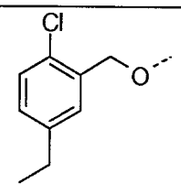
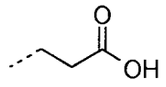
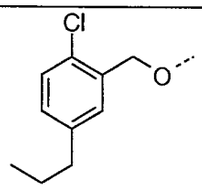
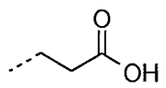
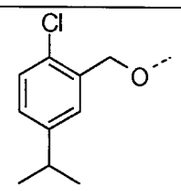
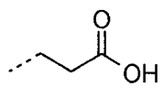
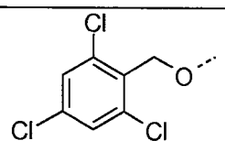
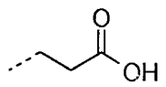
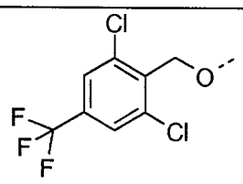
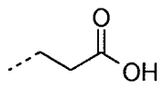
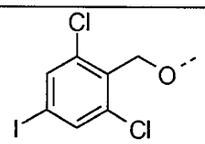
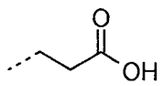
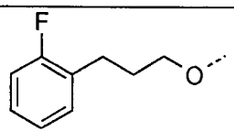
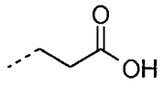
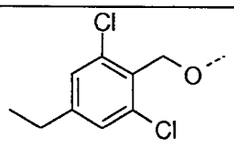
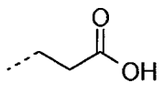
Comp no.	R1-A	R2	R3	R4	R5	Meth.
101		2-Me		H	H	C
102		2-Me		H	H	C
103		2-Me		H	H	C
104		2-Me		H	H	C
105		2-Me		H	H	C
106		2-Me		H	H	C
107		2-Me		H	H	C
108		2-Me		H	H	C
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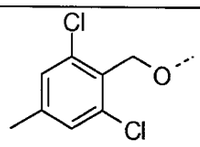
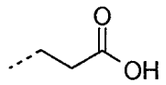
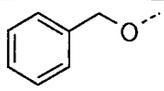
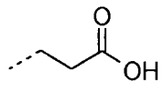
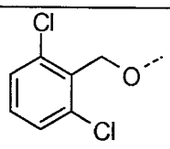
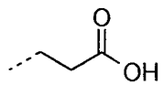
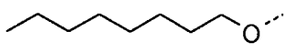
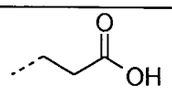
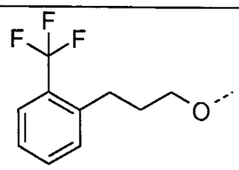
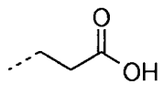
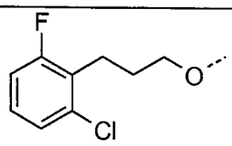
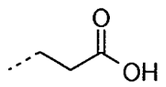
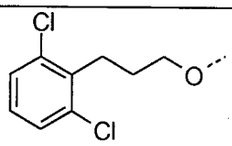
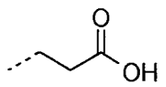
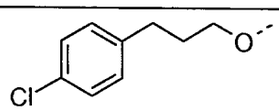
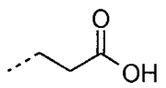
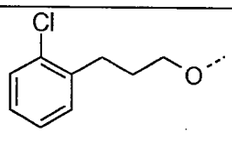
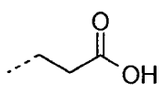
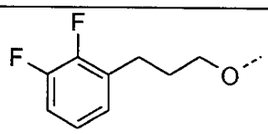
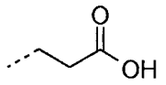
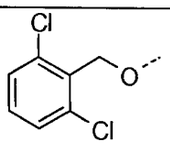
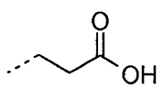
Comp no.	R1-A	R2	R3	R4	R5	Meth.
113		2-Me		H	H	C
114		2-Me		H	H	C
115		2-Me		H	H	C
116		2-Me		H	H	C
117		2-Me		H	H	C
118		2-Me		H	H	C
119		2-Me		H	H	C
120		2-Me		H	H	C
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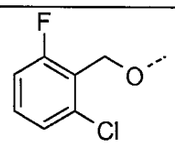
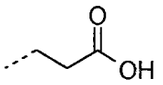
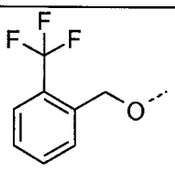
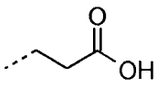
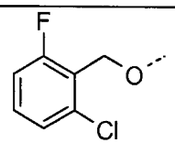
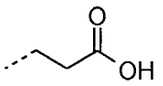
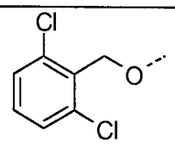
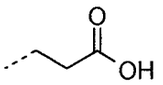
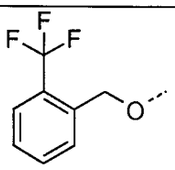
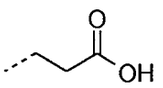
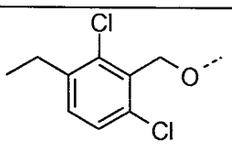
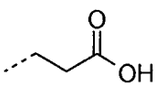
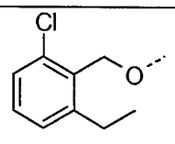
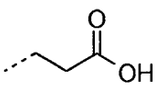
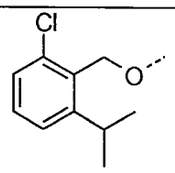
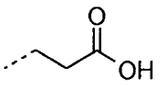
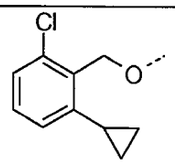
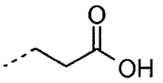
Comp no.	R1-A	R2	R3	R4	R5	Meth.
125		2-Me		H	H	C
126		2-Me		H	H	C
127		2-Me		H	H	C
128		2-Me		H	H	C
129		2-Me		H	H	C
130		2-Me		H	H	D
131		3-CF_3		H	H	D
132		H		H	H	E
133		H		H	H	F
134		H		H	H	G
135		H		H	H	H
136		H		H	H	I

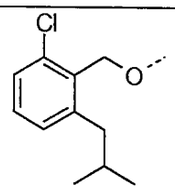
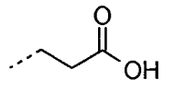
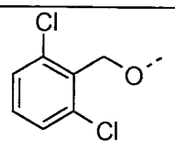
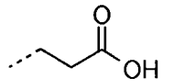
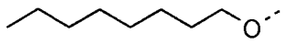
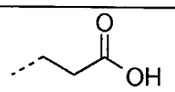
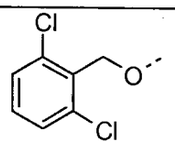
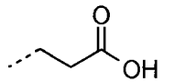
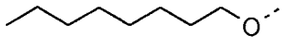
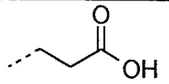
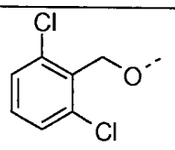
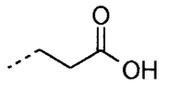
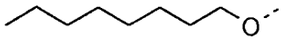
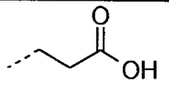
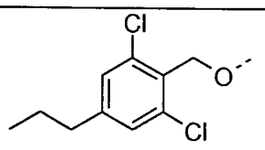
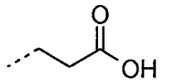
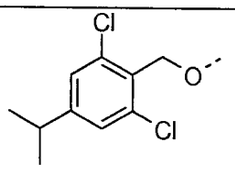
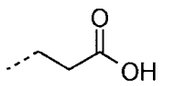
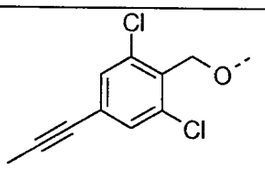
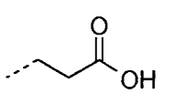
Comp no.	R1-A	R2	R3	R4	R5	Meth.
137		H		H	H	I
138		H		H	H	J
139		H		H	H	B
140		H		H	H	B
141		H		H	H	H
142		H		H	H	B
143		3-Me		H	H	B
144		3-Me		H	H	B
145		3-Me		H	H	B
146		H		H	H	I

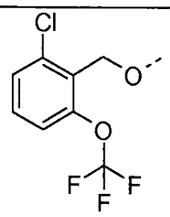
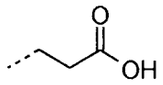
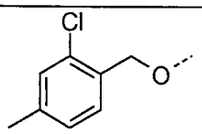
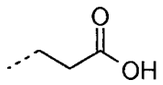
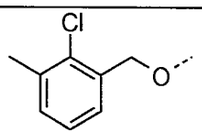
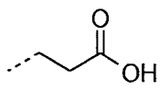
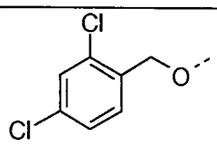
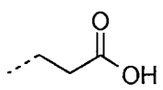
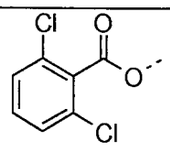
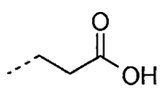
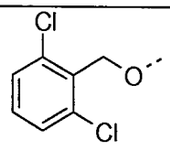
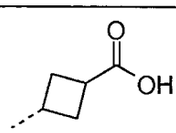
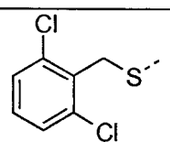
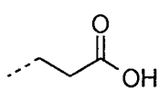
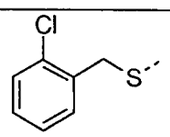
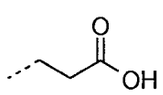
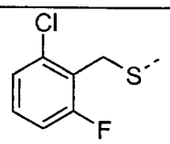
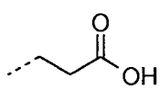
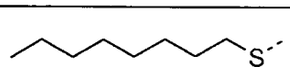
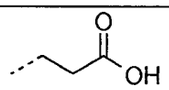
Comp no.	R1-A	R2	R3	R4	R5	Meth.
147		H		H	H	B
148		H		H	H	B
149		H		H	H	K
150		H		H	H	G
151		H		H	H	F
152		H		H	H	B
153		H		H	H	B
154		H		H	H	B
155		H		H	H	B

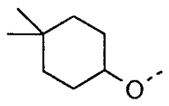
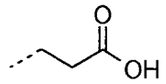
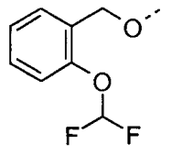
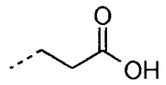
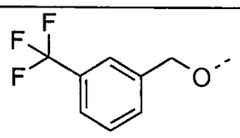
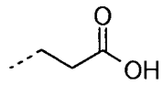
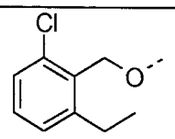
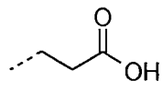
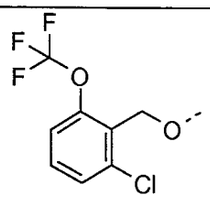
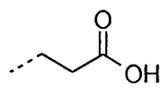
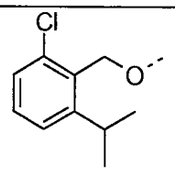
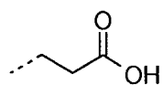
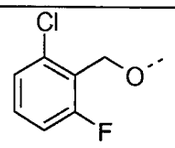
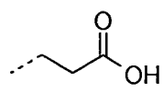
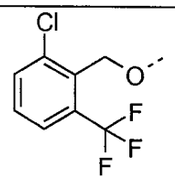
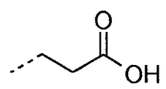
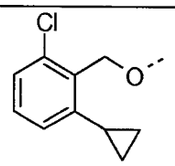
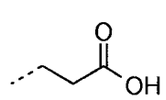
Comp no.	R1-A	R2	R3	R4	R5	Meth.
156		H		H	H	B
157		H		H	H	B
158		H		H	H	B
159		H		H	H	B
160		H		H	H	B
161		H		H	H	B
162		H		H	H	B
163		H		H	H	B
164		H		H	H	B

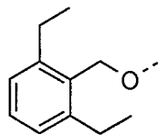
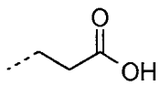
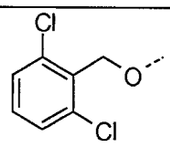
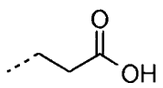
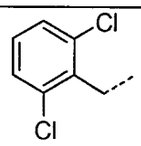
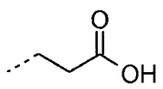
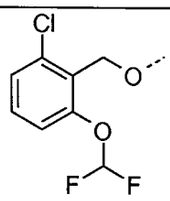
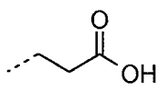
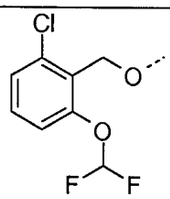
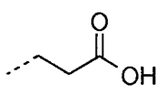
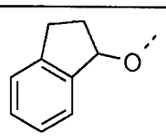
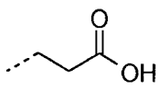
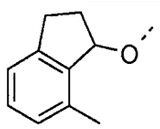
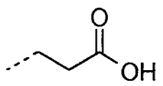
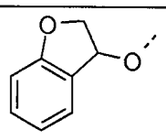
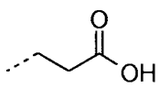
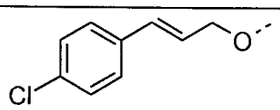
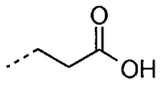
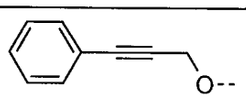
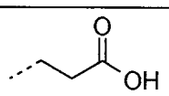
Comp no.	R1-A	R2	R3	R4	R5	Meth.
165		H		H	H	B
166		H		H	5-oxo	B
167		H		H	5-oxo	B
168		H		H	5-oxo	B
169		H		H	H	B
170		H		H	H	B
171		H		H	H	B
172		H		H	H	B
173		H		H	H	B
174		H		H	H	B
175		3-Cl		H	H	B

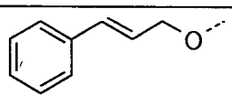
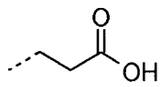
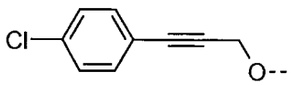
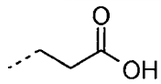
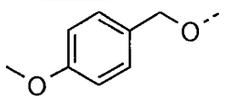
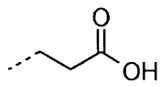
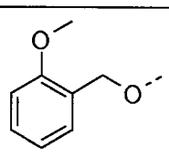
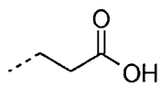
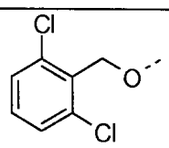
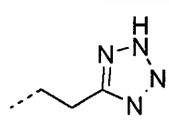
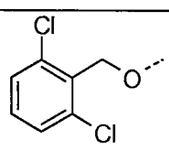
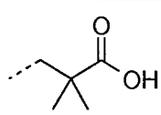
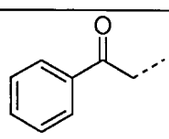
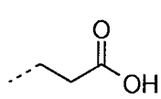
Comp no.	R1-A	R2	R3	R4	R5	Meth.
176		3-Cl		H	H	B
177		3-Cl		H	H	B
178		2-F		H	H	B
179		2-F		H	H	B
180		2-F		H	H	B
181		H		H	H	B
182		H		H	H	B
183		H		H	H	B
184		H		H	H	B

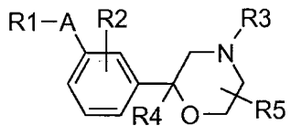
Comp no.	R1-A	R2	R3	R4	R5	Meth.
185		H		H	H	B
186		H		H	5,5-Me_2	B
187		H		H	5,5-Me_2	B
188		2-CF_3		H	H	B
189		2-CF_3		H	H	B
190		H		H	2,2-Me_2	B
191		H		H	2,2-Me_2	B
192		H		H	H	B
193		H		H	H	B
194		H		H	H	B

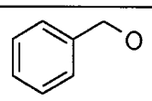
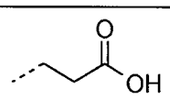
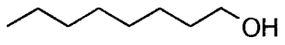
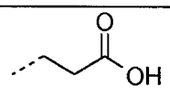
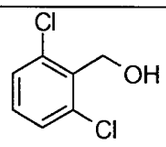
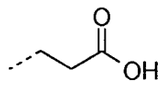
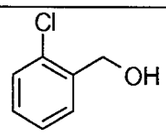
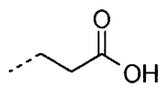
Comp no.	R1-A	R2	R3	R4	R5	Meth.
195		H		H	H	B
196		H		H	H	B
197		H		H	H	B
198		H		H	H	B
199		H		H	H	B
200		H		H	H	B
201		H		H	H	B
202		H		H	H	B
203		H		H	H	B
204		H		H	H	B

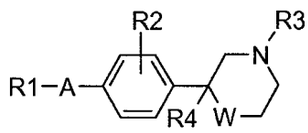
Comp no.	R1-A	R2	R3	R4	R5	Meth.
205		H		H	H	B
206		H		H	H	B
207		2-CF_3		H	H	B
208		2-CF_3		H	H	B
209		2-CF_3		H	H	B
210		2-CF_3		H	H	B
211		2-CF_3		H	H	B
212		2-CF_3		H	H	B
213		2-CF_3		H	H	B

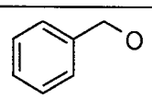
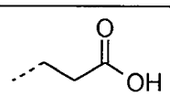
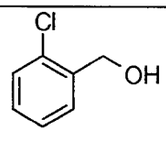
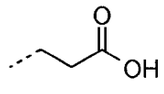
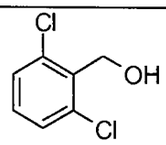
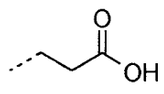
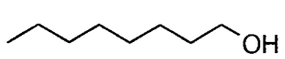
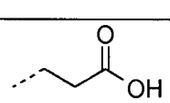
Comp no.	R1-A	R2	R3	R4	R5	Meth.
214		H		H	H	B
215		2-Cl		H	H	B
216		H		H	H	B
217		H		H	H	B
218		2-CF_3		H	H	B
219		H		H	H	E
220		H		H	H	E
221		H		H	H	E
222		H		H	H	E
223		H		H	H	E

Comp no.	R1-A	R2	R3	R4	R5	Meth.
224		H		H	H	E
225		H		H	H	E
226		H		H	H	E
227		H		H	H	E
228		H		H	H	L
229		H		H	H	M
239		H		H	H	B



Comp no.	R1-A	R2	R3	R4	R5	Meth.
230		H		H	H	B
231		H		H	H	B
232		H		H	H	B
233		H		H	H	B



Comp no.	R1-A	R2	R3	R4	W	Meth.
234		H		H	S	B
235		H		H	S	B
236		H		H	S	B
237		H		H	S	B

5

§5. PHARMACEUTICAL FORMULATION

A suitable example of a pharmaceutical composition according to the present invention is presented below.

A tablet was produced via direct compression having to the following composition:

compound	**function**	**amount**
compound **34b**	active pharmaceutical ingredient	0.4 - 6 %
Ac-di-Sol® (= sodium crosscarmellose)	disintegrant	3 %
PRUV® (= sodium stearyl fumarate)	lubricant	2 %
Aerosil® (=silica)	glidant	2 %
MCC (=micro cristalline cellulose)	filler	30 %
lactose monohydrate DCL 15	filler	rest

Tablet strengths: 2, 10 and 30 mg of compound **34b** / unit. Tablet weight: 500 mg.

§6. PHARMACOLOGICAL TESTS & DATA

***In vitro* functional activity (agonism) on human S1P5 receptors**

The CHO-human-S1P5-Aeqorin assay was bought from Euroscreen, Brussels (Euroscreen, Technical dossier, Human Lysophospholid S1P5 (Edg8) receptor, DNA clone and CHO AequoScreen™ recombinant cell-line, catalog n°: ES-593-A, September 2006). Human-S1P5-Aequorin cells express mitochondrial targeted apo-Aequorin. Cells have to be loaded with coelanterazine, in order to reconstitute active Aequorin. After binding of agonists to the human S1P5 receptor the intracellular calcium concentration increases and binding of calcium to the apo-Aequorin/coelenterazine complex leads to an oxidation reaction of coelenterazine, which results in the production of apo-Aequorin, coelenteramide, CO_2 and light (λ_{max} 469nm). This luminescent response is dependent on the agonist concentration. Luminescence is measured using the MicroBeta Jet (Perkin Elmer). Agonistic effects of compounds are expressed as pEC_{50}. Compounds were tested at a 10 points half log concentration range, and 3 independent experiments were performed in single point's measurements.

***In vitro* functional activity (agonism) on human S1P3 receptors**

The CHO-human-S1P3- Aeqorin assay (CHO/Gα16/AEQ/h-$S1P_3$) was established at Solvay Pharmaceuticals. The plasmid DNA coding for the S1P3 receptor (accession number in GenBank NM_005226 was purchased from UMR cDNA resource Centre (Rolla, MO). The pcDNA3.1/hS1P3 construct carrying the mitochondrially targeted apo-Aeqorin and Gα16 protein was transfected in CHO K1 cell-line.

Human-S1P3-Aequorin cells express mitochondrial targeted apo-Aequorin. Cells have to be loaded with coelanterazine, in order to reconstitute active Aequorin. After binding of agonists to the human S1P3 receptor the intracellular calcium concentration increases and binding of calcium to the apo-Aequorin/coelenterazine complex leads to an oxidation reaction of coelenterazine, which results in the production of apo-Aequorin, coelenteramide, CO_2 and light (λ_{max} 469nm). This luminescent response is dependent on the agonist concentration. Luminescence is measured using the MicroBeta Jet (Perkin Elmer). Agonistic effects of compounds are expressed as pEC_{50}. Compounds were tested at a 10 points half log concentration range, and 3 independent experiments were performed in single point's measurements.

***In vitro* functional activity (agonism) on human S1P1 receptors**

The CHO-K1-Human S1P1-c-AMP assay was performed at Euroscreen*fast,* Brussels (Euroscreen, Human S1P1 coupling $G_{i/0,}$ (Edg1) receptor, catalog n°: FAST-0197C, December 2009).

Recombinant CHO-K1 cells expressing human S1P1, grown to mid-log Phase in culture media without antibiotics, detached, centrifuged and re-suspended. For agonist testing cells are mixed with compound and Forskolin and incubated at room temperature. Cells are lyses and cAMP concentration are estimated, according to the manufacturer specification, With the HTRF kit from CIS-BIO International (cat n°62AM2PEB).

Agonistic effects of compounds are expressed as a percentage of the activity of the reference compound at its EC_{100} concentration, EC_{50} is calculated and results are reported as pEC_{50}. Compounds were tested at a 10 points half log concentration range duplicated in 1 experiment.

Pharmacological data (receptor agonism) for selected compounds:

Compound	S1P5 pEC_{50}	S1P1 pEC_{50}	S1P3 pEC_{50}
3	5.0	nd	4.8
16	6.0	nd	5.4
24	6.2	nd	<4.5
34a	6.2	nd	<4.5
34b	7.5	<5.5	<4.5
41	6.6	<5.5	5.6
53	5.7	nd	<5.0
66	6.2	nd	<5.0
76	5.6	nd	<5.0
84	5.4	nd	<5.0
92	5.3	nd	<5.0
100	5.4	nd	<5.0
117	5.4	nd	<5.0
127	6.2	nd	<5.0
130	7.1	<5.5	<4.5
131	6.0	nd	<5.0
137	7.0	nd	6.3
144	6.2	nd	<5.0
150	6.2	nd	<5.0
153	7.0	<5.5	<5.0
164	6.5	nd	5.7
174	5.8	nd	5.3
179	6.9	<5.5	<5.0
187	6.1	nd	5.5
189	6.8	5.8	5.8
196	6.0	nd	nd
204	6.4	nd	nd
220	6.8	nd	6.6
228	6.8	<5.5	<5.0
231	6.6	nd	<5.0

nd = not determined.

In vivo therapeutic model; T-maze

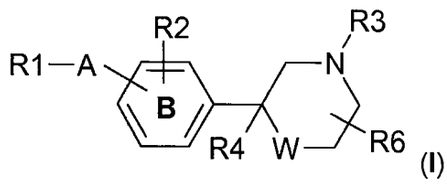
Age-related memory deficits occur in humans and rodents. Spontaneous alternation is the innate tendency of rodents to alternate free choices in a T-maze over a series of successive runs. This sequential procedure relies on working memory and is sensitive to various pharmacological manipulations affecting memory processes *(Aging and the physiology of spatial memory.* Barnes C.A. *Neurobiol. Aging* **1988***:563-8;* Dember WN, Fowler H. *Spontaneous alternation behavior. Psychol. Bull.* **1958**, *55(6):412–427;* Gerlai R. *A new continuous alternation task in T-maze detects hippocampal dysfunction in mice. A strain comparison and lesion study. Behav Brain Res* **1998** *95(1):91-101).*

For this study, male C57BL/6J mice of 2 months or 12 months old were used in the spontaneous alternation task in the T-maze. In short, mice were subjected to 1 session containing 15 trials, consisting of 1 "forced-choice" trial, followed by 14 "free-choice" trials. The animal was considered as entering one of the arms of the maze when all four paws are placed within this arm. A session is terminated and the animal is removed from the maze as soon as 14 free-choice trials have been performed or 15 min have elapsed, whatever event occurs first. The percentage of alternation over the 14 free-choice trials was determined for each mouse and was used as an index of working memory performance. Compound **34b** was administrated p.o. for 21 days prior the T-maze assay and on the day of the T-maze at t = -30 min. It was shown that compound **34b** at a dose of 10 mg/kg/day reversed the age-related cognitive decline in the 12-month old C57BL6J mice with 100%. Thus, treated 12 month old mice were identical in their performance as 2 months old vehicle-treated mice.

Conclusion: compounds of the present invention have a positive effect on age-related cognitive decline.

CLAIMS

1. A (thio)morpholine derivative of the formula (**I**)



(**I**)

wherein

R1 is selected from

cyano,

(2-4C)alkynyl,

(1-4C)alkyl,

(3-6C)cycloalkyl,

(4-6C)cycloalkenyl,

(6-8C)bicycloalkyl, (8-10C)bicyclic group, each optionally substituted with (1-4C)alkyl,

phenyl, biphenyl, naphthyl, each optionally substituted with one or more substituents independently selected from halogen, (1-4C)alkyl optionally substituted with one or more fluoro atoms, (2-4C)alkynyl, (1-4C)alkoxy optionally substituted with one or more fluoro atoms, amino, di(1-4C)alkylamino, $-SO_2$-(1-4C)alkyl, -CO-(1-4C)alkyl, -CO-O-(1-4C)alkyl, -NH-CO-(1-4C)alkyl and (3-6C)cycloalkyl,

phenyl substituted with phenoxy, benzyl, benzyloxy, phenylethyl or monocyclic heterocycle, each optionally substituted with (1-4C)alkyl,

monocyclic heterocycle optionally substituted with halogen, (1-4C)alkyl or with phenyl optionally substituted with (1-4C)alkyl,

and

bicyclic heterocycle optionally substituted with (1-4C)alkyl;

A is selected from -CO-O-, -O-CO-, -NH-CO-, -CO-NH, -C=C-, $-CCH_3$-O- and the linking group –Y-$(CH_2)_n$-X- wherein

Y is attached to R1 and selected from a bond, -O-, -S-, -SO-, $-SO_2$-, $-CH_2$-O-, -CO-, -O-CO-, -CO-O-, -CO-NH-, -NH-CO-, -C=C- and -C≡C- ;

n is an integer from 1 to 10; and.

X is attached to the phenylene / pyridyl group and selected from a bond, -O-, -S-, -SO-, $-SO_2$-, -NH, -CO-, -C=C- and -C≡C-;

ring structure **B** optionally contains one nitrogen atom;

R2 is H, (1-4C)alkyl optionally substituted with one or more fluoro atoms, (1-4C)alkoxy optionally substituted with one or more fluoro atoms, or halogen; and

R3 is (1-4C)alkylene-R5 wherein the alkylene group may be substituted with $(CH_2)_2$ to form a cyclopropyl moiety or one or two halogen atoms, or R3 is is (3-6C)cycloalkylene-R5 or -CO-CH_2-R5, wherein R5 is -OH, -PO_3H_2, -OPO_3H_2, -COOH, -COO(1-4C)alkyl or tetrazol-5-yl;

R4 is H or (1-4C)alkyl;

R6 is one or more substituents independently selected from H, (1-4C)alkyl or oxo;

W is -O-, -S-, -SO- or -SO_2-;

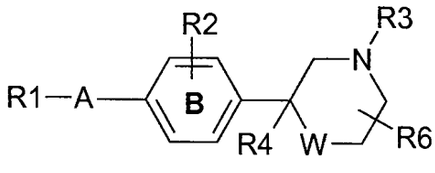
or a pharmaceutically acceptable salt, a solvate or hydrate thereof; with the proviso that the derivative of formula (**I**) is not

2-(4-ethylphenyl)-4-morpholinoethanol or

4-[4-(2-hydroxyethyl)-2-morpholinyl]benzeneacetonitrile.

2. The compound of claim 1, wherein the ring structure **B** is phenylene.

3. The compound of claim 1 or 2, having the structure (**II**)



(**II**).

4. The compound of any one of claims 1 to 3, wherein R3 is selected from -$(CH_2)_2$-OH, -CH_2-COOH, -$(CH_2)_2$-COOH, -$(CH_2)_3$-COOH, -CH_2-$CHCH_3$-COOH, -CH_2-$C(CH_3)_2$-COOH, -$CHCH_3$-CH_2-COOH, -CH_2-CF_2-COOH, -CO-CH_2-COOH, 1,3-cyclobutylene-COOH, -$(CH_2)_2$-PO_3H_2, -$(CH_2)_3$-PO_3H_2, -$(CH_2)_2$-OPO_3H_2, -$(CH_2)_3$-OPO_3H_2, -CH_2-tetrazol-5-yl, -$(CH_2)_2$-tetrazol-5-yl and -$(CH_2)_3$-tetrazol-5-yl; and W is -O- or -S-.

5. The compound of any one of claims 1 to 4, wherein R2 is H, methyl, methoxy, trifluoromethyl, difluoromethyl, trifluoromethoxy, difluoromethoxy, Cl or F; and R4 is H or methyl.

6. The compound of any one of claims 1 to 5, wherein A is selected from -CO-O-, -NH-CO-, -CO-NH, -C=C-, -CCH_3-O- and the linking group –Y-$(CH_2)_n$-X- wherein Y is attached to R1 and selected from a bond, -O-, -SO_2-, -CH_2-O-, -CO-, -CO-O-,

-NH-CO-, -C=C- and -C≡C-; n is an integer from 1 to 7; and X is attached to the phenylene / pyridyl group and selected from a bond, -O-, -S- and –NH.

7. The compound of any one of claims 1 to 6, wherein R1 is selected from cyano, ethynyl, (1-4C)alkyl, cyclopentyl, cyclohexyl, cyclohexenyl, 6,6-dimethyl-bicyclo[3.1.1]hept-2-yl, indanyl optionally substituted with methyl, biphenyl, naphthyl,
phenyl optionally substituted with one, two or three substituents independently selected from chloro, fluoro, bromo, (1-4C)alkyl, (2-4C)alkynyl, (1-4C)alkoxy, dimethylamino, trifluoromethyl, trifluoromethoxy and (3-6C)cycloalkyl,
phenyl monosubstituted with phenoxy, benzyl, benzyloxy, phenylethyl, pyrazolyl or triazolyl,
pyrazolyl, thiazolyl, oxadiazolyl, thienyl, tetrahydrofuranyl, pyridinyl, tetrahydro-pyranyl, each optionally substituted with chloro, (1-4C)alkyl or phenyl substituted with (1-4C)alkyl, and
indolyl, imidazopyridinyl, dihydrobenzofuranyl and benzdioxanyl, each optionally substituted with (1-4C)alkyl.

8. The compound of claim 7, wherein R1 is selected from (1-4C)alkyl, cyclopentyl, cyclohexyl, pyridinyl and phenyl, wherein the latter two groups are optionally substituted with one or two substituents independently selected from chloro, fluoro, bromo, (1-4C)alkyl, (1-4C)alkoxy and trifluoromethyl.

9. The compound of claim 8, wherein R1 is selected from (1-4C)alkyl and dichlorophenyl.

10. The compound of claim 1, having the structure (**II**), wherein R1 is 2,6-dichlorophenyl; A is the linking group -Y-$(CH_2)_n$-X-, wherein Y is attached to R1 and is a bond, n is 1 and X is attached to the phenylene group and is -O-; the ring structure **B** is phenylene; R2 is H; R3 is -$(CH_2)_2$-COOH and R4 is H.

11. The compound of claim 1, having the structure (**II**), wherein R1 is (1-4C)alkyl; A is the linking group -Y-$(CH_2)_n$-X-, wherein Y is attached to R1 and is a bond, n is an integer selected from 1 to 6 and X is attached to the phenylene group and is -O- or a bond; the ring structure **B** is phenylene; R2 is H; R3 is selected from -$(CH_2)_2$-COOH, -$(CH_2)_3$-COOH, -CH_2-$CHCH_3$-COOH, -CH_2-$C(CH_3)_2$-COOH,

-$CHCH_3$-CH_2-COOH, -$(CH_2)_2$-PO_3H_2, -$(CH_2)_3$-PO_3H_2 and -$(CH_2)_2$-OPO_3H_2; and R4 is H.

12. The compound of claim 11, wherein R1 and -$(CH_2)_n$- together are a linear octyl group, X is -O- and R3 is -$(CH_2)_2$-PO_3H_2.

13. The compound of claim 1, selected from
(3-{2-[4-(benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(6-Methyl-imidazo[1,2-a]pyridin-2-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid
3-(2-{4-[3-(2-Propyl-thiazol-5-yloxy)-propoxy]-phenyl}-morpholin-4-yl)-propionic acid,
3-{2-[4-(2-Benzyloxy-ethoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Phenoxy-ethoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-[2-(4-Hex-5-ynyloxy-phenyl)-morpholin-4-yl]-propionic acid,
3-{2-[4-(4-Acetoxy-butoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-(2-{4-[3-(4-Fluoro-phenoxy)-propoxy]-phenyl}-morpholin-4-yl)-propionic acid,
3-(2-{4-[2-(Naphthalen-2-yloxy)-ethoxy]-phenyl}-morpholin-4-yl)-propionic acid,
3-[2-(4-Phenylcarbamoylmethoxy-phenyl)-morpholin-4-yl]-propionic acid,
3-{2-[4-(4-Pyrazol-1-yl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(1-Methyl-1H-pyrazol-3-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(4-Chloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(6-Cyano-hexyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-[2-(4-Phenethyloxy-phenyl)-morpholin-4-yl]-propionic acid,
3-{2-[4-(3-Phenyl-propoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3-Benzyloxy-propoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(7-Methoxy-heptyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-(2-{4-[3-(4-tert-Butyl-phenyl)-[1,2,4]oxadiazol-5-ylmethoxy]-phenyl}-morpholin-4-yl)-propionic acid,
3-{2-[4-(5-Oxo-hexyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(4-Phenyl-butoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3-Methoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-[2-(4-Cyclohexylmethoxy-phenyl)-morpholin-4-yl]-propionic acid,
3-{2-[4-(2-Benzenesulfonyl-ethoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3-Phenoxy-propoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(4-[1,2,4]Triazol-1-yl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2,3-Dihydro-benzofuran-2-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Biphenyl-4-yl-2-oxo-ethoxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(4-Phenoxy-butoxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Oxo-2-phenyl-ethoxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(3-Chloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-(2-{4-[2-(1H-Indol-3-yl)-ethoxy]-phenyl}-morpholin-4-yl)-propionic acid,

3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

(+)-3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

(-)-3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-(2-(4-Octyl-phenyl)-morpholin-4-yl)-propionic acid,

4-[2-(4-Octyl-phenyl)-morpholin-4-yl]-butyric acid,

3-[2-(4-Hexyloxy-phenyl)-morpholin-4-yl]-propionic acid,

4-[2-(4-Hexyloxy-phenyl)-morpholin-4-yl]-butyric acid,

3-[2-(4-Heptyloxy-phenyl)-morpholin-4-yl]-propionic acid,

4-[2-(4-Heptyloxy-phenyl)-morpholin-4-yl]-butyric acid,

3-(2-(4-Octyloxy-phenyl)-morpholin-4-yl)-propionic acid,

(+)-3-[2-(4-Octyloxy-phenyl)-morpholin-4-yl]-propionic acid,

(-)-3-[2-(4-Octyloxy-phenyl)-morpholin-4-yl]-propionic acid,

4-[2-(4-Octyloxy-phenyl)-morpholin-4-yl]-butyric acid,

2,2-Dimethyl-3-(2-(4-octyloxy-phenyl)-morpholin-4-yl)-propionic acid,

3-[2-(4-octyloxy-phenyl)-morpholin-4-yl]-butyric acid,

2-Methyl-3-[2-(4-octyloxy-phenyl)-morpholin-4-yl]-propionic acid,

3-{2-[4-(2-Chloro-6-fluorobenzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2,6-Difluoro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(3-Trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid ,

3-{2-[4-(2,6-Dimethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(3,5-Dichloro-pyridin-4-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2,4-Dichloro-pyridin-3-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2,6-Dichloro-phenylcarbamoyl)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2,6-Dichloro-phenoxymethyl)-phenyl]-morpholin-4-yl}-propionic acid,

3-(2-{4-[2-(2,6-Dichloro-phenyl)-vinyl]-phenyl}-morpholin-4-yl)-propionic acid,

3-[2-(4-Phenethyl-phenyl)-morpholin-4-yl]-propionic acid,

3-{2-[4-(2,6-Dichloro-benzylamino)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2,6-Dichloro-benzoylamino)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-methyl-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Chloro-6-fluoro-benzyloxy)-phenyl]-2-methyl-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Trifluoromethyl-benzyloxy)-phenyl]-2-methyl-morpholin-4-yl}-propionic acid,

3-[2-Methyl-2-(4-octyloxy-phenyl)-morpholin-4-yl]-propionic acid,

4-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-butyric acid,

3-(2-{4-[1-(2,6-Dichloro-phenyl)-ethoxy]-phenyl}-morpholin-4-yl)-propionic acid,

3-(2-{4-[2-(2,6-Dichloro-phenyl)-ethyl]-phenyl}-morpholin-4-yl)-propionic acid,

3-{2-[3-Methoxy-4-(2-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Chloro-6-fluoro-benzyloxy)-3-methoxy-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2,6-Dichloro-benzyloxy)-3-methoxy-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(3-Methoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(5-Bromo-2-methoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2,4-Dichloro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2,3-Dimethoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,

3-[2-(4-Cyclopentylmethoxy-2-methyl-phenyl)-morpholin-4-yl]-propionic acid,

3-{2-[4-(2,5-Dichloro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[2-Methyl-4-(pyridin-3-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[2-Methyl-4-(naphthalen-2-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(Benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Methoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[2-Methyl-4-(6-methyl-pyridin-2-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Chloro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2,5-Dimethoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Bromo-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[2-Methyl-4-(2-methyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(6,6-Dimethyl-bicyclo[3.1.1]hept-2-ylmethoxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Chloro-6-fluoro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(Biphenyl-2-ylmethoxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(2-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3,5-Dichloro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(3-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(4-Chloro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(4-Isopropyl-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(3-phenoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(4-Methoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(2-phenethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3,4-Dimethoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3,5-Dimethyl-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(4-Benzyloxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(thiophen-2-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3-Fluoro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3-Benzyloxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(4-Fluoro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(Biphenyl-4-ylmethoxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(pyridin-2-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(4-Butoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-[2-(4-Cyclohexylmethoxy-2-methyl-phenyl)-morpholin-4-yl]-propionic acid,
3-{2-[2-Methyl-4-(tetrahydro-furan-2-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(3-methyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,3-Difluoro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(4-trifluoromethoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3-Chloro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(tetrahydro-pyran-2-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[2-Methyl-4-(4-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(3,4-Difluoro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[2-Methyl-4-(2,3,4-trimethoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(Cyclohex-3-enylmethoxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(4-Butyl-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid

3-{2-[2-Methyl-4-(4-methyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(3-Dimethylamino-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[2-Methyl-4-(pyridin-4-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Iodo-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(3,5-Dimethoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2,4-Difluoro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[2-Methyl-4-(2,4,5-trimethoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(3-Bromo-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(4-Bromo-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(4-tert-Butyl-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2,5-Difluoro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[2-Methyl-4-(tetrahydro-furan-3-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2,6-Dichloro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2,6-Dichloro-benzyloxy)-3-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid,

{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-acetic acid,

3-[2-(4-Octyloxy-phenyl)-morpholin-4-yl]-3-oxo-propionic acid,

2,2-Difluoro-3-[2-(4-octyloxy-phenyl)-morpholin-4-yl]-propionic acid,

2-[2-(4-Octyloxy-phenyl)-morpholin-4-yl]-ethanol,

2-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-ethanol,

{3-[2-(4-Octyloxy-phenyl)-morpholin-4-yl]-propyl}-phosphonic acid,

{2-[2-(4-Octyloxy-phenyl)-morpholin-4-yl]-ethyl}-phosphonic acid,

Phosphoric acid mono-{2-[2-(4-octyloxy-phenyl)-morpholin-4-yl]-ethyl} ester,

3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-2-methyl-propionic acid,

3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-butyric acid,

Phosphoric acid mono-(2-{2-[4-(2,6-dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-ethyl) ester,

3-{2-[3-Methyl-4-(2-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Chloro-6-fluoro-benzyloxy)-3-methyl-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2,6-Dichloro-benzyloxy)-3-methyl-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2,3-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Chloro-5-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Chloro-3-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Chloro-6-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2,3,6-Trichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Chloro-6-methyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Chloro-5-methyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Chloro-5-ethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Chloro-5-propyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,.

3-{2-[4-(2-Chloro-5-isopropyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2,4,6-Trichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2,6-Dichloro-4-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2,6-Dichloro-4-iodo-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-(2-{4-[3-(2-Fluoro-phenyl)-propoxy]-phenyl}-morpholin-4-yl)-propionic acid,

3-{2-[4-(2,6-Dichloro-4-ethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2,6-Dichloro-4-methyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-[2-(4-Benzyloxy-phenyl)-5-oxo-morpholin-4-yl]-propionic acid,

3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-5-oxo-morpholin-4-yl}-propionic acid,

3-[2-(4-Octyloxy-phenyl)-5-oxo-morpholin-4-yl]-propionic acid·

3-(2-{4-[3-(2-Trifluoromethyl-phenyl)-propoxy]-phenyl}-morpholin-4-yl)-propionic acid,

3-(2-{4-[3-(2-Chloro-6-fluoro-phenyl)-propoxy]-phenyl}-morpholin-4-yl)-propionic acid,

3-(2-{4-[3-(2,6-Dichloro-phenyl)-propoxy]-phenyl}-morpholin-4-yl)-propionic acid,

3-(2-{4-[3-(4-Chloro-phenyl)-propoxy]-phenyl}-morpholin-4-yl)-propionic acid,

3-(2-{4-[3-(2-Chloro-phenyl)-propoxy]-phenyl}-morpholin-4-yl)-propionic acid,

3-(2-{4-[3-(2,3-Difluoro-phenyl)-propoxy]-phenyl}-morpholin-4-yl)-propionic acid,
3-{2-[3-Chloro-4-(2,6-dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[3-Chloro-4-(2-chloro-6-fluoro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[3-Chloro-4-(2-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-6-fluoro-benzyloxy)-2-fluoro-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Dichloro-benzyloxy)-2-fluoro-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Fluoro-4-(2-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Dichloro-3-ethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-6-ethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-6-isopropyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-6-cyclopropyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-6-isobutyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-5,5-dimethyl-morpholin-4-yl}-propionic acid,
3-[5,5-Dimethyl-2-(4-octyloxy-phenyl)-morpholin-4-yl]-propionic acid,
3-{2-[4-(2,6-Dichloro-benzyloxy)-2-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid,
3-[2-(4-Octyloxy-2-trifluoromethyl-phenyl)-morpholin-4-yl]-propionic acid,
3-{6-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2,2-dimethyl-morpholin-4-yl}-propionic acid,
3-[2,2-Dimethyl-6-(4-octyloxy-phenyl)-morpholin-4-yl]-propionic acid,
3-{2-[4-(2,6-Dichloro-4-propyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Dichloro-4-isopropyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Dichloro-4-prop-1-ynyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-6-trifluoromethoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-4-methyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-3-methyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,4-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
2,6-Dichloro-benzoic acid 4-[4-(2-carboxy-ethyl)-morpholin-2-yl]-phenyl ester,

3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-cyclobutanecarboxylic acid,

3-{2-[4-(2,6-Dichloro-benzylsulfanyl)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Chloro-benzylsulfanyl)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Chloro-6-fluoro-benzylsulfanyl)-phenyl]-morpholin-4-yl}-propionic acid,

3-[2-(4-Octylsulfanyl-phenyl)-morpholin-4-yl]-propionic acid,

3-{2-[4-(4,4-Dimethyl-cyclohexyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Difluoromethoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(3-Trifluoromethyl-benzyloxy)-2-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Chloro-6-ethyl-benzyloxy)-2-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Chloro-6-trifluoromethoxy-benzyloxy)-2-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Chloro-6-isopropyl-benzyloxy)-2-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Chloro-6-fluoro-benzyloxy)-2-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Chloro-6-trifluoromethyl-benzyloxy)-2-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Chloro-6-cyclopropyl-benzyloxy)-2-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2,6-Diethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid

3-{2-[2-Chloro-4-(2,6-dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2,6-Dichloro-benzyl)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Chloro-6-difluoromethoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Chloro-6-difluoromethoxy-benzyloxy)-2-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid,

3-[2-(3-Benzyloxy-phenyl)-morpholin-4-yl]-propionic acid,

3-[2-(3-Octyloxy-phenyl)-morpholin-4-yl]-propionic acid,

3-{2-[3-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[3-(2-Chloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-[2-(4-Benzyloxy-phenyl)-thiomorpholin-4-yl]-propionic acid,

3-{2-[4-(2-Chloro-benzyloxy)-phenyl]-thiomorpholin-4-yl}-propionic acid,

3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-thiomorpholin-4-yl}-propionic acid,

3-[2-(4-Octyloxy-phenyl)-thiomorpholin-4-yl]-propionic acid,

3-{2-[5-(2,6-Dichloro-benzyloxy)-pyridin-2-yl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(Indan-1-yloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(7-Methyl-indan-1-yloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,3-Dihydro-benzofuran-3-yloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-(2-{4-[3-(4-Chloro-phenyl)-allyloxy]-phenyl}-morpholin-4-yl)-propionic acid,
3-{2-[4-(3-Phenyl-prop-2-ynyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-(2-{4-[3-phenyl-allyloxy]-phenyl}-morpholin-4-yl)-propionic acid,
3-(2-{4-[3-(4-Chloro-phenyl)-prop-2-ynyloxy]-phenyl}-morpholin-4-yl)-propionic acid,
3-{2-[4-(4-Methoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Methoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-3-oxo-propionic acid,
3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-2,2-difluoro-propionic acid,
(3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propyl)-phosphonic acid,
2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-4-(1(2)H-tetrazol-5-ylmethyl)-morpholine,
3-{2-[4-(2-Oxo-2-phenyl-ethyl)-phenyl]-morpholin-4-yl}-propionic acid
2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-4-[2-(2H-tetrazol-5-yl)-ethyl]-morpholine
and
3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-2,2-dimethyl-propionic acid
or a pharmaceutically acceptable salt, a solvate or hydrate thereof.

14. The compound of claim 1, being (-)-3-{2-[4-(2,6-dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid.

15. The compound of any one of claims 1 to 14 for use in therapy.

16. A pharmaceutical composition comprising the compound of any one of claims 1 to 14 and at least one pharmaceutically acceptable auxiliary.

17. Use of the compound of any one of claims 1 to 14 for the manufacture of a medicament for the treatment, alleviation or prevention of diseases and conditions in which any S1P receptor is involved or in which modulation of the endogenous S1P signaling system via any S1P receptor is involved.

18. The use of claim 17, wherein the disease is a CNS disorder, such as a neurodegenerative disorder, in particular selected from a cognitive disorder, Alzheimer's disease, (vascular) dementia, Nieman's Pick disease, and cognitive deficits in schizophrenia, obsessive-compulsive behavior, major depression, autism, multiple sclerosis and pain, and specifically the disease is a cognitive disorder, such as age-related cognitive decline.

19. Use of a S1P5 agonist for the manufacture of a medicament for the treatment, alleviation or prevention of a neurodegenerative disorder selected from a cognitive disorder, Alzheimer's disease, (vascular) dementia, Nieman's Pick disease, and cognitive deficits in schizophrenia, obsessive-compulsive behavior, major depression, autism, multiple sclerosis and pain, and specifically the disorder is a cognitive disorder, such as age-related cognitive decline.

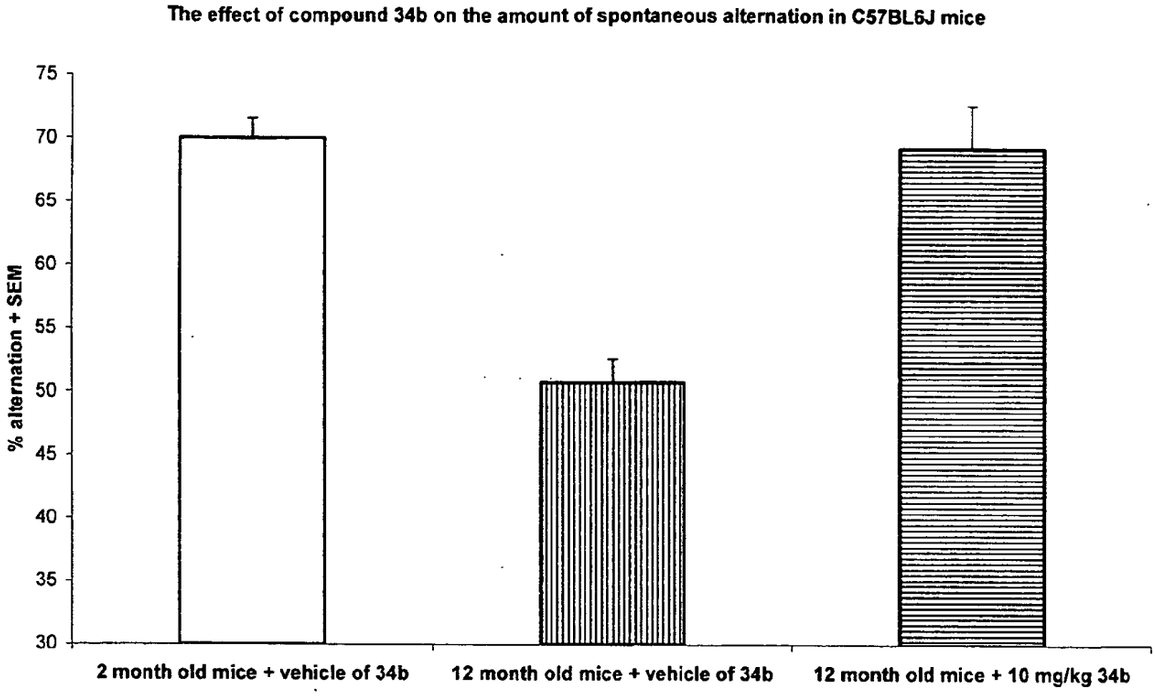

The effect of compound 34b on the amount of spontaneous alternation in C57BL6J mice
% alternation + SEM
75
70
65
60
55
50
45
40
35
30
2 month old mice + vehicle of 34b
12 month old mice + vehicle of 34b
12 month old mice + 10 mg/kg 34b

Figure 1

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2010/062552

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D265/30 C07D265/32 C07D413/12 C07D419/12 C07D471/04
A61K31/5377 A61P25/04 A61P25/06 A61P25/16 A61P25/18
A61P25/24 A61P25/28 C07D279/12 C07D417/12 C07D487/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 2008, HU, AI-XI ET AL: "Synthesis and cyclooxygenase-2 inhibitory activity of 2-(2-arylmorpholino)ethyl ester of naproxen" XP002558960 retrieved from STN Database accession no. 2008:1527686 * abstract & HUAXUE XUEBAO , 66(22), 2553-2557 CODEN: HHHPA4; ISSN: 0567-7351, 2008, -/--	1-8

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 September 2010	14/10/2010
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Brandstetter, T

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2010/062552

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	YORDANOVA, K. ET AL: "2-(Arylmorpholino)ethanols and some of their derivatives" FARMATSIYA (SOFIA), vol. 45, no. 1, 1998, pages 3-11, XP009126794 compound 6E	1-8
X	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 2005, Hu, Ai-xi; He, Li-min; Wu, Hong-yan; Lou, Cheng-li; Cao, Gao: "Synthesis and characterization of 2-arylmorpholine hydrochloride" XP002602146 retrieved from STN Database accession no. 2005:1091431 * abstract; compounds RN910580-49-3	1-8
X	& HU, AI-XI; HE, LI-MIN; WU, HONG-YAN; LOU, CHENG-LI; CAO, GAO: "Synthesis and characterization of 2-arylmorpholine hydrochloride" HUNAN DAXUE XUEBAO, ZIRAN KEXUEBAN, vol. 32, no. 4, 2005, pages 72-76, compounds 910580-49-3	1-8
A	WO 2006/047195 A (MERCK & CO INC [US]; HALE JEFFREY JOHN [US]; YAN LIN [US]) 4 May 2006 (2006-05-04) claim 1 page 5, paragraph 2 page 16, line 29 - line 30 page 11, line 34	1-18

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2010/062552

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2006047195 A	04-05-2006	AU 2005299851 A1	04-05-2006
		CA 2583681 A1	04-05-2006
		CN 101043887 A	26-09-2007
		EP 1804793 A2	11-07-2007
		JP 2008517915 T	29-05-2008
		US 2009042954 A1	12-02-2009

PATENT COOPERATION TREATY

PCT

000183

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference SPW0912 WO	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2010/062552	International filing date *(day/month/year)* 27.08.2010	Priority date *(day/month/year)* 31.08.2009
International Patent Classification (IPC) or national classification and IPC INV. C07D265/30		
Applicant Abbott Healthcare Products B.V.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 15 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see paragraph 3*bis* of Annex C of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
14.12.2010	08.04.2011
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	Authorized officer Brandstetter, T Telephone No. +49 89 2399-5847

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2010/062552

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1, 2, 4-148 as originally filed

   3, 3a filed with the demand for preliminary international examination

   Claims, Numbers

   1-19 filed with the letter of 05-01-2011

   Drawings, Sheets

   1 as originally filed

   ☐ a sequence listing - see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since either they are considered to go beyond the disclosure as filed, or they were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in the Supplemental Box (Rules 70.2(c) and (c-bis)):
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:

5. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 70.2 (e)).

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No. PCT/EP2010/062552

6. ☐ Supplementary international search report(s) from Authority(ies) have been received and taken into account in drawing up this report (Rule 45bis.8(b) and (c)).

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 19

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

   ☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 19 are so unclear that no meaningful opinion could be formed *(specify)*:

   see separate sheet

   ☒ the claims, or said claims Nos. 19 are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*.

   see separate sheet

   ☐ no international search report has been established for the said claims Nos.

   ☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

   ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

   ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

   ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

   ☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2010/062552

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-18
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-18
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-18
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

1 Reference is made to the following documents:

D1 DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 2008 , HU, AI-XI ET AL: "Synthesis and cyclooxygenase-2 inhibitory activity of 2-(2-arylmorpholino)ethyl ester of naproxen" XP002558960 retrieved from STN Database accession no. 2008:1527686 ; & HUAXUE XUEBAO , 66(22), 2553-2557 CODEN: HHHPA4; ISSN: 0567-7351, 2008,

D2 YORDANOVA, K. ET AL: "2-(Arylmorpholino)ethanols and some of their derivatives"FARMATSIYA (SOFIA), vol. 45, no. 1, 1998 , pages 3-11, XP009126794

D3 DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 2005 , Hu, Ai-xi; He, Li-min; Wu, Hong-yan; Lou, Cheng-li; Cao, Gao: "Synthesis and characterization of 2-arylmorpholine hydrochloride" XP002602146 retrieved from STN Database accession no. 2005:1091431 ; & HU, AI-XI; HE, LI-MIN; WU, HONG-YAN; LOU, CHENG-LI; CAO, GAO: "Synthesis and characterization of 2-arylmorpholine hydrochloride"HUNAN DAXUE XUEBAO, ZIRAN KEXUEBAN,vol. 32, no. 4, 2005, pages 72-76,

D4 WO 2006/047195 A (2006-05-04)

Re Item III

2 Claim 19 encompasses compounds defined only by their desired function, contrary to the requirement of clarity in Article 6 PCT, because the "result - to - be - achieved" type of definition does not allow the scope of the claim to be ascertained. The fact that any compound could be screened does not overcome this objection, as the skilled person would not know beforehand whether it fell within the scope claimed, except for the compounds disclosed in the description (see table 1). Undue experimentation would be required to screen compounds randomly. This non-compliance with the substantive provisions is such that a meaningful search of the whole claimed subject-matter of the claim 19 could not be carried out.

The search of claim 19 was consequently restricted to the use of compounds of formula (I) of claim 1.

Re Item V

3 Amendments

3.1 The amendments filed with the letter dated 14.12.2010 consist of the disclaimer of one compound which had been disclosed in D3. D3 can be considered as an accidental anticipation, because only the compound itself and its synthesis have been disclosed without any reference to pharmaceutical activity.

3.2 Subject-matter which extends beyond the content of the application as filed has not been added and the amendments therefore comply with Article 34(2) (b) PCT.

4 Novelty

4.1 The present application refers to (thio)morpholine derivatives of formula I (claim 1) having affinity to S1P receptors, compositions comprising them (claim 16), their medical use (claims 15 and 17) and the medical use of S1P agonists for the preparation of a medicamnet for the treatment, alleviation or prevention of a neurodegenerative disorder (claim 19).

4.2 Documents D1-D3 disclose 2-(4-ethylphenyl)-4-morpholinoethanol, 4-[4-(2-hydroxyethyl)-2-morpholinyl]benzeneacetonitrile, and 3-methyl-2-[4-(phenylmethoxy)phenyl]-4-morpholineethanol hydrochloride respectively, three compounds of formula (I), which have however been disclaimed by proviso.

4.3 Other compounds of formula I have not been disclosed in the prior art and the subject-matter of claim 1 is therefore new. Claims 2-15 are dependent on claim 1 and their subject-matter is therefore also new. Claims 15-18 refer to said new compounds and their subject-matter is therefore also new.

5 Inventive step

5.1 The subject-matter of the present application also involves an inventive step within the meaning of Article 33(3) PCT.

5.2 Document D4 is considered to be the closest prior art to the subject-matter of the present application and discloses (the references in parentheses applying to this document) compounds of formula (I) (claim 1) which are S1P receptor agonists (p. 5, paragraph 2) and a pharmaceutical composition comprising said compounds (claim 17). These compounds are useful for treating amongst others Alzheimer's disease (p. 16, l. 29-30) or dementia (p. 11, l. 34).

5.3 The present compounds differ from this known aryl-substituted saturated heterocyclic compounds in that they contain a oxygen or sulfur atom in the saturated ring moiety and in that the acidic/polar moiety (present R^5, A in D4) is connected to the saturated heterocycle via the nitrogen atom.

5.4 The problem to be solved by the present invention may therefore be regarded as the provision of alternative S1P receptor agonists for the treatment of neurodegenerative disorders, such as Alzheimer's disease. It has been solved by the present compounds which are S1P5 receptor agonists (see table on page 134).

5.5 The solution proposed in claims 1-18 of the present application can be considered to involve an inventive step (Articles 33(3) PCT), for the following reasons: The use of aryl-(thio)morpholine derivatives of formula (I) as S1P receptor agonists for the treatment of neurodegenerative disorders has not been proposed in the prior art nor was it rendered obvious by the teaching of D4. In view of the significant structural differences of the present compounds compared to the closest prior art, inventive step can be acknowledged.

Re Item VIII

6 Clarity

6.1 Claim 17 does not meet the requirements of Article 6 PCT for the following reasons. The therapeutic application of the products is functionally defined by a mechanism of action (i.e. by their capability of modulating the S1P receptor), which does not allow any practical application in the form of a defined, real treatment of a pathological condition (disease))

The objection could be overcome by either introducing in the claims a list of pathological conditions (diseases) cited in the application, e.g in claim 18, or by showing that means are available (in the form of experimental tests or testable criteria, either disclosed in the patent application or known from the common general knowledge), which would allow the skilled person to recognise which additional conditions fall within the functional definition.

A is selected from -CO-O-, -O-CO-, -NH-CO-, -CO-NH, -C=C-, -CCH_3-O- and the linking group –Y-$(CH_2)_n$-X- wherein

Y is attached to R1 and selected from a bond, -O-, -S-, -SO-, -SO_2-, -CH_2-O-, -CO-, -O-CO-, -CO-O-, -CO-NH-, -NH-CO-, -C=C- and -C≡C- ;

n is an integer from 1 to 10; and

X is attached to the phenylene / pyridyl group and selected from a bond, -O-, -S-, -SO-, -SO_2-, -NH, -CO-, -C=C- and -C≡C-;

ring structure B optionally contains one nitrogen atom;

R2 is H, (1-4C)alkyl optionally substituted with one or more fluoro atoms, (1-4C)alkoxy optionally substituted with one or more fluoro atoms, or halogen; and

R3 is (1-4C)alkylene-R5 wherein the alkylene group may be substituted with $(CH_2)_2$ to form a cyclopropyl moiety or one or two halogen atoms, or R3 is is (3-6C)cycloalkylene-R5 or -CO-CH_2-R5, wherein R5 is -OH, -PO_3H_2, -OPO_3H_2, -COOH, -COO(1-4C)alkyl or tetrazol-5-yl;

R4 is H or (1-4C)alkyl;

R6 is one or more substituents independently selected from H, (1-4C)alkyl or oxo;

W is -O-, -S-, -SO- or -SO_2-;

or a pharmaceutically acceptable salt, a solvate or hydrate thereof; with the proviso that the derivative of formula (I) is not 2-(4-ethylphenyl)-4-morpholino-ethanol, 4-[4-(2-hydroxyethyl)-2-morpholinyl]benzeneacetonitrile or 3-methyl-2-[4-(phenylmethoxy)phenyl]-4-morpholinoethanol hydrochloride.

display affinity for S1P receptors. In particular, compounds of the invention show selective affinity for the S1P5 receptor over the S1P1 and/or S1P3 receptor(s).

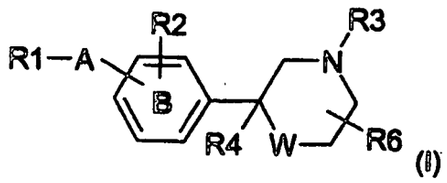
The use of the compound 2-(4-ethylphenyl)-4-morpholinoethanol as a reagent in the production of 2-(2-arylmorpholino)ethyl esters of naproxen is described in Database CA [Online] Chemical Abstracts Service, Columbus, OHIO, US; 2008, Hu, Ai-Xi et al, XP002558960 retrieved from STN database accession no. 2008:1527686; & Huaxue Xuebao, 66(22), 2553-2557 Coden: HHHPA4; ISSN: 0567-7351, 2008. No pharmacological activity of the compound is reported.

Similarly, in Farmatsiya (Sofia), Vol.45, no.1, 1998, pages 3-11, XP009126794 Yordanova, K. et al. describe the use of 4-[4-(2-hydroxyethyl)-2-morpholinyl]-benzeneacetonitrile as a reagent in the production of antidepressant phenylmorpholine derivatives. No pharmacological activity of the compound is reported.

Further, only the synthesis and characterization of 3-methyl-2-[4-(phenylmethoxy)phenyl]-4-morpholinoethanol hydrochloride is mentioned in Database CA [Online] Chemical Abstracts Service, Columbus, OHIO, US; 2005, Hu, Ai-Xi et al, XP002602146 retrieved from STN database accession no. 2005:1091431; & Hu, Ai-Xi et al.: "Synthesis and characterization of 2-arylmorpholine hydrochloride" Hunan Daxue Xuebao, Ziran Kexueban, vol.32, no. 4, 2005, pages 72-76. No pharmacological activity of the compound is reported.

CLAIMS

1. A (thio)morpholine derivative of the formula (I)



(I)

wherein
R1 is selected from
cyano,
(2-4C)alkynyl,
(1-4C)alkyl,
(3-6C)cycloalkyl,
(4-6C)cycloalkenyl,
(6-8C)bicycloalkyl, (8-10C)bicyclic group, each optionally substituted with (1-4C)alkyl,
phenyl, biphenyl, naphthyl, each optionally substituted with one or more substituents independently selected from halogen, (1-4C)alkyl optionally substituted with one or more fluoro atoms, (2-4C)alkynyl, (1-4C)alkoxy optionally substituted with one or more fluoro atoms, amino, di(1-4C)alkylamino, $-SO_2$-(1-4C)alkyl, -CO-(1-4C)alkyl, -CO-O-(1-4C)alkyl, -NH-CO-(1-4C)alkyl and (3-6C)cycloalkyl,
phenyl substituted with phenoxy, benzyl, benzyloxy, phenylethyl or monocyclic heterocycle, each optionally substituted with (1-4C)alkyl,
monocyclic heterocycle optionally substituted with halogen, (1-4C)alkyl or with phenyl optionally substituted with (1-4C)alkyl,
and
bicyclic heterocycle optionally substituted with (1-4C)alkyl;
A is selected from -CO-O-, -O-CO-, -NH-CO-, -CO-NH, -C=C-, $-CCH_3$-O- and the linking group $-Y-(CH_2)_n-X-$ wherein
Y is attached to R1 and selected from a bond, -O-, -S-, -SO-, $-SO_2$-, $-CH_2$-O-, -CO-, -O-CO-, -CO-O-, -CO-NH-, -NH-CO-, -C=C- and -C≡C- ;
n is an integer from 1 to 10; and
X is attached to the phenylene / pyridyl group and selected from a bond, -O-, -S-, -SO-, $-SO_2$-, -NH, -CO-, -C=C- and -C≡C-;
ring structure B optionally contains one nitrogen atom;

R2 is H, (1-4C)alkyl optionally substituted with one or more fluoro atoms, (1-4C)alkoxy optionally substituted with one or more fluoro atoms, or halogen; and

R3 is (1-4C)alkylene-R5 wherein the alkylene group may be substituted with $(CH_2)_2$ to form a cyclopropyl moiety or one or two halogen atoms, or R3 is is (3-6C)cycloalkylene-R5 or $-CO-CH_2-R5$, wherein R5 is -OH, $-PO_3H_2$, $-OPO_3H_2$, -COOH, -COO(1-4C)alkyl or tetrazol-5-yl;

R4 is H or (1-4C)alkyl;

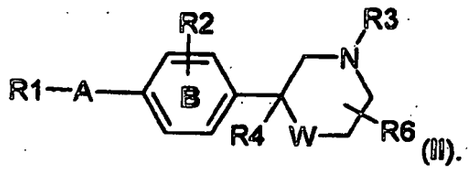
R6 is one or more substituents independently selected from H, (1-4C)alkyl or oxo;

W is -O-, -S-, -SO- or $-SO_2-$;

or a pharmaceutically acceptable salt, a solvate or hydrate thereof; with the proviso that the derivative of formula (I) is not 2-(4-ethylphenyl)-4-morpholino-ethanol, 4-[4-(2-hydroxyethyl)-2-morpholinyl]benzeneacetonitrile or 3-methyl-2-[4-(phenylmethoxy)phenyl]-4-morpholinoethanol hydrochloride.

2. The compound of claim 1, wherein the ring structure B is phenylene.

3. The compound of claim 1 or 2, having the structure (II)



(II).

4. The compound of any one of claims 1 to 3, wherein R3 is selected from $-(CH_2)_2-OH$, $-CH_2-COOH$, $-(CH_2)_2-COOH$, $-(CH_2)_3-COOH$, $-CH_2-CHCH_3-COOH$, $-CH_2-C(CH_3)_2-COOH$, $-CHCH_3-CH_2-COOH$, $-CH_2-CF_2-COOH$, $-CO-CH_2-COOH$, 1,3-cyclobutylene-COOH, $-(CH_2)_2-PO_3H_2$, $-(CH_2)_3-PO_3H_2$, $-(CH_2)_2-OPO_3H_2$, $-(CH_2)_3-OPO_3H_2$, $-CH_2$-tetrazol-5-yl, $-(CH_2)_2$-tetrazol-5-yl and $-(CH_2)_3$-tetrazol-5-yl; and W is -O- or -S-.

5. The compound of any one of claims 1 to 4, wherein R2 is H, methyl, methoxy, trifluoromethyl, difluoromethyl, trifluoromethoxy, difluoromethoxy, Cl or F; and R4 is H or methyl.

6. The compound of any one of claims 1 to 5, wherein A is selected from -CO-O-, -NH-CO-, -CO-NH, -C=C-, $-CCH_3-O-$ and the linking group $-Y-(CH_2)_n-X-$ wherein Y is attached to R1 and selected from a bond, -O-, $-SO_2-$, $-CH_2-O-$, -CO-, -CO-O-,

-NH-CO-, -C=C- and -C≡C-; n is an integer from 1 to 7; and X is attached to the phenylene / pyridyl group and selected from a bond, -O-, -S- and –NH.

7. The compound of any one of claims 1 to 6, wherein R1 is selected from cyano, ethynyl, (1-4C)alkyl, cyclopentyl, cyclohexyl, cyclohexenyl, 6,6-dimethyl-bicyclo[3.1.1]hept-2-yl, indanyl optionally substituted with methyl, biphenyl, naphthyl,
phenyl optionally substituted with one, two or three substituents independently selected from chloro, fluoro, bromo, (1-4C)alkyl, (2-4C)alkynyl, (1-4C)alkoxy, dimethylamino, trifluoromethyl, trifluoromethoxy and (3-6C)cycloalkyl,
phenyl monosubstituted with phenoxy, benzyl, benzyloxy, phenylethyl, pyrazolyl or triazolyl,
pyrazolyl, thiazolyl, oxadiazolyl, thienyl, tetrahydrofuranyl, pyridinyl, tetrahydropyranyl, each optionally substituted with chloro, (1-4C)alkyl or phenyl substituted with (1-4C)alkyl, and
indolyl, imidazopyridinyl, dihydrobenzofuranyl and benzdioxanyl, each optionally substituted with (1-4C)alkyl.

8. The compound of claim 7, wherein R1 is selected from (1-4C)alkyl, cyclopentyl, cyclohexyl, pyridinyl and phenyl, wherein the latter two groups are optionally substituted with one or two substituents independently selected from chloro, fluoro, bromo, (1-4C)alkyl, (1-4C)alkoxy and trifluoromethyl.

9. The compound of claim 8, wherein R1 is selected from (1-4C)alkyl and dichlorophenyl.

10. The compound of claim 1, having the structure (II), wherein R1 is 2,6-dichlorophenyl; A is the linking group -Y-$(CH_2)_n$-X-, wherein Y is attached to R1 and is a bond, n is 1 and X is attached to the phenylene group and is -O-; the ring structure B is phenylene; R2 is H; R3 is -$(CH_2)_2$-COOH and R4 is H.

11. The compound of claim 1, having the structure (II), wherein R1 is (1-4C)alkyl; A is the linking group -Y-$(CH_2)_n$-X-, wherein Y is attached to R1 and is a bond, n is an integer selected from 1 to 6 and X is attached to the phenylene group and is -O- or a bond; the ring structure B is phenylene; R2 is H; R3 is selected from -$(CH_2)_2$-COOH, -$(CH_2)_3$-COOH, -CH_2-$CHCH_3$-COOH, -CH_2-$C(CH_3)_2$-COOH,

$-CHCH_3-CH_2-COOH$, $-(CH_2)_2-PO_3H_2$, $-(CH_2)_3-PO_3H_2$ and $-(CH_2)_2-OPO_3H_2$; and R4 is H.

12. The compound of claim 11, wherein R1 and $-(CH_2)_n-$ together are a linear octyl group, X is -O- and R3 is $-(CH_2)_2-PO_3H_2$.

13. The compound of claim 1, selected from
(3-{2-[4-(benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(6-Methyl-imidazo[1,2-a]pyridin-2-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid
3-(2-{4-[3-(2-Propyl-thiazol-5-yloxy)-propoxy]-phenyl}-morpholin-4-yl)-propionic acid,
3-{2-[4-(2-Benzyloxy-ethoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Phenoxy-ethoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-[2-(4-Hex-5-ynyloxy-phenyl)-morpholin-4-yl]-propionic acid,
3-{2-[4-(4-Acetoxy-butoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-(2-{4-[3-(4-Fluoro-phenoxy)-propoxy]-phenyl}-morpholin-4-yl)-propionic acid,
3-(2-{4-[2-(Naphthalen-2-yloxy)-ethoxy]-phenyl}-morpholin-4-yl)-propionic acid,
3-[2-(4-Phenylcarbamoylmethoxy-phenyl)-morpholin-4-yl]-propionic acid,
3-{2-[4-(4-Pyrazol-1-yl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(1-Methyl-1H-pyrazol-3-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(4-Chloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(6-Cyano-hexyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-[2-(4-Phenethyloxy-phenyl)-morpholin-4-yl]-propionic acid,
3-{2-[4-(3-Phenyl-propoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3-Benzyloxy-propoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(7-Methoxy-heptyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-(2-{4-[3-(4-tert-Butyl-phenyl)-[1,2,4]oxadiazol-5-ylmethoxy]-phenyl}-morpholin-4-yl)-propionic acid,
3-{2-[4-(5-Oxo-hexyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(4-Phenyl-butoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3-Methoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-[2-(4-Cyclohexylmethoxy-phenyl)-morpholin-4-yl]-propionic acid,
3-{2-[4-(2-Benzenesulfonyl-ethoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3-Phenoxy-propoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(4-[1,2,4]Triazol-1-yl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2,3-Dihydro-benzofuran-2-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Biphenyl-4-yl-2-oxo-ethoxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(4-Phenoxy-butoxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Oxo-2-phenyl-ethoxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(3-Chloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-(2-{4-[2-(1H-Indol-3-yl)-ethoxy]-phenyl}-morpholin-4-yl)-propionic acid,

3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

(+)-3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

(-)-3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-(2-(4-Octyl-phenyl)-morpholin-4-yl)-propionic acid,

4-[2-(4-Octyl-phenyl)-morpholin-4-yl]-butyric acid,

3-[2-(4-Hexyloxy-phenyl)-morpholin-4-yl]-propionic acid,

4-[2-(4-Hexyloxy-phenyl)-morpholin-4-yl]-butyric acid,

3-[2-(4-Heptyloxy-phenyl)-morpholin-4-yl]-propionic acid,

4-[2-(4-Heptyloxy-phenyl)-morpholin-4-yl]-butyric acid,

3-(2-(4-Octyloxy-phenyl)-morpholin-4-yl)-propionic acid,

(+)-3-[2-(4-Octyloxy-phenyl)-morpholin-4-yl]-propionic acid,

(-)-3-[2-(4-Octyloxy-phenyl)-morpholin-4-yl]-propionic acid,

4-[2-(4-Octyloxy-phenyl)-morpholin-4-yl]-butyric acid,

2,2-Dimethyl-3-(2-(4-octyloxy-phenyl)-morpholin-4-yl)-propionic acid,

3-[2-(4-octyloxy-phenyl)-morpholin-4-yl]-butyric acid,

2-Methyl-3-[2-(4-octyloxy-phenyl)-morpholin-4-yl]-propionic acid,

3-{2-[4-(2-Chloro-6-fluorobenzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2,6-Difluoro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(3-Trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid ,

3-{2-[4-(2,6-Dimethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(3,5-Dichloro-pyridin-4-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2,4-Dichloro-pyridin-3-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2,6-Dichloro-phenylcarbamoyl)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2,6-Dichloro-phenoxymethyl)-phenyl]-morpholin-4-yl}-propionic acid,

3-(2-{4-[2-(2,6-Dichloro-phenyl)-vinyl]-phenyl}-morpholin-4-yl)-propionic acid,

3-[2-(4-Phenethyl-phenyl)-morpholin-4-yl]-propionic acid,

3-{2-[4-(2,6-Dichloro-benzylamino)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2,6-Dichloro-benzoylamino)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-methyl-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Chloro-6-fluoro-benzyloxy)-phenyl]-2-methyl-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Trifluoromethyl-benzyloxy)-phenyl]-2-methyl-morpholin-4-yl}-propionic acid,

3-[2-Methyl-2-(4-octyloxy-phenyl)-morpholin-4-yl]-propionic acid,

4-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-butyric acid,

3-(2-{4-[1-(2,6-Dichloro-phenyl)-ethoxy]-phenyl}-morpholin-4-yl)-propionic acid,

3-(2-{4-[2-(2,6-Dichloro-phenyl)-ethyl]-phenyl}-morpholin-4-yl)-propionic acid,

3-{2-[3-Methoxy-4-(2-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Chloro-6-fluoro-benzyloxy)-3-methoxy-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2,6-Dichloro-benzyloxy)-3-methoxy-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(3-Methoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(5-Bromo-2-methoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2,4-Dichloro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2,3-Dimethoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,

3-[2-(4-Cyclopentylmethoxy-2-methyl-phenyl)-morpholin-4-yl]-propionic acid,

3-{2-[4-(2,5-Dichloro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[2-Methyl-4-(pyridin-3-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[2-Methyl-4-(naphthalen-2-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(Benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Methoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[2-Methyl-4-(6-methyl-pyridin-2-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Chloro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2,5-Dimethoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Bromo-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[2-Methyl-4-(2-methyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(6,6-Dimethyl-bicyclo[3.1.1]hept-2-ylmethoxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Chloro-6-fluoro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(Biphenyl-2-ylmethoxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(2-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3,5-Dichloro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(3-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(4-Chloro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(4-Isopropyl-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(3-phenoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(4-Methoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(2-phenethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3,4-Dimethoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3,5-Dimethyl-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(4-Benzyloxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(thiophen-2-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3-Fluoro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3-Benzyloxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(4-Fluoro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(Biphenyl-4-ylmethoxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(pyridin-2-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(4-Butoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-[2-(4-Cyclohexylmethoxy-2-methyl-phenyl)-morpholin-4-yl]-propionic acid,
3-{2-[2-Methyl-4-(tetrahydro-furan-2-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(3-methyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,3-Difluoro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(4-trifluoromethoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3-Chloro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(tetrahydro-pyran-2-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[2-Methyl-4-(4-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3,4-Difluoro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(2,3,4-trimethoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(Cyclohex-3-enylmethoxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(4-Butyl-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid
3-{2-[2-Methyl-4-(4-methyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3-Dimethylamino-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(pyridin-4-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Iodo-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3,5-Dimethoxy-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,4-Difluoro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(2,4,5-trimethoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(3-Bromo-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(4-Bromo-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(4-tert-Butyl-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,5-Difluoro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Methyl-4-(tetrahydro-furan-3-ylmethoxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Dichloro-benzyloxy)-2-methyl-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Dichloro-benzyloxy)-3-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid,
{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-acetic acid,
3-[2-(4-Octyloxy-phenyl)-morpholin-4-yl]-3-oxo-propionic acid,
2,2-Difluoro-3-[2-(4-octyloxy-phenyl)-morpholin-4-yl]-propionic acid,
2-[2-(4-Octyloxy-phenyl)-morpholin-4-yl]-ethanol,
2-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-ethanol,
{3-[2-(4-Octyloxy-phenyl)-morpholin-4-yl]-propyl}-phosphonic acid,
{2-[2-(4-Octyloxy-phenyl)-morpholin-4-yl]-ethyl}-phosphonic acid,
Phosphoric acid mono-{2-[2-(4-octyloxy-phenyl)-morpholin-4-yl]-ethyl} ester,
3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-2-methyl-propionic acid,
3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-butyric acid,

Phosphoric acid mono-(2-{2-[4-(2,6-dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-ethyl) ester,

3-{2-[3-Methyl-4-(2-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Chloro-6-fluoro-benzyloxy)-3-methyl-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2,6-Dichloro-benzyloxy)-3-methyl-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2,3-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Chloro-5-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Chloro-3-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Chloro-6-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2,3,6-Trichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Chloro-6-methyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Chloro-5-methyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Chloro-5-ethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Chloro-5-propyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Chloro-5-isopropyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2,4,6-Trichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2,6-Dichloro-4-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2,6-Dichloro-4-iodo-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-(2-{4-[3-(2-Fluoro-phenyl)-propoxy]-phenyl}-morpholin-4-yl)-propionic acid,

3-{2-[4-(2,6-Dichloro-4-ethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2,6-Dichloro-4-methyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-[2-(4-Benzyloxy-phenyl)-5-oxo-morpholin-4-yl]-propionic acid,

3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-5-oxo-morpholin-4-yl}-propionic acid,

3-[2-(4-Octyloxy-phenyl)-5-oxo-morpholin-4-yl]-propionic acid·

3-(2-{4-[3-(2-Trifluoromethyl-phenyl)-propoxy]-phenyl}-morpholin-4-yl)-propionic acid,

3-(2-{4-[3-(2-Chloro-6-fluoro-phenyl)-propoxy]-phenyl}-morpholin-4-yl)-propionic acid,

3-(2-{4-[3-(2,6-Dichloro-phenyl)-propoxy]-phenyl}-morpholin-4-yl)-propionic acid,

3-(2-{4-[3-(4-Chloro-phenyl)-propoxy]-phenyl}-morpholin-4-yl)-propionic acid,

3-(2-{4-[3-(2-Chloro-phenyl)-propoxy]-phenyl}-morpholin-4-yl)-propionic acid,

3-(2-{4-[3-(2,3-Difluoro-phenyl)-propoxy]-phenyl}-morpholin-4-yl)-propionic acid,
3-{2-[3-Chloro-4-(2,6-dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[3-Chloro-4-(2-chloro-6-fluoro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[3-Chloro-4-(2-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-6-fluoro-benzyloxy)-2-fluoro-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Dichloro-benzyloxy)-2-fluoro-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[2-Fluoro-4-(2-trifluoromethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Dichloro-3-ethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-6-ethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-6-isopropyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-6-cyclopropyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-6-isobutyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-5,5-dimethyl-morpholin-4-yl}-propionic acid,
3-[5,5-Dimethyl-2-(4-octyloxy-phenyl)-morpholin-4-yl]-propionic acid,
3-{2-[4-(2,6-Dichloro-benzyloxy)-2-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid,
3-[2-(4-Octyloxy-2-trifluoromethyl-phenyl)-morpholin-4-yl]-propionic acid,
3-{6-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2,2-dimethyl-morpholin-4-yl}-propionic acid,
3-[2,2-Dimethyl-6-(4-octyloxy-phenyl)-morpholin-4-yl]-propionic acid,
3-{2-[4-(2,6-Dichloro-4-propyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Dichloro-4-isopropyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Dichloro-4-prop-1-ynyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-6-trifluoromethoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-4-methyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Chloro-3-methyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,4-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
2,6-Dichloro-benzoic acid 4-[4-(2-carboxy-ethyl)-morpholin-2-yl]-phenyl ester,

3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-cyclobutanecarboxylic acid,

3-{2-[4-(2,6-Dichloro-benzylsulfanyl)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Chloro-benzylsulfanyl)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Chloro-6-fluoro-benzylsulfanyl)-phenyl]-morpholin-4-yl}-propionic acid,

3-[2-(4-Octylsulfanyl-phenyl)-morpholin-4-yl]-propionic acid,

3-{2-[4-(4,4-Dimethyl-cyclohexyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Difluoromethoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(3-Trifluoromethyl-benzyloxy)-2-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Chloro-6-ethyl-benzyloxy)-2-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Chloro-6-trifluoromethoxy-benzyloxy)-2-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Chloro-6-isopropyl-benzyloxy)-2-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Chloro-6-fluoro-benzyloxy)-2-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Chloro-6-trifluoromethyl-benzyloxy)-2-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Chloro-6-cyclopropyl-benzyloxy)-2-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2,6-Diethyl-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid

3-{2-[2-Chloro-4-(2,6-dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2,6-Dichloro-benzyl)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Chloro-6-difluoromethoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[4-(2-Chloro-6-difluoromethoxy-benzyloxy)-2-trifluoromethyl-phenyl]-morpholin-4-yl}-propionic acid,

3-[2-(3-Benzyloxy-phenyl)-morpholin-4-yl]-propionic acid,

3-[2-(3-Octyloxy-phenyl)-morpholin-4-yl]-propionic acid,

3-{2-[3-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-{2-[3-(2-Chloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,

3-[2-(4-Benzyloxy-phenyl)-thiomorpholin-4-yl]-propionic acid,

3-{2-[4-(2-Chloro-benzyloxy)-phenyl]-thiomorpholin-4-yl}-propionic acid,

3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-thiomorpholin-4-yl}-propionic acid,

3-[2-(4-Octyloxy-phenyl)-thiomorpholin-4-yl]-propionic acid,

3-{2-[5-(2,6-Dichloro-benzyloxy)-pyridin-2-yl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(Indan-1-yloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(7-Methyl-indan-1-yloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,3-Dihydro-benzofuran-3-yloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-(2-{4-[3-(4-Chloro-phenyl)-allyloxy]-phenyl}-morpholin-4-yl)-propionic acid,
3-{2-[4-(3-Phenyl-prop-2-ynyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-(2-{4-[3-phenyl-allyloxy]-phenyl}-morpholin-4-yl)-propionic acid,
3-(2-{4-[3-(4-Chloro-phenyl)-prop-2-ynyloxy]-phenyl}-morpholin-4-yl)-propionic acid,
3-{2-[4-(4-Methoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2-Methoxy-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid,
3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-3-oxo-propionic acid,
3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-2,2-difluoro-propionic acid,
(3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propyl)-phosphonic acid,
2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-4-(1(2)H-tetrazol-5-ylmethyl)-morpholine,
3-{2-[4-(2-Oxo-2-phenyl-ethyl)-phenyl]-morpholin-4-yl}-propionic acid
2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-4-[2-(2H-tetrazol-5-yl)-ethyl]-morpholine and
3-{2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-2,2-dimethyl-propionic acid
or a pharmaceutically acceptable salt, a solvate or hydrate thereof.

14. The compound of claim 1, being (-)-3-{2-[4-(2,6-dichloro-benzyloxy)-phenyl]-morpholin-4-yl}-propionic acid.

15. The compound of any one of claims 1 to 14 for use in therapy.

16. A pharmaceutical composition comprising the compound of any one of claims 1 to 14 and at least one pharmaceutically acceptable auxiliary.

17. Use of the compound of any one of claims 1 to 14 for the manufacture of a medicament for the treatment, alleviation or prevention of diseases and conditions in which any S1P receptor is involved or in which modulation of the endogenous S1P signaling system via any S1P receptor is involved.

18. The use of claim 17, wherein the disease is a CNS disorder, such as a neurodegenerative disorder, in particular selected from a cognitive disorder, Alzheimer's disease, (vascular) dementia, Nieman's Pick disease, and cognitive deficits in schizophrenia, obsessive-compulsive behavior, major depression, autism, multiple sclerosis and pain, and specifically the disease is a cognitive disorder, such as age-related cognitive decline.

19. Use of a S1P5 agonist for the manufacture of a medicament for the treatment, alleviation or prevention of a neurodegenerative disorder selected from a cognitive disorder, Alzheimer's disease, (vascular) dementia, Nieman's Pick disease, and cognitive deficits in schizophrenia, obsessive-compulsive behavior, major depression, autism, multiple sclerosis and pain, and specifically the disorder is a cognitive disorder, such as age-related cognitive decline.

DERIVADOS DE (TIO)MORFOLINA COMO MODULADORES DE S1P

Campo de la invención

Esta invención se refiere a nuevos derivados de (tio)morfolina que tienen afinidad por los receptores de S1P, una composición farmacéutica que contiene dichos compuestos, como también el uso de dichos compuestos para la preparación de un medicamento para tratar, aliviar o prevenir enfermedades y dolencias en las cuales cualquier receptor de S1P está involucrado o en el cual la modulación del sistema de señalización de S1P endógeno a través de cualquier receptor de S1P está involucrado.

Fundamento de la invención

El esfingosin-1-fosfato (S1P) es un esfingolípidos que media una amplia variedad de respuestas celulares, tales como la proliferación, organización cito esquelética y migración, adherencia y montaje de unión hermética, y morfogénesis. El S1P puede unirse con los miembros de la familia génica de diferenciación celular endotelial (receptores de EDG) de los receptores acoplados a las proteínas G localizadas en la membrana plasmática. Hasta la fecha, se han identificado cinco miembros de esta familia como los receptores de S1P en diferentes tipos de células, S1P1 (EDG-1), S1P2 (EDG-5), S1P3 (EDG-3), S1P4 (EDG-6) y S1P5 (EDG-8). El S1P puede producir reordenamientos cito esqueléticos en muchos tipos de células para regular el tráfico de células inmunológicas, la homeóstasis vascular y la comunicación celular en el sistema nervioso central (SNC) y en sistemas de órganos periféricos.

Se sabe que S1P se secreta a través del endotelio vascular y está presente en la sangre en concentraciones de 200-900 nanomolar y se une a través de la albúmina y otras proteínas plasmáticas. Esto proporciona tanto un reservorio estable en los fluidos extracelulares como la administración eficiente a receptores de superficie celular de alta afinidad. El S1P se une con baja afinidad nanomolar a los cinco receptores S1P1-5. Además, las plaquetas también contienen S1P y pueden liberarse en forma local para producir por ej., vasoconstricción. Los subtipos del receptor S1P1, S1P2 y S1P3 se expresan ampliamente y representan receptores dominantes. En forma adicional, S1P1 también es un receptor sobre los linfocitos. Los receptores de S1P4 se encuentran casi exclusivamente en el sistema hematopoyético y linfoide. El S1P5 se expresa principalmente (aunque no en forma exclusiva) en el sistema nervioso central. La expresión de S1P5 está restringida a los oligodendrocitos en ratones, las células mielinantes del cerebro, mientras que en la rata y el hombre la expresión al nivel de los astrocitos y las células endoteliales se encontró aunque no sobre los oligodendrocitos.

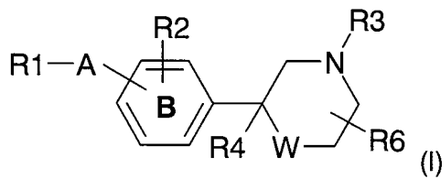
Los moduladores del receptor de S1P son compuestos que se señalan como (ant)agonistas en uno o más receptores de S1P. La presente invención se refiere a

moduladores del receptor de S1P5, en particular agonistas, y con preferencia a agonistas con selectividad por sobre los receptores S1P1 y/o S1P3, si se tienen en cuenta los efectos inmunomoduladores y/o cardiovasculares no deseados. Se ha encontrado que los agonistas de S1P5 pueden usarse en el tratamiento de trastornos cognitivos, en particular la decadencia cognitiva relacionada con el proceso de envejecimiento.

Aunque se encuentra en curso la investigación para desarrollar productos terapéuticos que puedan usarse para tratar la decadencia cognitiva relacionada con el proceso de envejecimiento y la demencia, aún esto no ha producido muchos candidatos exitosos. Por lo tanto, existe la necesidad de lograr nuevos agentes terapéuticos con las propiedades deseadas.

Descripción de la invención

Se ha encontrado que los derivados de (tio)morfolina que tienen la fórmula (I)



(I)

en donde

R1 se selecciona de

ciano,

alquinilo (2-4C),

alquilo (1-4C),

cicloalquilo (3-6C),

cicloalquenilo (4-6C),

bicicloalquilo (6-8C), grupo bicíclico (8-10C), cada uno sustituido en forma opcional con alquilo (1-4C),

fenilo, bifenilo, naftilo, cada uno sustituido en forma opcional con uno o más sustituyentes se selecciona en forma independiente de halógeno, alquilo (C1-4C) sustituido en forma opcional con uno o más átomos de fluoro, alquinilo (2-4C), alcoxi (C1-4C) sustituido en forma opcional con uno o más átomos de fluoro, amino, dialquilamino (C1-4C) , -SO2-alquilo (1-4C), -CO-alquilo (1-4C), -CO-O-alquilo (1-4C), -NH-CO-alquilo (C1-4C) y cicloalquilo (3-6C),

fenilo sustituido con fenoxi, bencilo, benciloxi, feniletilo o heterociclo monocíclico, cada uno sustituido en forma opcional con alquilo (1-4C),

heterociclo monocíclico sustituido en forma opcional con halógeno, alquilo (C1-4C) o con fenilo sustituido en forma opcional con alquilo (1-4C),

y

heterociclo bicíclico sustituido en forma opcional con alquilo (C1-4C);

A se selecciona de -CO-O-, -O-CO-, -NH-CO-, -CO-NH, -C=C-, -CCH3-O- y el grupo de enlace –Y-(CH2)n-X- en donde

Y está unido a R1 y se selecciona de un enlace, -O-, -S-, -SO-, -SO2-, -CH2-O-, -CO-, -O-CO-, -CO-O-, -CO-NH-, -NH-CO-, -C=C- y -C≡C- ;

n es un número entero desde 1 hasta 10; y

X está unido al grupo fenileno / piridilo y se selecciona de un enlace, -O-, -S-, -SO-, -SO2-, -NH, -CO-, -C=C- y -C≡C-;

la estructura del anillo B contiene en forma opcional un átomo de nitrógeno;

R2 es H, alquilo (C1-4C) sustituido en forma opcional con uno o más átomos de fluoro, alcoxi (C1-4C) sustituido en forma opcional con uno o más átomos de fluoro, o halógeno; y

R3 es alquileno (1-4C)-R5 en donde el grupo alquileno puede estar sustituido con (CH2)2 para formar un resto ciclopropilo o uno o dos átomos de halógeno, o R3 es cicloalquileno (3-6C)-R5 o -CO-CH2-R5, en donde R5 es -OH, -PO3H2, -OPO3H2, -COOH, -COOalquilo (C1-4C) o tetrazol-5-ilo;

R4 es H o alquilo (C1-4C);

R6 es uno o más sustituyentes se selecciona en forma independiente de H, alquilo (C1-4C) o oxo;

W es -O-, -S-, -SO- o -SO2-;

o una sal, un solvato o un hidrato aceptables desde el punto de vista farmacéutico de los anteriores; con la salvedad de que el derivado que tiene la fórmula (I) no sea 2-(4-etilfenil)-4-morfolinoetanol o 4-[4-(2-hidroxietil)-2-morfolinil]bencenacetonitrilo.

muestren afinidad por los receptores de S1P. En particular, los compuestos de la invención muestran afinidad selectiva por el receptor de S1P5 por sobre el(los) receptor(es) S1P1 y/o S1P3.

El uso del compuesto 2-(4-etilfenil)-4-morfolinoetanol como reactivo en la producción de ésteres de 2-(2-arilmorfolino)etilo de naproxeno se describe en la base de datos Database CA [Online] Chemical Abstracts Service, Columbus, OHIO, USA; 2008, Hu, Ai-Xi et al, XP002558960 recuperado de la base de datos STN con no. de acceso 2008:1527686; & Huaxue Xuebao, 66(22), 2553-2557 Coden: HHHPA4; ISSN: 0567-7351, 2008. No se presentaron reportes de actividad farmacológica del compuesto.

De manera similar, en Farmatsiya (Sofia), Vol,45, no,1, 1998, pages 3-11, XP009126794 Yordanova, K. et al., describe el uso de 4-[4-(2-hidroxietil)-2-morfolinil]-bencenacetonitrilo como reactivo en la producción de derivados de fenilmorfolina como

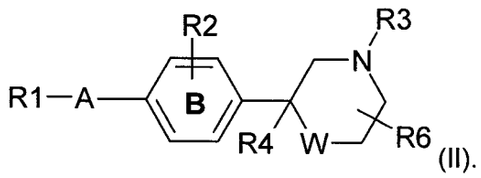
agente antidepresivo. No se presentaron reportes de la actividad farmacológica del compuesto.

En forma adicional, sólo la síntesis y caracterización del clorhidrato de 3-metil-2-[4-(fenilmetoxi)fenil]-4-morfolinoetanol se menciona en la base de datos Database CA [Online] Chemical Abstracts Service, Columbus, OHIO, USA; 2005, Hu, Al-Xi et al, XP002602146 recuperada del no. de acceso a la base de datos de STN 2005:1091431; & Hu, Al-XI et al.: "Synthesis and Characterization of 2-arylmorpholine hydrochloride" Hunan Daxue Xuebao, Ziran Kexueban, vol. 32, no. 4, 2005, páginas 72-76. No se presentaron reportes de la actividad farmacológica del compuesto.

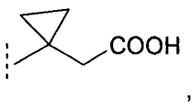
Los compuestos de la invención son moduladores del receptor de S1P, en particular del receptor de S1P5. Más específicamente, los compuestos de la invención son agonistas del receptor de S1P5. Los compuestos de la invención son útiles para tratar, aliviar y prevenir enfermedades y dolencias en las cuales (cualquier) receptor(es) de S1P - en particular S1P5 – está (están) involucrados o en las cuales está involucrada la modulación del sistema de señalización de S1P endógeno a través de cualquier receptor de S1P. En particular, los compuestos de la presente invención pueden usarse para tratar, aliviar o prevenir trastornos del SNC (sistema nervioso central), tales como trastornos neurodegenerativos, en particular -aunque sin carácter limitativo- trastornos cognitivos (en particular decadencia cognitiva relacionada con el proceso de envejecimiento) y dolencias relacionadas, Enfermedad de Alzheimer, demencia (vascular), Enfermedad de Nieman-Pick, y déficits cognitivos en pacientes con esquizofrenia, comportamiento obsesivo compulsivo, depresión mayor, autismo, esclerosis múltiple, dolor, etc.. Con preferencia, los compuestos de la presente invención pueden usarse para tratar, aliviar o prevenir trastornos cognitivos (en particular decadencia cognitiva relacionada con el proceso de envejecimiento) y dolencias relacionadas.

En algunas realizaciones de la invención, la estructura del anillo B es fenileno.

En una realización de la invención, los compuestos tienen la estructura (II)



(II).

En otra realización de la invención, los compuestos tienen la fórmula (I) en donde R3 se selecciona de -(CH2)2-OH, -CH2-COOH, -(CH2)2-COOH, -(CH2)3-COOH, -CH2-CHCH3-COOH, -CH2-C(CH3)2-COOH, -CHCH3-CH2-COOH, 

,

-CH2-CF2-COOH, -CO-CH2-COOH, 1,3-ciclobutileno-COOH, -(CH2)2-PO3H2, -(CH2)3-PO3H2, -(CH2)2-OPO3H2, -(CH2)3-OPO3H2, -CH2-tetrazol-5-ilo, -(CH2)2-tetrazol-5-ilo y -(CH2)3-tetrazol-5-ilo. Los grupos R3 preferidos se seleccionan de -CH2-COOH, -(CH2)2-COOH, -(CH2)3-COOH, -CH2-CHCH3-COOH, -CH2-C(CH3)2-COOH, -CHCH3-CH2-COOH, -(CH2)2-PO3H2, -(CH2)3-PO3H2 y -(CH2)2-OPO3H2 y en particular -(CH2)2-COOH y -(CH2)2-PO3H2. El más preferido es -(CH2)2-COOH.

En otra realización, W es -O- o -S-. En realizaciones preferidas, W es -O-.

En una realización adicional de la invención, R4 es H o metilo y en particular, R4 es H.

En otra realización, los compuestos tienen la fórmula (I) en donde R2 es H, metilo, metoxi, trifluorometilo, difluorometilo, trifluorometoxi, difluorometoxi, Cl o F. En realizaciones preferidas adicionales, R2 es H o trifluorometilo.

En forma adicional, en una realización de la invención, A se selecciona de -CO-O-, -NH-CO-, -CO-NH, -C=C-, -CCH3-O- y el grupo de enlace –Y-(CH2)n-X- en donde

Y está unido a R1 y se selecciona de un enlace, -O-, -SO2-, -CH2-O-, -CO-, -CO-O-, -NH-CO-, -C=C- y -C≡C-; n es un número entero desde 1 hasta 7; y X está unido al grupo fenileno / piridilo y se selecciona de un enlace, -O-, -S- y -NH. Con preferencia, A se selecciona de -CO-NH, -C=C-, -CCH3-O- y el grupo de enlaces -(CH2)n-X- y -O-(CH2)n-X-. En realizaciones preferidas A es CH2-O-.

En realizaciones adicionales de la invención, R1 se selecciona de ciano, etinilo, alquilo (1-4C), ciclopentilo, ciclohexilo, ciclohexenilo, 6,6-dimetil-biciclo[3,1,1]hept-2-ilo, indanilo sustituido en forma opcional con metilo, bifenilo, naftilo, fenilo sustituido en forma opcional con uno, dos o tres sustituyentes se selecciona en forma independiente de cloro, fluoro, bromo, alquilo (1-4C), alquinilo (2-4C), alcoxi (C1-4C) , dimetilamino, trifluorometilo, trifluorometoxi y cicloalquilo (3-6C), y R1 se selecciona en forma adicional de fenilo mono sustituido con fenoxi, bencilo, benciloxi, feniletilo, pirazolilo o triazolilo, y R1 se selecciona en forma adicional de pirazolilo, tiazolilo, oxadiazolilo, tienilo, tetrahidrofuranilo, piridinilo, tetrahidropiranilo, cada uno sustituido en forma opcional con cloro, alquilo (C1-4C) o fenilo sustituido con alquilo (1-4C), y R1 se selecciona en forma adicional de indolilo, imidazopiridinilo, dihidrobenzofuranilo y benzdioxanilo cada uno sustituido en forma opcional con (1-4C)alquilo. En realizaciones preferidas, R1 se selecciona de etinilo, alquilo (1-4C), ciclopentilo, ciclohexilo, ciclohexenilo, bifenilo, naftilo, fenilo sustituido en forma opcional con uno, dos o tres sustituyentes se selecciona en forma independiente de cloro, fluoro, bromo, alquilo (1-4C), alcoxi (C1-4C) , dimetilamino, trifluorometilo y trifluorometoxi, y en forma adicional se selecciona de fenilo mono sustituido con fenoxi, bencilo, benciloxi, feniletilo, pirazolilo o triazolilo,

y en forma adicional se selecciona de tiazolilo, tienilo, tetrahidrofuranilo, piridinilo, tetrahidropiranilo, cada uno sustituido en forma opcional con cloro o alquilo (1-4C), y benzodioxanilo. En particular, R1 se selecciona de alquilo (1-4C), ciclopentilo, ciclohexilo, piridinilo y fenilo, en donde los últimos dos grupos están sustituidos en forma opcional con uno o dos substituents se selecciona en forma independiente de cloro, fluoro, bromo, alquilo (1-4C), alcoxi (C1-4C) y trifluorometilo. En realizaciones preferidas, R1 es alquilo (C1-4C) o diclorofenilo.

En una realización altamente preferida de la invención, R1 es 2,6-diclorofenilo; A es el grupo de enlace -Y-(CH2)n-X-, en donde Y está unido a R1 y es un enlace, n es 1 y X está unido al grupo fenileno y es -O-; R2 es H; R3 es -(CH2)2-COOH; y R4 es H.

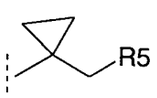
En realizaciones preferidas adicionales de la invención, R1 es alquilo (C1-4C); A es el grupo de enlace -Y-(CH2)n-X-, en donde Y está unido a R1 y es un enlace, n es un número entero seleccionado de 1 hasta 6 y X está unido al grupo fenileno / piridilo y es -O- o un enlace; R2 es H; R3 se selecciona de -(CH2)2-COOH, -(CH2)3-COOH, -CH2-CHCH3-COOH, -CH2-C(CH3)2-COOH, -CHCH3-CH2-COOH, -(CH2)2-PO3H2, -(CH2)3-PO3H2 y -(CH2)2-OPO3H2; y R4 es H. Con preferencia, R1 y -(CH2)n- juntos son un grupo octilo lineal. Se prefiere en forma adicional que el R3 sea -(CH2)2-PO3H2. En una realización preferida adicional, X es -O-.

El término halógeno se refiere a fluoro, cloro, bromo, o yodo. Los halógenos preferidos son fluoro y cloro, y en particular cloro.

El término alquilo (C1-4C) se refiere a un grupo alquilo ramificado o no ramificado que tiene 1-4 átomos de carbono, por ejemplo metilo, etilo, propilo, isopropilo y butilo. Un grupo alquilo preferido es metilo.

El término alcoxi (C1-4C) se refiere a un grupo alcoxi que tiene 1-4 átomos de carbono, en donde el resto alquílico es como se lo definió con anterioridad. Un grupo alcoxi preferido es metoxi.

El término alquileno (1-4C) significa un grupo alquileno ramificado o no ramificado que tiene 1-4 átomos de carbono, por ejemplo metileno, -CCH3CH2-, y otros similares. En la definición de R3 que es alquileno (1-4C)-R5, uno o más átomos de carbono en el grupo alquileno pueden (entre otros) estar sustituidos en forma independiente con (CH2)2 para formar un resto ciclopropilo, lo que significa para formar un grupo R3 tales como

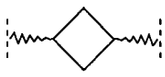


El término alquinilo (2-4C) se refiere a un grupo alquinilo ramificado o no ramificado que tiene 2-4 átomos de carbono, en donde el enlace triple puede estar presentes en posiciones diferentes en el grupo, por ejemplo etinilo, propargilo, 1-butinilo, 2-butinilo, etc.

El término cicloalquilo (3-6C) se refiere a un grupo alquilo cíclico que tiene 3-6 átomos de carbono, de este modo ciclopropilo, ciclobutilo, ciclopentilo o ciclohexilo. Se prefieren ciclopentilo y ciclohexilo.

El término cicloalquenilo (4-6C) se refiere a un grupo alquenilo cíclico que tiene 4-6 átomos de carbono y comprende uno o dos enlaces dobles, por ejemplo ciclohexenilo.

El término cicloalquileno (3-6C) se refiere a un grupo alquilo cíclico que tiene dos puntos de unión. Se prefiere el 1,3-ciclobutileno, que tiene la estructura



El término bicicloalquilo (6-8C), se refiere a un sistema anular fusionado de dos grupos cicloalquilo que tienen juntos 6-8 átomos de carbono, por ejemplo el grupo biciclo[3,1,1]hept-2-ilo.

El término grupo bicíclico (8-10C) se refiere a un sistema anular fusionado de una estructura del anillo aromático o no aromático que tiene juntos 8-10 átomos de carbono, por ejemplo el grupo indano.

El término heterociclo monocíclico abarca grupos heteroarilo monocíclicos y grupos heteromonocíclicos no aromáticos, por ejemplo furanilo, tienilo, pirrolilo, oxazolilo, tiazolilo, imidazolilo, pirazolilo, isoxazolilo, isotiazolilo, triazolilo, oxadiazolilo, piridilo, piridazinilo, pirimidinilo, pirazinilo, triazinilo, tetrahidrofuranilo, tetrahidropiranilo, dioxanilo, morfolinilo, y otros similares.

El término heterociclo bicíclico abarca grupos heteroarilo bicíclicos y grupos heterocibíclicos no aromáticos, por ejemplo indolilo, indazolilo, isoindolilo, indolizinilo, benzimidazolilo, imidazotiazolilo, imidazopiridinilo, benzfuranilo, dihidrobenzofuranilo, benzdioxanilo, quinolinilo, isoquinolinilo, quinolizinilo, tetrahidroisoquinolinilo, y otros similares.

Con referencia a los sustituyentes, el término "en forma independiente" significa que los sustituyentes pueden ser iguales o diferentes entre sí en la misma molécula.

Los compuestos de la invención pueden prepararse de manera apropiada por métodos disponibles en el arte, y como se ilustra en la sección experimental de esta descripción.

Los compuestos de la presente invención pueden contener uno o más centros asimétricos y pueden ocurrir de este modo como racematos y mezclas racémicas,

enantiómeros simples, mezclas de diastereómeros y diastereómeros individuales. Los centros asimétricos adicionales pueden estar presentes dependiendo de la naturaleza de los varios sustituyentes en la molécula. Cada uno de dichos centros asimétricos producirán en forma independiente produce dos isómeros ópticos y se pretende que la totalidad de los isómeros ópticos posibles y diastereómeros en las mezclas y como compuestos puros o parcialmente purificados se incluyan dentro del ámbito de esta invención. La presente invención pretende abarcar todas dichas formas isoméricas de estos compuestos. Las síntesis independientes de estos diastereómeros o sus separaciones cromatográficas pueden lograrse como se conoce en el arte por modificación apropiada de la metodología divulgada en esta memoria. Su estereoquímica absoluta puede determinarse por cristalografía por rayos x de los productos cristalinos o intermediarios cristalinos que derivan, si es necesario, con un reactivo que contiene un centro asimétrico de configuración absoluta conocida. Si se desea, las mezclas racémicas de los compuestos pueden separarse de manera tal que se aíslen los enantiómeros individuales. La separación puede llevarse a cabo por aplicación de métodos muy conocidos en el arte, tales como el acoplamiento de una mezcla racémica de compuestos a un compuesto enantioméricamente puro para formar una mezcla diasteromérica, seguido de separación de los diasterómeros individuales por métodos estándar, tales como cristalización fraccional o cromatografía.

Los compuestos pueden existir como polimorfos y como tales pretenden incluirse en la presente invención. Además, los compuestos pueden formar solvatos con agua (es decir, hidratos) o solventes orgánicos comunes, y dichos solvatos también pretenden abarcarse dentro del alcance de esta invención.

El compuesto marcado en forma isotópica que tiene la fórmula (I) o sus sales aceptables desde el punto de vista farmacéutico, incluyendo compuestos que tienen la fórmula (I) marcada isotópicamente para ser detectable por PET o SPECT, también caen dentro del alcance de la invención. Lo mismo se aplica a compuestos que tiene la fórmula (I) marcados con [13C]-, [14C]-, [3H]-, [18F]-, [125I]- u otros átomos isotópicamente enriquecidos, aptos para estudios de metabolismo o de unión a los receptores.

El término "sal aceptable desde el punto de vista farmacéutico " se refiere a aquellas sales que son, dentro del alcance del criterio médico de peso, aptas para usar en contacto con tejidos de humanos o animales inferiores sin indebida toxicidad, irritación, respuesta alérgica, y otros similares, y se compensan con una proporción riesgo/beneficio razonable. Las sales aceptables desde el punto de vista farmacéutico se conocen muy bien en el arte. Éstas se pueden preparar in situ cuando se aíslan y se purifican los compuestos de la invención, o por separado al hacerlos reaccionar con ácidos o bases no

tóxicos aceptables desde el punto de vista farmacéutico, incluyendo bases orgánicas o inorgánicas y ácidos orgánicos o inorgánicos.

Los compuestos de la invención pueden administrarse por vía enteral o parenteral. La posología exacta y régimen de administración de estos compuestos y sus composiciones, dependerá de la actividad biológica del compuesto per se, la edad, el peso y el sexo del paciente, las necesidades del sujeto individual a quien se administra el medicamento, el grado de enfermedad o necesidad y el criterio del médico a cargo del tratamiento. En general, la administración parenteral requiere posologías más bajas que otros métodos de administración que dependen más de la adsorción. Sin embargo, las posologías para los humanos son con preferencia 0,001 – 10 mg por kg de peso corporal. En general, las posologías enterales y parenterales estarán en el rango de 0,1 hasta 1,000 mg por día del total de principios activos.

Mezclados con auxiliares apropiados desde el punto de vista farmacéutico, por ej., como se describe en el texto de referencia estándar "Remington, The Science and Practice of Pharmacy" (21st edition, Lippincott Williams & Wilkins, 2005, ver especialmente la Parte 5: Pharmaceutical Manufacturing) los compuestos pueden comprimirse para obtener unidades de dosificación sólida, tales como píldoras o comprimidos, o procesarse para obtener cápsulas o supositorios. Por medio de los líquidos apropiados desde el punto de vista farmacéutico, los compuestos también pueden aplicarse en forma de solución, suspensión o emulsión.

Para producir las unidades de dosificación, por ej., comprimidos, se contempla el uso de aditivos convencionales tales como rellenos, colorantes, aglutinantes poliméricos y otros similares. En general, puede utilizarse cualquier aditivo apropiado desde el punto de vista farmacéutico que no interfiera con la función de los compuestos activos.

Los vehículos apropiados con los cuales pueden administrarse los compuestos de la invención incluyen, por ejemplo, lactosa, almidón, derivados de celulosa y otros similares, o mezclas de los anteriores, usados en las cantidades apropiadas. Las composiciones para administración por vía intravenosa pueden ser, por ejemplo, soluciones de los compuestos de la invención en buffer acuoso isotónico estéril. Donde corresponda, las composiciones para administración intravenosa pueden incluir por ejemplo agentes que mejoran la solubilidad, agentes que brindan estabilidad y/o un anestésico local para aliviar el dolor en el sitio donde se aplica la inyección.

Las composiciones farmacéuticas de la invención pueden formularse para cualquier vía de administración y comprender por lo menos un compuesto de la presente invención y sus sales aceptables desde el punto de vista farmacéutico, con cualquier ingrediente,

excipiente, vehículo, adyuvante o portador apropiado desde el punto de vista farmacéutico.

Por "apropiado desde el punto de vista farmacéutico" se entiende que el vehículo, diluyente o excipiente debe ser compatible con los otros componentes de la formulación y no perjudiciales para la persona que los recibe.

En una realización de la invención, se proporciona un paquete o kit farmacéutico que comprende uno o más envases llenados con una o más composiciones farmacéuticas de la invención. Pueden incluirse con dicho(s) envase(s) materiales escritos tales como instrucciones de uso, o una notificación en la forma indicada por la agencia gubernamental que regula la fabricación, el uso o la venta de productos farmacéuticos, cuya nota refleje la aprobación de la agencia sobre la fabricación, el uso o la venta para administración en humanos o veterinaria.

Salvo que se defina de otro modo, todos los términos técnicos y científicos usados aquí tienen el mismo significado que entiende comúnmente una persona con experiencia en el arte al cual pertenece esta invención. Aunque los métodos y materiales similares o equivalentes a los que se describen en esta memoria pueden usarse en la práctica o evaluación de la presente invención, en este documento se describen los métodos y materiales apropiados.

LEYENDA DE LA FIGURA

Figura 1 Porcentaje de alternación de ratones macho jóvenes y viejos C57BL/6J en el laberinto T con cualquier vehículo (grupos de control) o compuesto 34b (10 mg/kg; por vía oral)

Los siguientes ejemplos tienen como finalidad adicional ilustrar la invención en mayor detalle.

EJEMPLOS

§1. MATERIALES Y MÉTODOS

Los espectros de Resonancia magnética nuclear (1H RMN) se determinaron en el solvente indicado con el uso de un Bruker Avance-I 400 con un magneto 9,4T (1H: 400 MHz, 13C: 100 MHz), equipado con un cabezal de sonda de banda ancha BBI inversie con gradiente Z y ATM, o un Bruker Avance-DRX 600 con un magneto de 14,1T, equipado con un cabezal de criosonda de resonancia triple invertida TXI con gradiente Z y ATM, a 300 K, salvo que se indique de otro modo. Los espectros se determinaron en cloroformo deuterado (CDCl3) con 99,8 % atómico de D; o en dimetilsulfóxido-d6 (DMSO-d6) que contenía 0,03 % v/v de tetrametilsilano; ambos adquiridos a Aldrich Chemical, las desviaciones (δ) se presentan en ppm a partir del tetrametilsilano. Las constantes de acoplamiento J se presentan en Hz. Las formas de los picos en los espectros de RMN se

indican con los símbolos 'q' (cuarteto), 'dq' (doble cuarteto), 't' (triplete), 'dt' (doble triplete), 'd' (duplete), 'dd' (doble duplete), 's' (singulete), 'bs' (singulete amplio) y 'm' (multiplete). Las señales de NH y OH se identificaron después de mezclar la muestra con una gota de D2O.

Los puntos de fusión se registraron en un aparato para medir los puntos de fusión Büchi B-545.

Todas las reacciones que involucraron compuestos o condiciones sensibles a la humedad se llevaron a cabo a atmósfera de nitrógeno anhidra.

Las reacciones se monitorearon usando cromatografía de fase delgada (TLC) sobre láminas de plástico recubiertas con sílice (F254 previamente recubiertas con gel de sílice 60 de Merck) con el eluyente indicado. Las manchas se visualizaron con luz UV (254 nm) o I2.

Cromatografía líquida- Espectrometría de masa (LC-MS)

Sistema A: Columna: Acquity UPLC BEH C18 1,7 µm, 50 x 2,1 mm con 1,7 µm de partículas. La columna se coloca por calor en un horno de columna a 45°C.

Detección: Disposición de diodos entre 210 y 260 nm

etapa	tiempo total(min)	flujo (µl/min)	A(%)	B(%)
0	0	800	95	5
1	0,1	800	95	5
2	4,5	800	10	90
3	5	800	10	90
4	5,01	800	95	5

A= 99,9% de Agua con 0,1% CH3COOH

B= 99,9% CH3CN con 0,1% CH3COOH

Sistema B: Columna: Waters Sunfire C18, 30 x 4,6 mm con 2,5 □m de partículas. La columna se coloca por calor en un horno de columna a 23°C.

Detección: medidor de UV/VIS con la longitud de onda configurada a 254 nm + detector de difracción de luz por evaporación que funciona a 700 Celsius y 1,7 bares de presión de N2.

etapa	tiempo total (min)	flujo (ul/min)	A(%)	B(%)
0	0	1800	95	5
1	1,8	1800	0	100
2	2,6	1800	0	100
3	2,8	1800	95	5
4	3,0	1800	95	5

A= 99,9% de Agua con 0,1% de HCOOH

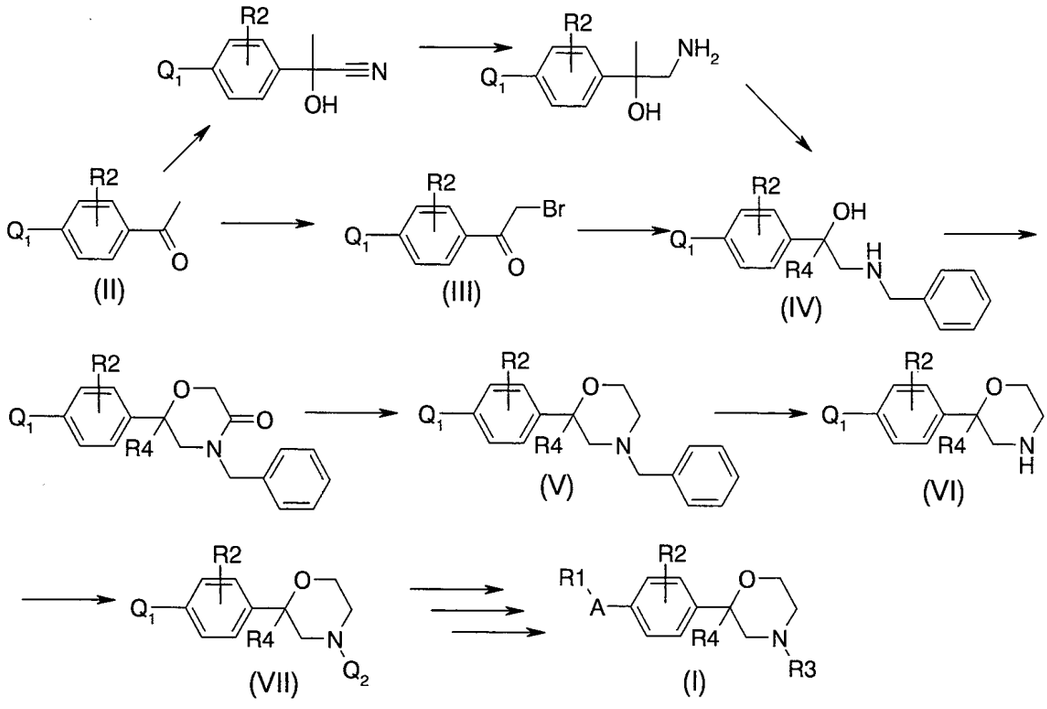
B= 99,9% CH3CN con 0,1% de HCOOH

Los tiempos de retención declarados (Rt), para el Sistema B, son para el pico en la el cromatograma de Corriente Iónica Total (TIC) que mostró la masa para [M+H]+ dentro de 0,5 amu de exactitud del peso molecular exacto calculado y tenían un pico asociado en el cromatograma de Difracción de Luz por Evaporación (ELS) con un % de área relativo (pureza) de >85%.

§2. ASPECTOS GENERALES DE SÍNTESIS

Las síntesis apropiadas de los compuestos e intermediarios reivindicados que contienen restos 2-aril-morfolina siguen las vías que se describen en el Esquema 1

Esquema 1



Q1 es un grupo igual a R1-A, o un grupo que puede convertirse en R1-A. Q2 es un grupo igual a R3, o un grupo que puede convertirse en R3. Para obtener detalles, remitirse a los detalles completos que se presentan a continuación.

La síntesis comienza con una acetofenona sustituida en forma apropiada (II). Las acetofenonas sustituidas en forma apropiada se encuentran disponibles en el mercado o pueden obtenerse de otras acetofenonas comerciales. Por ejemplo por O-alquilación de 4-hidroxiacetofenonas (in)sustituidas. Esta O-alquilación puede realizarse con un agente de alquilación apropiado como 1-bromooctano o bromuro de bencilo, en solventes tales como dimetilsulfóxido (DMSO), acetona, o acetonitrilo, en presencia de una base como hidróxido de potasio o carbonato de potasio, a temperaturas comprendidas entre 0°C y 60°C. Como otro ejemplo, la 1-(4-benciloxi-3-trifluorometil-fenil)-etanona se obtuvo a partir

de 4'-fluoro-3'-(trifluorometil)acetofenona por medio de la reacción con alcohol bencílico en presencia de una base fuerte como ter-butóxido de potasio, en un solvente como tetrahidrofurano, a una temperatura de alrededor de 70°C.

La acetofenona (II) sustituida en forma apropiada se somete a bromo para producir 2'-bromoacetofenonas (III). La bromación puede realizarse con bromuro de cobre (II) en un solvente apropiado como acetato de etilo con aplicación de calor a reflujo; a través de la reacción del correspondiente éter enólico de sililo, preparado con DIPEA y TMSOTf, a 0°C, con NBS en un solvente como diclorometano, a temperatura ambiente; o con tribromuro de tetra-N-butilamonio, en un solvente como metanol, a temperatura ambiente.

La reacción de las 2'-bromoacetofenonas (III) con bencil amina, en un solvente como etanol y cloroformo, a temperaturas comprendidas entre 0°C y temperatura ambiente, produjo aminocetonas (R4 = H) que se redujeron directamente con un agente reductor como borohidruro de sodio en un solvente como etanol y cloroformo, a temperaturas comprendidas entre 0°C y temperatura ambiente, para producir los alcoholes de amino (IV, R4 = H). En forma alternativa, las 2'-bromoacetofenonas (III) pueden reducirse con un agente reductor apropiado como NaBH4, en un solvente tal como 1,4-dioxano, a temperatura ambiente, seguido del tratamiento con una base, tales como KOH, en una mezcla de agua y un solvente apropiado, tales como Et2O, para producir 2-ariloxiranos, los cuales después del tratamiento con bencil amina a una temperatura de 80°C, produce los alcoholes de amino (IV, R4 = H). Otro método para la síntesis de aminoalcoholes (IV, R4 = Me) es por medio de la reacción de una acetofenona sustituida en forma apropiada con cianuro de trimetilsililo en presencia de un ácido de lewis, como yoduro de zinc, a temperatura ambiente, en el compuesto puro. Seguido de la reducción del intermediario cianohidrina con un agente reductor, como hidruro doble de litio y aluminio, en un solvente como tetrahidrofurano, y la posterior formación de imina con benzaldehído en presencia de un catalizador ácido, como ácido p-toluensulfónico, en un solvente tal como tolueno, y finalmente la reducción del intermediario imina con borohidruro de sodio, en un solvente como metanol, a temperaturas comprendidas entre -15°C y temperatura ambiente.

Los alcoholes de amino (IV) pueden someterse a reacción con un ácido cloroacético activado o ácido bromoacético en un solvente tal como diclorometano con una base tales como trietilamina, y posteriormente someterse a ciclación en un solvente tal como 2-propanol con una base tales como hidróxido de potasio para producir morfolin-3-onas. Esas morfolin-3-onas pueden reducirse a continuación con un agente reductor tales como borano en un solvente tal como tetrahidrofurano, a temperaturas comprendidas entre 0°C y temperatura ambiente, para producir las N-bencil morfolinas (V). Algunas de las N-bencil

morfolinas (V) pueden convertirse en otras N-bencil morfolinas (V), ver Esquema 2. Por ejemplo la N-bencil-2-(4-bromofenil)-morfolina (V-Br) se utilizó como material de partida en las siguientes secuencias:

De este modo, el tratamiento de V-Br con n-butil litio a -75°C, en un solvente como tetrahidrofurano o éter dietílico, seguido de inactivación con una formamida, como N,N-dimetilformamida o N-formilmorfolina, produce la formación de V-CHO. Si la especie litio intermediario se desactiva con un isocianato apropiado entonces se forman las correspondientes amidas V-CONHG.

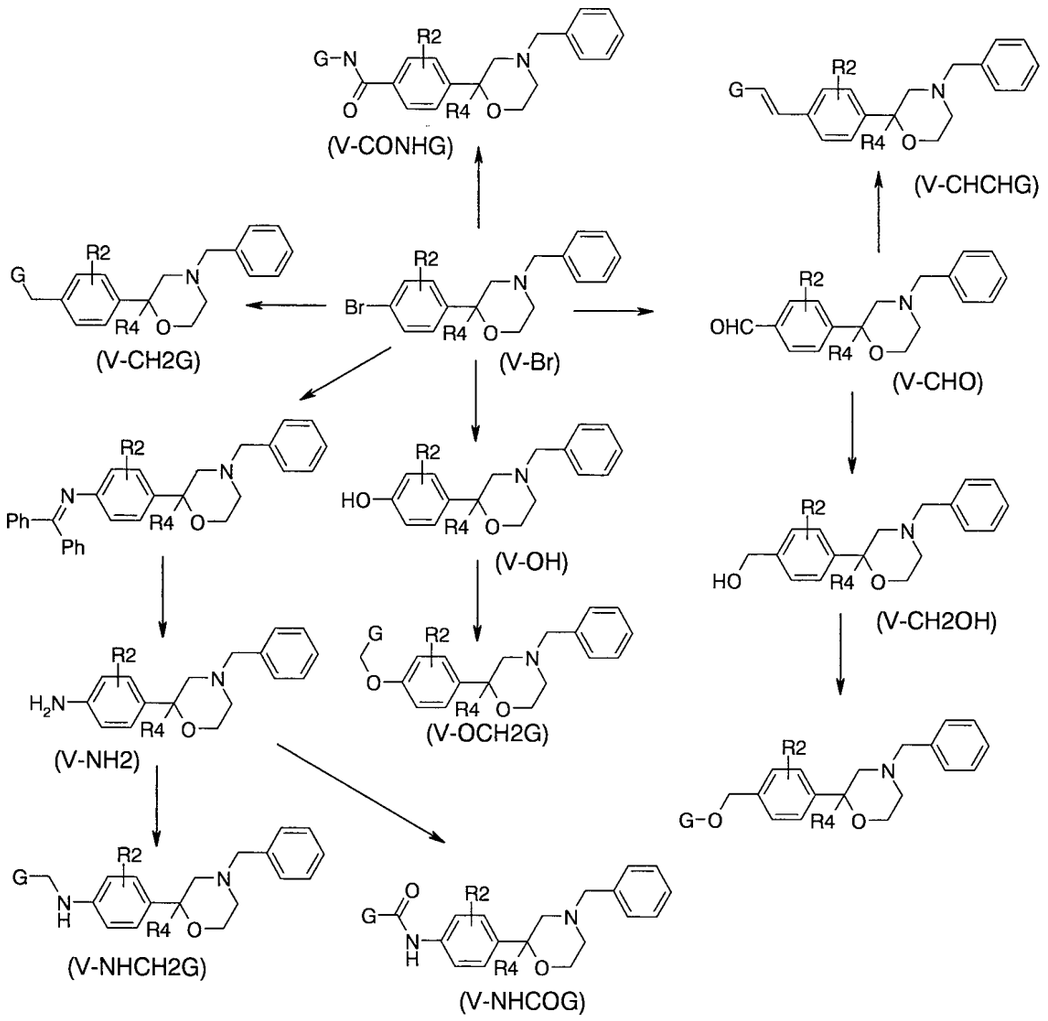
La reducción de V-CHO, con un agente reductor como borohidruro de sodio, en un solvente como metanol, a temperaturas comprendidas entre 0°C y temperatura ambiente, produjo los alcoholes bencílicos V-CH2OH.

Los compuestos del tipo V-CH2OH pueden acoplarse en condiciones de Mitsunobu con fenoles, en un solvente tal como tetrahidrofurano o diclorometano, a temperatura ambiente.

Los compuestos del tipo V-CHO también pueden acoplarse con una ilida de fosfonio apropiada, en un solvente tal como tetrahidrofurano a una temperatura que rodea los 70°C, para producir los compuestos del tipo V-CHCHG. La ilida puede generarse a partir de una sal de fosfonio apropiada con una base fuerte tales como hidruro de sodio en un solvente tal como tetrahidrofurano, a temperaturas que rodean los 0°C.

V-Br también podría convertirse en V-OH, con un catalizador de paladio apropiado, en un solvente como 1,4-dioxano (Anderson K.W.; Ikawa T., Tundel R.E., Buchwald S.L. J. Am. Chem. Soc. 2006 128(33), 10694-10695). Los compuestos V-OH pueden someterse a alquilación, por ejemplo en condiciones de transferencia de fases en un solvente tal como agua y 1,4-dioxano, con una base tal como hidróxido de potasio y un catalizador de transferencia de fases como bromuro de tetrabutilamonio, a temperaturas que rodean el punto de ebullición del solvente.

Esquema 2



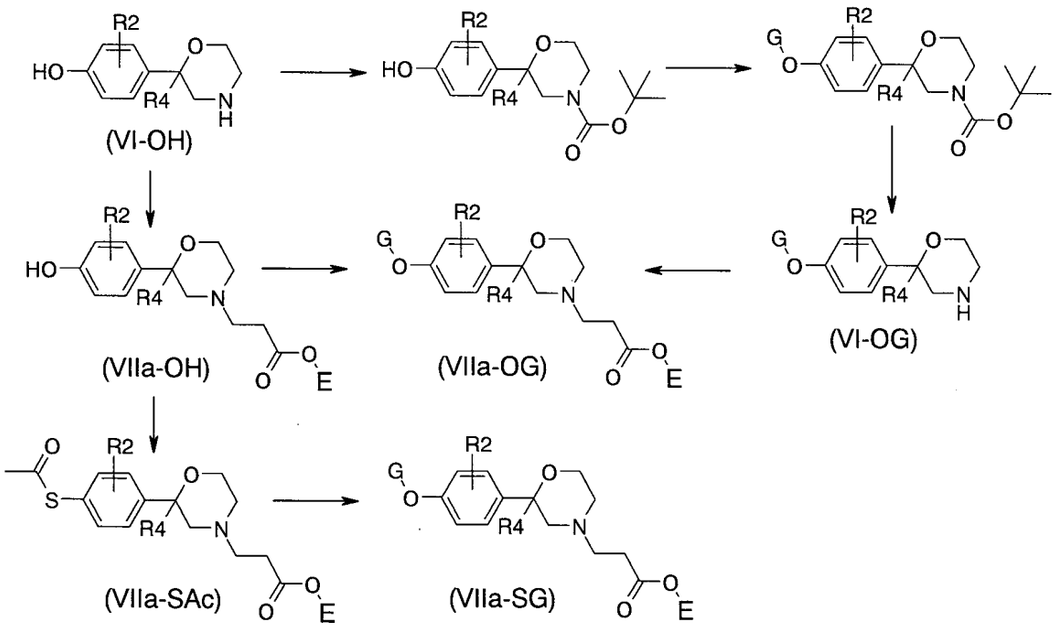
G es un grupo que es parte de R1-A en el compuesto final I.

Cuando se somete a catálisis con paladio IV-Br también puede convertirse en V-CH2G con un reactivo organometálico apropiado como un reactivo borónico (Reacción de Suzuki), o un reactivo de zinc (reacción de Negishi), en un solvente como tolueno o tetrahidrofurano, a temperaturas cercanas al punto de ebullición del solvente. Además V-Br puede acoplarse con un donante apropiado amina, como benzofenona imina, cuando se somete a catálisis con paladio en presencia de una base, como ter-butóxido de sodio, en un solvente como tolueno a temperaturas que rodean los 100°C. El tratamiento posterior con un ácido acuoso, como ácido clorhídrico, a temperatura ambiente, conduce a intermediarios V-NH2. V-NH2 puede someterse a reacción con un agente de alquilación apropiado y una base como N-etildiisopropilamina, en un solvente como metanol a temperatura ambiente para producir las aminas secundarias V-NHCH2G. V-NH2 también puede someterse a reacción con un reactivo de acilación apropiado como un cloruro de

acilo, con una base apropiada como N-etildiisopropilamina, en un solvente como acetonitrilo, a temperaturas comprendidas entre 0°C y temperatura ambiente para producir las amidas V-NHCOG.

La eliminación del grupo N-bencilo en las N-bencil morfolinas (V), puede realizarse por hidrogenación en un solvente tal como etanol y un catalizador como hidróxido de paladio, o en forma alternativa por medio de la reacción con ACE-Cl en un solvente tal como 1,2-dicloroetano, seguido de de la reacción del intermediario carbamato con metanol. Las morfolinas obtenidas (VI) pueden convertirse en otras morfolinas (VI) en una secuencia de etapas. Ver Esquema 3. Por ejemplo, (VI-OH) puede protegerse a el nitrógeno con un grupo protector apropiado (P.G.M. Wuts, T.W. Greene Protective groups in organic synthesis, 4th ed., John Wiley & Sons, 2006), tales como ter-butiloxicarbonilo (BOC), por medio de la reacción con dicarbonato de di-ter-butilo en un solvente tal como acetonitrilo a temperatura ambiente. Con posterioridad, el grupo fenólico puede someterse a reacción con un agente de alquilación apropiado en un solvente tal como acetonitrilo, en presencia de una base tales como carbonato de potasio, a temperatura ambiente. Luego de lo anterior el grupo ter-butiloxicarbonilo (BOC) puede eliminarse por el tratamiento con un ácido, tales como cloruro de hidrógeno, en un solvente tal como etanol, a temperaturas comprendidas entre temperatura ambiente y 60°C, para producir una morfolina modificada (VI-OG).

Esquema 3



Las morfolinas (VI) pueden someterse a reacción con un éster del ácido (met)acrílico, en la llamada incorporación de Michael, en un solvente tal como acetonitrilo,

metanol, o N,N-dimetilformamida, a temperaturas comprendidas entre temperatura ambiente y 85°C, y finalmente con la incorporación de alguna base como trietilamina o 1,8-diazabiciclo[5,4,0]undec-7-eno, para producir ésteres del ácido morfolin-4-il-propiónico (VIIa, Q2 = CH2CH2COOR'). En el caso que esos ésteres del ácido morfolin-4-il-propiónico (VIIa, Q2 = CH2CH2COOR') contengan un grupo fenólico (VIIa-OH), esos compuestos pueden modificarse del siguiente modo: Por medio de la reacción con un agente de alquilación apropiado, tales como un bromuro de alquilo o un cloruro de alquilo, en presencia de una base, tales como carbonato de potasio o carbonato de cesio, en un solvente tal como acetonitrilo y / o tetrahidrofurano, a temperatura ambiente, para producir los compuestos del tipo VIIa-OG. En forma alternativa, VIIa-OH puede convertirse en VIIa-OG, por medio de la reacción con un alcohol apropiado, en presencia de trifenilfosfina, y un reactivo azo apropiado, como diisopropilo azodicarboxilato, en un solvente tal como tetrahidrofurano o diclorometano. En forma adicional, VII-OH puede convertirse en el correspondiente éster del ácido trifluorometansulfónico por medio de la reacción con N-fenilbis(trifluorometano-sulfonimida) en presencia de una base, tales como Et3N, en un solvente, tales como CHCl3, a una temperatura entre temperatura ambiente 60°C. Esos ésteres del ácido trifluorometansulfónico pueden hacerse reaccionar a continuación con tioacetato cuando se somete a catálisis con paladio, en un solvente tal como tolueno, a 110°C, para producir los tioésteres VIIa-SAc. La hidrólisis alcalina del tioéster, con una base tal como NaOH, en un solvente tal como EtOH y agua, a 0°C, seguido directamente de alquilación con un agente de alquilación apropiado, a temperatura ambiente, produce los tioéteres VIIa-SG.

Los compuestos del tipo VIIa-OG y VIIa-SG pueden convertirse en los compuestos finales I por hidrólisis ácida o alcalina del éster, dependiendo de la naturaleza del grupo E. Como ejemplo, los ésteres de ter-butilo (E = C(CH3)3) pueden someterse a tratamiento con un ácido, tales como ácido trifluoroacético o cloruro de hidrógeno, en un solvente tal como CH2Cl2 o 1,4-dioxano, a temperatura ambiente. Como ejemplo adicional, los ésteres de etilo (E = CH2CH3) pueden tratarse con una base, tales como hidróxido de sodio o hidróxido de litio, en solventes tales como etanol, THF, y/o agua, a temperaturas comprendidas entre temperatura ambiente y 70°C.

Los compuestos del tipo VI también pueden sustituirse en el nitrógeno por medio de la reacción con un agente de alquilación apropiado como un bromuro de alquilo o cloruro de alquilo, en presencia de una base como carbonato de potasio, trietilamina, o 1,8-diazabiciclo[5,4,0]undec-7-eno, en forma opcional en presencia de yoduro de sodio, en un solvente tal como acetonitrilo o DMF, a temperaturas comprendidas entre temperatura ambiente y 100°C. En forma adicional, los compuestos del tipo VI también pueden

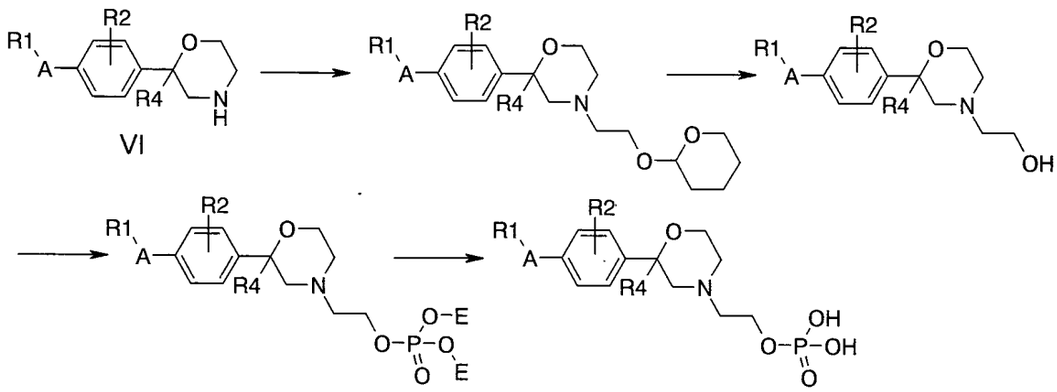
acilarse en el nitrógeno, con un cloruro ácido u otro agente de acilación activado, en presencia de una base tales como N-etildiisopropilamina, en un solvente tal como acetonitrilo, a temperatura ambiente.

Los compuestos del tipo VI también pueden modificarse en el nitrógeno con un grupo éster del ácido 2,2-difluoro-propiónico, por medio de la siguiente secuencia de etapas (Cheguillaume A., Lacroix S., Marchand-Brynaert J. Tetrahedron Letters 2003, 44, 2375): Primero, la reacción con 1H-benzotriazol-1-metanol en un solvente tal como etanol, a temperaturas que rodean los 50°C; seguido de de la reacción con un reactivo de zinc preparado a partir de polvo de zinc, cloruro de trimetilsililo y un bromodifluoroacetato, en un solvente tal como tetrahidrofurano, a temperaturas que rodean los 70°C.

Las morfolinas del tipo VI también pueden modificarse en el nitrógeno por medio de la reacción con un diéster de vinil-fosfonato, en un solvente tal como acetonitrilo a temperaturas que rodean los 85°C.

Los compuestos del tipo I en donde R3 = (CH2)2OPO3H2 puede sintetizarse como se muestra en el esquema 4.

Esquema 4

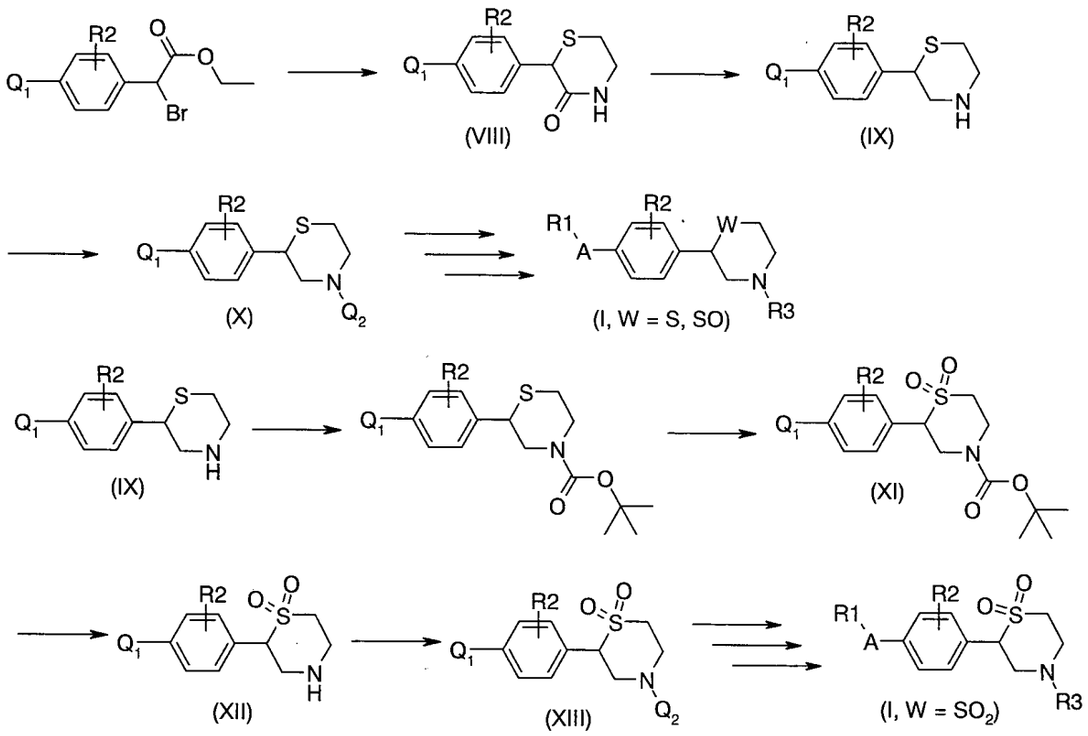


De este modo una morfolina sustituida apropiada VI se hace reaccionar con 2-(2-cloro-etoxi)tetrahidro-2H-pirano, en presencia de una base, tales como carbonato de potasio, y yoduro de sodio, en un solvente tal como DMF, a una temperatura que rodea los 100°C. El grupo tetrahidro-2H-pirano se retira por tratamiento con un ácido tales como ácido p-toluensulfónico, en un solvente tal como metanol, a temperatura ambiente. El alcohol formado a continuación se trata con un reactivo del tipo fosforoamidita tales como N,N-diisopropilfosforoamidita de di-ter-butilo, en presencia de tetrazol, en una mezcla de solventes, tales como THF, CH2Cl2, y CH3CN, a temperatura ambiente, y con posterioridad se oxida con un reactivo de oxidación tales como peróxido de hidrógeno o ter-butilhidroperóxido en los mismos solventes, a temperatura ambiente. La hidrólisis parcial de los ésteres de fosfato puede realizarse en condiciones que dependen de la naturaleza de los grupos E. Por ejemplo los ésteres de di- ter-butilo pueden hidrolizarse

por tratamiento con un ácido, tales como TFA, en un solvente tal como CH2Cl2, a temperatura ambiente. Como otro ejemplo ésteres de di-etilo pueden someterse a reacción con bromotrimetilsilano en un solvente tal como CH2Cl2, a temperatura ambiente, seguido del tratamiento con metanol para efectuar la hidrólisis.

Los compuestos en donde W es -S-, -SO- o -SO2- pueden prepararse como se describe a continuación y como se muestra en el esquema 5.

Esquema 5



Q1 es un grupo igual a R1-A, o un grupo que puede convertirse en R1-A. Q2 es un grupo igual a R3, o un grupo que puede convertirse en R3. Para obtener detalles, remitirse a los detalles completos que se presentan a continuación.

La síntesis comienza con un éster del ácido bromo-fenil-acético sustituido en forma apropiada. Los ésteres del ácido bromo-fenil-acético sustituido en forma apropiada se encuentran disponibles en el mercado o pueden obtenerse de acuerdo con métodos conocidos en la literatura. El éster del ácido bromo-fenil-acético se hace reaccionar con 2-aminoetanotiol, en presencia de una base, tales como carbonato de potasio, en un solvente tal como etanol, a temperatura ambiente, para obtener 2-aril-tiomorfolin-3-onas (VIII). Esas tiomorfolin-3-onas pueden reducirse a continuación con un agente reductor tales como borano en un solvente tal como tetrahidrofurano, a temperaturas comprendidas entre 0°C y temperatura ambiente, para producir las 2-aril-tiomorfolinas

(IX). Las tiomorfolinas (IX) pueden someterse a reacción con un éster del ácido (met)acrílico, en la llamada incorporación de Michael, en un solvente tal como acetonitrilo, metanol, o N,N-dimetilformamida, a temperaturas comprendidas entre temperatura ambiente y 85°C, y finalmente con la incorporación de alguna base como trietilamina o 1,8-diazabiciclo[5,4,0]undec-7-eno, para producir ésteres del ácido morfolin-4-il-propiónico (X, Q2 = CH2CH2COOR'). En el caso que esos tioésteres del ácido morfolin-4-il-propiónico (X, Q2 = CH2CH2COOR') estén sustituidos con bromo (X, Q1 = Br), el bromo puede reemplazarse por yodo (X, Q1 = I) en una reacción con yoduro de sodio, catalizada por yoduro de cobre (I), en presencia de N,N-dimetiletilenediamina, en un solvente tal como 1,4-dioxano, a temperaturas que rodean los 130°C, en un recipiente cerrado. Con posterioridad, el yodo (X, Q1 = I), puede sustituirse por un alcohol apropiado, en presencia de una base tales como carbonato de cesio, y catalizarse con yoduro de cobre (I) y 1,10-fenanthroline, en un solvente tal como tolueno, a una temperatura que rodea los 110°C, para obtener compuestos en los cuales Q1 es igual a R1-A, y Q2 = CH2CH2COOR'. En el caso que R' sea ter-butilo, el éster puede hidrolizarse con ácido, tales como ácido clorhídrico, en un solvente tal como 1,4-dioxano, a temperaturas comprendidas entre temperatura ambiente y 80°C, para producir compuestos (I, W = S). Las tiomorfolinas (X, W = S, Q1 = R1-A, Q2 = CH2CH2COOR'), puede oxidarse con un reactivo de oxidación tales como peroximonosulfato de potasio (Oxone®), en un solvente tal como metanol/agua, a temperaturas comprendidas entre 0°C y temperatura ambiente para producir los 1-óxidos de tiomorfolina (X, W = SO, Q1 = R1-A, Q2 = CH2CH2COOR'). En el caso que R' sea ter-butilo la hidrólisis ácida como se describe para las tiomorfolinas produce los compuestos (I, W = SO).

Las tiomorfolinas (IX) pueden protegerse en el nitrógeno con un grupo protector apropiado (P.G.M. Wuts, T.W. Greene Protective groups in organic synthesis, 4th ed., John Wiley & Sons, 2006), tales como ter-butiloxicarbonilo (BOC), por medio de la reacción con dicarbonato de di-ter-butilo en un solvente tal como acetonitrilo a temperatura ambiente. Con posterioridad, las tiomorfolinas pueden oxidarse con un reactivo de oxidación tales como ácido 3-cloroperoxibenzoico, en un solvente tal como diclorometano, a temperaturas comprendidas entre 0°C y temperatura ambiente, para obtener 1,1-dióxidos de tiomorfolina (XI). Luego de lo anterior el grupo ter-butiloxicarbonilo (BOC) puede eliminarse por el tratamiento con un ácido, tales como cloruro de hidrógeno, en un solvente tal como etanol, a temperaturas comprendidas entre temperatura ambiente y 60°C, para producir los 1,1-dióxidos de tiomorfolina modificada (XII). Los 1,1-dióxidos de tiomorfolina pueden someterse a reacción con posterioridad en la llamada reacción de Michael como se describió con anterioridad para las tiomorfolinas, para obtener

compuestos XIII (Q2 = CH2CH2COOR'). En el caso que los compuestos XIII estén sustituidos con bromo (Q1 = Br), pueden sustituirse por un alcohol apropiado, en presencia de una base tales como carbonato de cesio, y catalizarse con un catalizador de paladio, tales como Pd(AcO)2, y un ligando tipo fosfina apropiado, en un solvente tal como tolueno, a una temperatura que rodea los 100°C, para obtener los compuestos XIII (W = SO2, Q1 = R1-A, Q2 = CH2CH2COOR'). En el caso que R' sea ter-butilo, la hidrólisis ácida como se describe para las tiomorfolinas produce los compuestos (I, W = SO2).

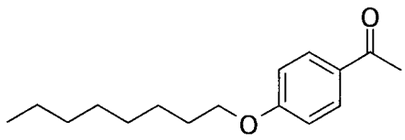
Abreviaturas

ACE-Cl	cloroformiato de 1-cloroetilo
AcCl	Cloruro de acetilo
AlCl3	Cloruro de aluminio
9-BBN	dímero de 9-borabiciclo[3,3,1]nonano
BH3·THF	Complejo de borano tetrahidrofurano
n-BuLi	n-Butil litio
nBu4NBr	Cloruro de tetrabutilamonio
CHCl3	Cloroformo
CH2Cl2	Diclorometano
CH3CN	Acetonitrilo
Cs2CO3	Carbonato de cesio
CuBr2	Bromuro de cobre (II)
CuI	Yoduro de cobre (I)
DBU	1,8-Diazabiciclo[5,4,0]undec-7-eno
DIAD	Diisopropilo azodicarboxilato
DIPEA	N,N-Diisopropiletilamina
DMF	N,N-dimetilformamida
DMSO	Dimetil sulfóxido
Et3N	Trietilamina
Et2O	Éter dietílico
EtOH	Etanol
EtOAc	Acetato de etilo
HCl	Cloruro de hidrógeno
H2SO4	Ácido sulfúrico
K2CO3	Carbonato de potasio
KHCO3	Bicarbonato de potasio
KI	Yoduro de potasio

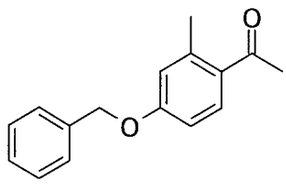
KOH	Hidróxido de potasio
KOtBu	Ter-butóxido de potasio
LiAlH4	Hidruro doble de litio y aluminio
LiHMDS	Bis(trimetilsilil)amida de litio
LiOH	Hidróxido de litio
MeI	Yoduro de metilo
MeMgBr	Bromuro de metilmagnesio
MeOH	Metanol
min	minutos
NaBH4	Borohidruro de sodio
NaHCO3	Bicarbonato de sodio
NaI	Yoduro de sodio
NaN3	Azida de sodio
NaOH	Hidróxido de sodio
NaOtBu	Ter-butóxido de sodio
Na2SO4	Sulfato de sodio
NBS	N-Bromosuccinimida
PBr3	Tribromuro de fósforo
Pd2dba3	Tris(dibencilideneacetona)dipaladio(0)
Pd(dppf)Cl2	[1,1'-bis(difenilfosfino)ferroceno]dicloropaladio(II)
PdCl2(PPh3)2	Dicloruro de bis(trifenilfosfina)paladio(II)
Pd(PPh3)4	Tetrakis(trifenilfosfina)paladio(0)
iPr2O	Diisopropil éter
RT	Temperatura ambiente
SiO2	Gel de sílice
TFA	Ácido trifluoroacético
THF	Tetrahidrofurano
TMSCl	Clorotrimetilsilano
TMSOTf	Trifluorometansulfonato de trimetilsililo
p-TsOH	ácido p-Toluensulfónico monohidrato
ZrCl4	Tetracloruro de zirconia

§3. SÍNTESIS DE INTERMEDIARIOS

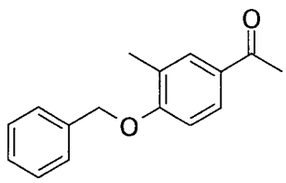
Aril(TIO)morfolinas



1-(4-Octiloxi-fenil)-etanona: A una solución de 4'-hidroxiacetofenona (25,0 g; 183,6 mmol) en DMSO (300. ml) se agregó KOH (11,3 g; 201,9 mmol.) y la mezcla de reacción se agitó durante 1 hora a temperatura ambiente. Después de 1 hora la mezcla de reacción se enfrió (0oC) y se agregó 1-bromooctano (34,9 ml; 201,9 mmol). Se retiró el baño de ácido y la mezcla de reacción se agitó hasta la mañana siguiente a temperatura ambiente. La mezcla de reacción se extrajo con EtOAc/ solución acuosa al 5% de NaHCO3. La fase orgánica se secó con Na2SO4 y se concentró al vacío. El residuo se purificó por cromatografía en columna (SiO2, Et2O: hexanos 1:3) para producir 1-(4-octiloxi-fenil)-etanona (43,08 g)



1-(4-benciloxi-2-metilfenil)-etanona: Una mezcla de 4'-hidroxi-2'-metilacetofenona (24,88 g; 165,7 mmol)), KI (5,50 g; 33,1 mmol), K2CO3 (34,3 g; 248,5 mmol) y bromuro de bencilo (21,7 ml; 182,2 mmol) en acetona (200 ml) se agitó hasta la mañana siguiente a temperatura ambiente. Con posterioridad la mezcla resultante se filtró y se repartió entre EtOAc y NaHCO3 al 5%. La fase orgánica se secó (Na2SO4), se filtró y se concentró al vacío para producir 1-(4-benciloxi-2-metilfenil)-etanona, la cual se utilizó tal como estaba.

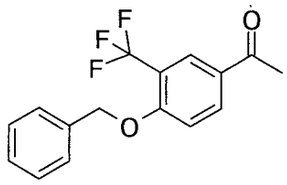


1-(4-benciloxi-3-metilfenil)-etanona: Una mezcla de 4'-hidroxi-3'-metilacetofenona (10,00 g; 66,6 mmol) y K2CO3 (13,80 g; 99,9 mmol) en acetona (100 ml) se agitó a temperatura ambiente durante 40 minutos. Con posterioridad, se agregó bromuro de bencilo (7,9 ml; 66,6 mmol) y la mezcla resultante se calentó a reflujo durante 2,5 h. Después de enfriar hasta alcanzar la temperatura ambiente la mezcla se concentró al vacío. El residuo se disolvió en EtOAc, se lavó con amoníaco acuoso al 5%, agua, y

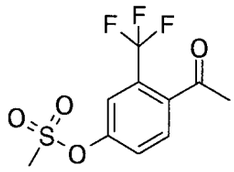
salmuera, se secó (MgSO4), se filtró y se concentró al vacío para producir 1-(4-benciloxi-3-metilfenil)-etanona (15,86 g).

El siguiente compuesto se obtuvo de acuerdo con un modo similar:

1-(4-Benciloxi-3-metoxi-fenil)-etanona



1-(4-Benciloxi-3-trifluorometil-fenil)-etanona : Una mezcla de alcohol bencílico (10,9 ml; 104,98 mmol) y KOtBu (12,96 g; 115,5 mmol) en THF (500 ml) se calentó a reflujo durante 10 minutos. Con posterioridad, se agregó 4'-fluoro-3'-(trifluorometil)acetofenona (21,64 g; 105 mmol) y la mezcla se calentó a reflujo durante otras 2 horas. Después de enfriar hasta alcanzar la temperatura ambiente, la mezcla se repartió entre EtOAc y una solución acuosa al 5% de NaHCO3. La fase orgánica se separó, se secó (Na2SO4), se filtró, y se concentró al vacío. El residuo se purificó por cromatografía en columna (SiO2, Et2O: hexanos 1:2,5) para producir 1-(4-Benciloxi-3-trifluorometil-fenil)-etanona (22,37 g).

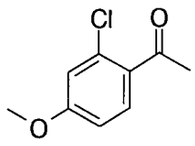


4-acetil-3-trifluorometil-fenil éster del ácido metansulfónico: A una solución de 1-(4-hidroxi-2-trifluorometil-fenil)-etanona (29,74 g; 145,7 mmol) en CH2Cl2 (300 ml) y THF (120 ml) se agregó Et3N (24,4 ml; 174,8 mmol), a 0°C. A la mezcla resultante se agregó gota a gota una solución de cloruro de metansulfonilo (12. 5 ml; 160,3 mmol) en CH2Cl2 (60 ml), a 0°C. Con posterioridad la mezcla se agitó hasta la mañana siguiente a temperatura ambiente, y se vertió en agua helada. Las fases se separaron y la fase orgánica se lavó con HCL acuoso 1 M y agua; se secó (MgSO4), se filtró y se concentró al vacío para producir 4-acetil-3-trifluorometil-fenil éster del ácido metansulfónico (40,47 g), que se utilizó tal como estaba.

Los siguientes compuestos se prepararon de un modo análogo:

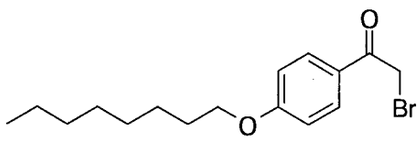
4-acetil-2-cloro-fenil éster del ácido metansulfónico

4-acetil-3-fluoro-fenil éster del ácido metansulfónico

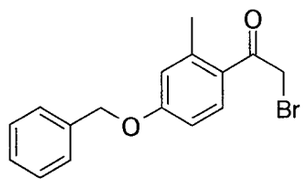


1-(2-Cloro-4-metoxi-fenil)-etanona

A una mezcla de AlCl3 (42,08 g; 315,60 mmol) en CH2Cl2 (300 ml) se agregó gota a gota 3-cloroanisol (22,50 g; 157,80 mmol), a -30°C. A la mezcla resultante se agregó gota a gota una solución de AcCl (10,50 ml; 147,63 mmol) en CH2Cl2 (100 ml) a una velocidad tal que se pudiera mantener la temperatura por debajo de -15°C. La mezcla resultante se agitó durante 4 horas a -10°C. Con posterioridad, la mezcla se vertió sobre hielo y se extrajo con CH2Cl2. Las fases orgánicas combinadas, se secaron (MgSO4), se filtraron, y se concentraron al vacío. El residuo se purificó por cromatografía en columna (SiO2, Et2O/hexanos 1:9) para producir 1-(2-cloro-4-metoxi-fenil)-etanona (17,68 g).



2-Bromo-1-(4-octiloxi-fenil)-etanona : A una solución de 1-(4-octiloxi-fenil)-etanona (43,0 g; 173,1 mmol) en EtOAc (200 ml) se agregó CuBr2 (77,3 g; 346,2 mmol) y se calentó hasta el reflujo durante 2 horas. La mezcla de reacción se filtró sobre Kieselguhr. La mezcla de reacción se lavó con solución acuosa al 10% de Tiosulfato de sodio y salmuera. La fase orgánica se secó sobre Na2SO4, se concentró al vacío y se purificó por cromatografía en columna (SiO2, Et2O: hexanos 1:7)) para producir 2-bromo-1-(4-octiloxi-fenil)-etanona (36,3 g)

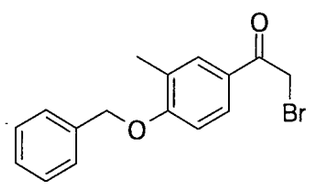


1-(4-Benciloxi-2-metil-fenil)-2-bromo-etanona: A una solución de 1-(4-benciloxi-2-metilfenil)-etanona (42,00 g; 174,8 mmol) en MeOH (300 ml) se agregó tribromuro de tetra-N-butilamonio (84,28 g; 174,8 mmol) y la mezcla se agitó hasta la mañana siguiente a temperatura ambiente. Con posterioridad, se evaporó el MeOH al vacío, y el residuo se repartió entre EtOAc (300 ml) y NaHCO3 al 5%. La fase orgánica se secó (Na2SO4), se

filtró, se concentró al vacío y se purificó por cromatografía en columna (SiO2, Et2O: hexanos 1:1) para producir 1-(4-benciloxi-2-metil-fenil)-2-bromo-etanona (49,93 g).

El siguiente compuesto se obtuvo de acuerdo con un modo similar:

1-(4-Benciloxi-3-trifluorometil-fenil)-2-bromo-etanona



1-(4-Benciloxi-3-metil-fenil)-2-bromo-etanona : A una solución de 1-(4-benciloxi-3-metil-fenil)-etanona (12,89 g; 53,1 mmol) en CH2Cl2 se agregó, gota a gota, a 0°C, DIPEA (10,9 ml; 63,7 mmol) y trimetilsililo trifluorometansulfonato (11,1 ml; 61,1 mmol). La mezcla resultante se agitó a 0°C durante 1 hora, y con posterioridad, NBS (10,87 g; 61,1 mmol) se agregó en una sola porción. La mezcla se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó hasta la mañana siguiente. A continuación, la mezcla se concentró al vacío, se disolvió el residuo en EtOAc, se lavó con agua dos veces, y salmuera, se secó (MgSO4), se filtró, y se concentró al vacío para producir 1-(4-benciloxi-3-metil-fenil)-2-bromo-etanona (11,90 g).

El siguiente compuesto se obtuvo de acuerdo con un modo similar:

1-(4-Benciloxi-3-metoxi-fenil)-2-bromo-etanona

4-(2-bromo-acetil)-3-trifluorometil-fenil éster del ácido metansulfónico

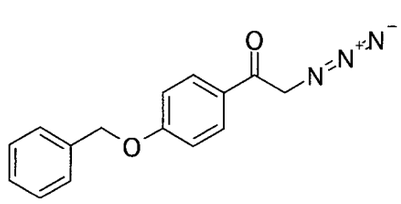
4-(2-bromo-acetil)-2-cloro-fenil éster del ácido metansulfónico

4-(2-bromo-acetil)-3-fluoro-fenil éster del ácido metansulfónico

1-(3-Benciloxi-fenil)-2-bromo-etanona

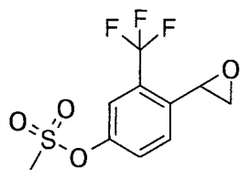
2-Bromo-1-(2-cloro-4-metoxi-fenil)-etanona

2-Bromo-1-(5-bromo-piridin-2-il)-etanona



2-Azido-1-(4-benciloxi-fenil)-etanona

A una mezcla de 1-(4-benciloxi-fenil)-2-bromo-etanona (28,55 g; 93,6 mmol) en CH2Cl2 (300 ml) y agua (30 ml) se agregó nBu4NBr (1,51 g; 4,7 mmol) y NaN3 (6,69 g; 102,9 mmol) en una porción. Después de 4h a temperatura ambiente, las fases se separaron. La fase orgánica se lavó con agua, se secó (Na2SO4), se filtró y se concentró al vacío para producir 2-azido-1-(4-benciloxi-fenil)-etanona (23,64 g).



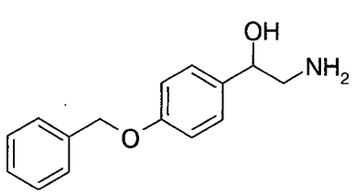
4-oxiranil-3-trifluorometil-fenil éster del ácido metansulfónico: A una solución de 4-(2-bromo-acetil)-3-trifluorometil-fenil éster del ácido metansulfónico (33,95 g; 89,3 mmol) en 1,4-dioxano (150 ml) se agregó gota a gota una solución de NaBH4 (2,37 g; 62,5 mmol) en agua (47 ml). La mezcla resultante se agitó a temperatura ambiente durante 2,5 horas, con posterioridad, se desactivó con HCl acuoso 0,5M (125 ml), y se extrajo con EtOAc. Las fases orgánicas combinadas se lavaron con agua, se secaron (MgSO4), se filtraron y se concentraron al vacío. El residuo se disolvió en Et2O (500 ml) y se trató con una solución de KOH (4,19 g; 74,7 mmol) en agua (100 ml). La mezcla resultante se calentó a reflujo durante 4 horas. Después de enfriar hasta alcanzar la temperatura ambiente, los elementos volátiles se retiraron al vacío y el residuo se repartió entre EtOAc y agua. La fase orgánica se lavó con agua, se secó (MgSO4), se filtró y se concentró al vacío. El residuo se purificó por cromatografía en columna (CH2Cl2) para producir 4-oxiranil-3-trifluorometil-fenil éster del ácido metansulfónico (23,54 g).

Los siguientes compuestos se prepararon de un modo análogo:

4-oxiranil-3-fluoro-fenil éster del ácido metansulfónico

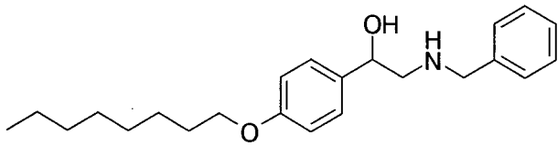
4-oxiranil-2-cloro-fenil éster del ácido metansulfónico

2-(2-Cloro-4-metoxi-fenil)-oxirano



2-Amino-1-(4-benciloxi-fenil)-etanol: A una suspensión de LiAlH4 (8,18 g; 215,6 mmol) en THF (100 ml), se agregó gota a gota una solución de 2-azido-1-(4-benciloxi-

fenil)-etanona (23,05 g; 86,2 mmol) en THF (200 ml), a 0°C. La mezcla se agitó a 0°C durante 20 min, y con posterioridad 2 horas a temperatura ambiente. A partir de entonces, agua (50 ml), y se agregó consecutivamente solución 2M acuosa de NaOH (150 ml). El precipitado formado se retiró por filtración sobre kieselguhr, y se lavó con MeOH. El filtrado se concentró al vacío y la fase acuosa remanente se extrajo con CH2Cl2. Las fases orgánicas combinadas se secaron (Na2SO4), se filtraron y se concentraron al vacío para producir 2-amino-1-(4-benciloxi-fenil)-etanol (20,10 g)



2-Bencilamino-1-(4-octiloxi-fenil)-etanol: A una suspensión enfriada (0ºC) de 2-Bromo-1-(4-octiloxi-fenil)-etanona (36,1 g; 110,3 mmol) en EtOH (500 ml) y CHCl3 (100 ml) se agregó bencilamina (48,2 ml; 441,2 mmol). Después de 30 minutos el baño de hielo se retiró y la mezcla se agitó durante otras 2 horas a temperatura ambiente. Con posterioridad la mezcla de reacción se enfrió nuevamente hasta 0°C y NaBH4 (6,26 g; 165,5 mmol) se agregó en pequeñas porciones. La mezcla resultante se agitó a 0°C durante 1 hora y a partir de entonces otras 4 horas a temperatura ambiente. La mezcla de reacción se desactivó con HCl 1M acuoso (750 ml) a 0°C y se agitó a temperatura ambiente durante 1 hora. La mezcla de reacción se concentró al vacío y el residuo se repartió entre EtOAc y NaOH 2 N acuoso. La fase orgánica se secó (Na2SO4), se filtró, se concentró al vacío y se purificó por cromatografía en columna (SiO2, EtOAc) para dar 2-bencilamino-1-(4-octiloxi-fenil)-etanol (22,58 g)

Los siguientes compuestos se obtuvieron de acuerdo con un modo similar:

2-Bencilamino-1-(4-bromo-fenil)-etanol

2-Bencilamino-1-(4-benciloxi-fenil)-etanol

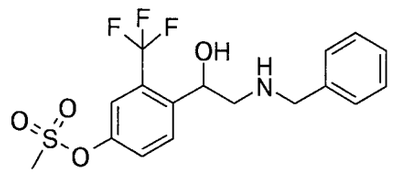
2-Bencilamino-1-(4-benciloxi-2-metil-fenil)-etanol

2-Bencilamino-1-(4-benciloxi-3-metil-fenil)-etanol

2-Bencilamino-1-(4-benciloxi-3-trifluorometil-fenil)-etanol

2-Bencilamino-1-(4-benciloxi-3-metoxi-fenil)-etanol 2-Bencilamino-1-(3-benciloxi-fenil)-etanol

2-(Benzhidril-amino)-1-(5-bromo-piridin-2-il)-etanol



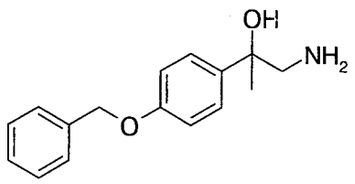
4-(2-bencilamino-1-hidroxi-etil)-3-trifluorometil-fenil éster del ácido metansulfónico: 4-oxiranil-3-trifluorometil-fenil éster del ácido matansulfónico (23,54 g; 79,2 mmol) se disolvió en bencilamina (26 ml). La mezcla resultante se agitó a 80°C durante 4h. Después de enfriar hasta alcanzar la temperatura ambiente, se agregó Et2O y la mezcla se enfrió hasta 0°C. El precipitado formado se recolectó por filtración sobre, se lavó con Et2O, y se secó con aplicación de vacío, a 40°C, para producir 4-(2-bencilamino-1-hidroxi-etil)-3-trifluorometil-fenil éster del ácido metansulfónico como un sólido blanco (26,87 g) que se utilizó tal como estaba.

Los siguientes compuestos se prepararon de un modo similar:

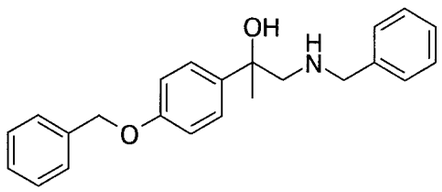
4-(2-bencilamino-1-hidroxi-etil)-3-fluoro-fenil éster del ácido metansulfónico

4-(2-bencilamino-1-hidroxi-etil)-2-cloro-fenil éster del ácido etansulfónico

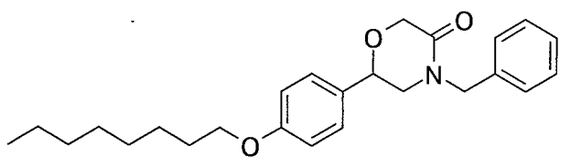
2-Bencilamino-1-(2-cloro-4-metoxi-fenil)-etanol



1-Amino-2-(4-benciloxi-fenil)-propan-2-ol: Una mezcla de 1-(4-benciloxi-fenil)-etanona (18,50 g; 81,8 mmol), yoduro de zinc (0,52 g; 1,6 mmol), y cianuro de trimetilsililo (33,8 ml; 269,8 mmol) se agitó hasta la mañana siguiente a temperatura ambiente. Con posterioridad, el exceso de cianuro de trimetilsililo se retiró al vacío, y se disolvió el residuo en THF (100 ml). La solución resultante se agregó, gota a gota, a una mezcla de hidruro doble de litio y aluminio (12,7 g; 335,2 mmol) en THF (200 ml). La mezcla resultante se calentó a reflujo durante 2 h. A continuación, la mezcla se enfrió hasta 0°C y se trató sucesivamente con agua (13 ml), NaOH 2M acuoso (26 ml), y agua (13 ml). A partir de entonces la mezcla se calentó a reflujo durante 15 minutos, se enfrió nuevamente hasta alcanzar la temperatura ambiente, se filtró sobre kieselguhr, y se concentró al vacío. El residuo se purificó por cromatografía en columna (SiO2, MeOH) para producir 1-Amino-2-(4-benciloxi-fenil)-propan-2-ol (18,15 g).



1-Bencilamino-2-(4-benciloxi-fenil)-propan-2-ol: Una mezcla de 1-amino-2-(4-benciloxi-fenil)-propan-2-ol (1,26 g; 4,9 mmol), benzaldehído (0,55 ml; 5,4 mmol), y ácido p-toluensulfónico (0,04 g; 0,24 mmol) en tolueno (30 ml) se calentó al reflujo en un aparato de Dean-Stark, hasta la mañana siguiente. Con posterioridad, la mezcla se enfrió hasta alcanzar la temperatura ambiente y el solvente se retiró al vacío. El residuo se suspendió en MeOH (30 ml), se enfrió hasta -15°C, y se trató con NaBH4 (0,74 g; 19,6 mmol), en porciones. Después de que se completó la incorporación la mezcla se entibió hasta alcanzar la temperatura ambiente y se agitó durante una hora. Con posterioridad, el MeOH se retiró al vacío. El residuo se repartió entre Et2O y NaHCO3 al 5%. La fase orgánica se secó (Na2SO4), se filtró, y se concentró al vacío. El residuo se purificó por cromatografía en columna (SiO2, Et2O: hexanos 2:1) para dar 1-bencilamino-2-(4-benciloxi-fenil)-propan-2-ol (1,07 g).



4-Bencil-6-(4-octiloxi-fenil)-morfolin-3-ona: A una solución de 2-bencilamino-1-(4-octiloxi-fenil)-etanol (22,50 g; 63,3 mmol) y Et3N (9,7 ml; 69,6 mmol) en CH2Cl2 (500 ml) se agregó gota a gota una solución de cloruro de cloroacetilo (5,5 ml; 69,6 mmol) en CH2Cl2 (25 ml), a 0°C. Después de 1 hora a 0°C la mezcla de reacción se desactivó con HCl 1M acuoso (200 ml). Las fases se separaron y la fase orgánica se lavó con a solución acuosa al 5% de NaHCO3, se secó (Na2SO4) y se concentró al vacío. El residuo se disolvió en 2-propanol (250 ml) y se agregó KOH (4,26 g; 76 mmol). La mezcla resultante se agitó a temperatura ambiente durante 1 hora y con posterioridad se concentró al vacío. El producto en bruto se repartió entre EtOAc y HCl acuoso 0,5 M. Las fases se separaron y la fase orgánica se lavó con solución acuosa al 5% de NaHCO3, se secó (Na2SO4) y se evaporó al vacío para producir 4-bencil-6-(4-octiloxi-fenil)-morfolin-3-ona (22,30 g) que se utilizó tal como estaba en una etapa posterior.

Los siguientes compuestos se obtuvieron de acuerdo con un modo similar:

4-Bencil-6-(4-bromo-fenil)-morfolin-3-ona

4-Bencil-6-(4-benciloxi-fenil)-morfolin-3-ona

4-Bencil-6-(4-benciloxi-2-metil-fenil)-morfolin-3-ona

4-Bencil-6-(4-benciloxi-3-metil-fenil)-morfolin-3-ona

4-Bencil-6-(4-benciloxi-3-metoxi-fenil)-morfolin-3-ona

4-Bencil-6-(4-benciloxi-3-trifluorometil-fenil)-morfolin-3-ona

4-Bencil-6-(4-benciloxi-fenil)-6-metil-morfolin-3-ona

4-Bencil-6-(3-benciloxi-fenil)-morfolin-3-ona

4-Bencil-6-(2-cloro-4-metoxi-fenil)-morfolin-3-ona

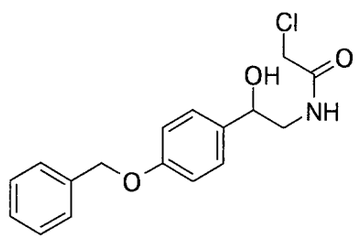
4-Benzhidril-6-(5-bromo-piridin-2-il)-morfolin-3-ona

Los siguientes compuestos se obtuvieron de acuerdo con un modo similar a partir de ésteres del ácido metansulfónico usando 2,5 equivalentes de KOH en lugar de 1,25 equivalentes.

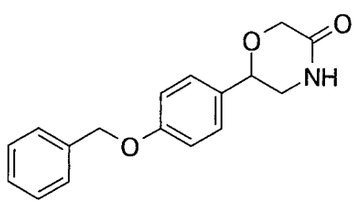
4-Bencil-6-(4-hidroxi-2-trifluorometil-fenil)-morfolin-3-ona

4-Bencil-6-(2-fluoro-4-hidroxi-fenil)-morfolin-3-ona

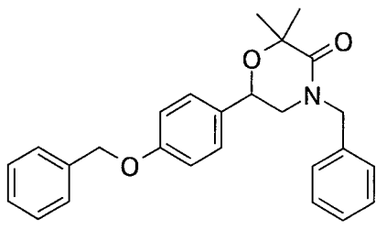
4-Bencil-6-(3-cloro-4-hidroxi-fenil)-morfolin-3-ona

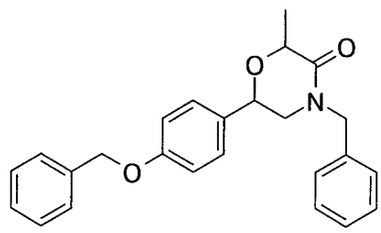


N-[2-(4-Benciloxi-fenil)-2-hidroxi-etil]-2-cloro-acetamida: A una mezcla de 2-amino-1-(4-benciloxi-fenil)-etanol (20,10 g; 82,6 mmol), Et3N (13,82 ml; 99,1 mmol), CH2Cl2 (200 ml) y MeOH (20 ml) se agregó gota a gota cloruro de cloroacetilo (7,24 ml; 90,9 mmol) a -10°C. La mezcla resultante se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó hasta la mañana siguiente, y con posterioridad se concentró al vacío. El residuo se purificó por cromatografía flash (SiO2, EtOAc) para producir N-[2-(4-benciloxi-fenil)-2-hidroxi-etil]-2-cloro-acetamida (17,45 g).

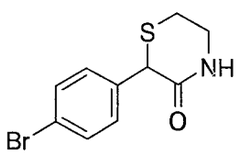


6-(4-Benciloxi-fenil)-morfolin-3-ona: A una solución de KOtBu (6,68 g; 59,5 mmol) en 2-metil-2-butanol (100 ml) se agregó gota a gota una solución de N-[2-(4-benciloxi-fenil)-2-hidroxi-etil]-2-cloro-acetamida (17,30 g; 54,1 mmol) en THF (100 ml). La mezcla resultante se agitó durante 1 hora a temperatura ambiente y a continuación se concentró al vacío. El residuo se disolvió en CH2Cl2 y se trató con una solución acuosa de 1M HCl, a 0°C. Las fases se separaron y la fase acuosa se extrajo con CH2Cl2. Las fases orgánicas combinadas se secaron (Na2SO4), se filtraron y se concentraron al vacío para producir 6-(4-benciloxi-fenil)-morfolin-3-ona (14,10 g).

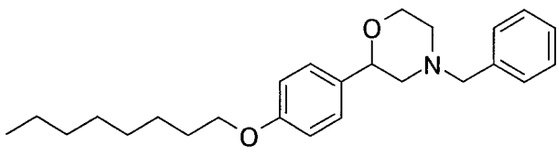




4-Bencil-6-(4-benciloxi-fenil)-2,2-dimetil-morfolin-3-ona y 4-Bencil-6-(4-benciloxi-fenil)-2-metil-morfolin-3-ona: A una solución de 4-bencil-6-(4-benciloxi-fenil)-morfolin-3-ona (6,90 g; 18,5 mmol) en THF (100 ml) se agregó gota a gota una solución de LiHMDS en THF (18,5 ml; 1,00 mol/l; 18,5 mmol), a -78°C. La mezcla resultante se agitó a -78°C durante 15 minutos, con posterioridad, se agregó MeI (1,15 ml; 18,5 mmol), y la mezcla resultante se agitó durante 1 hora a -78°C. La secuencia de incorporación de LiHMDS y MeI, se repitió tres veces. Después de la última incorporación de MeI la mezcla se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó hasta la mañana siguiente. A continuación se agregó solución acuosa al 5% de NaHCO3 se agregó en la mezcla extraída con EtOAc. Las fases orgánicas combinadas se secaron (Na2SO4), se filtró y se concentró al vacío. El residuo se purificó por cromatografía en columna (SiO2, Et2O/hexanos 1:1) para producir dos compuestos. El compuesto menos polar fue 4-bencil-6-(4-benciloxi-fenil)-2,2-dimetil-morfolin-3-ona (1,90 g), y el compuesto mas polar fue 4-bencil-6-(4-benciloxi-fenil)-2-metil-morfolin-3-ona (3,81 g).



2-(4-Bromo-fenil)-tiomorfolin-3-ona: A una solución de clorhidrato de 2-aminoetanotiol (6,93 g; 61 mmol) en EtOH (400 ml) se agregó K2CO3 (16,86 g; 122 mmol), a temperatura ambiente, seguido después de 15 minutos por etil éster del ácido bromo-(4-bromo-fenil)-acético (12 ml; 61 mmol). La mezcla resultante se agitó a temperatura ambiente durante dos días, con posterioridad, agua se agregó y la mezcla resultante se extrajo con EtOAc. Las fases orgánicas combinadas se secaron (MgSO4), se filtraron, y se concentraron al vacío. El residuo se recristalizó a partir de EtOH para producir 2-(4-bromo-fenil)-tiomorfolin-3-ona (12,8 g).



4-Bencil-2-(4-octiloxi-fenil)-morfolina: A una solución de 4-bencil-6-(4-octiloxi-fenil)-morfolin-3-ona (22,22 g; 56,2 mmol) en THF (400 ml) se agregó complejo de borano-THF (1M, 140,4 ml; 140,4 mmol) gota a gota, a 0°C. Después de 1 hora la mezcla se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante otras 2 horas. A la mezcla de reacción se agregó MeOH (30 ml), a 0°C, y la mezcla resultante se agitó a temperatura ambiente durante 30 minutos, y con posterioridad se concentró al vacío. El residuo se suspendió en MeOH (300 ml.) y NaOH acuoso 1 M (112 ml) se agregó y se calentó bajo reflujo durante 1 hora. La mezcla resultante se concentró al vacío y el residuo se repartió entre EtOAc y solución de NaHCO3 al 5%. La fase orgánica se secó (Na2SO4), se filtró, y se concentró al vacío para producir 4-bencil-2-(4-octiloxi-fenil)-morfolina (20,33 g), que se utilizó tal como estaba en una etapa posterior.

Los siguientes compuestos se obtuvieron de acuerdo con un modo similar:

4-Bencil-6-(4-bromo-fenil)-morfolina

4-Bencil-2-(4-benciloxi-fenil)-morfolina

4-Bencil-2-(4-benciloxi-2-metil-fenil)-morfolina

4-Bencil-2-(4-benciloxi-3-metil-fenil)-morfolina

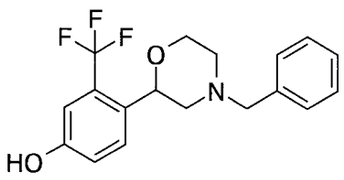
4-Bencil-2-(4-benciloxi-3-metoxi-fenil)-morfolina

4-Bencil-2-(4-benciloxi-3-trifluorometil-fenil)-morfolina

4-Bencil-2-(4-benciloxi-fenil)-2-metil-morfolina

4-Bencil-6-(4-benciloxi-fenil)-2,2-dimetil-morfolina

4-Benzhidril-2-(5-bromo-piridin-2-il)-morfolina



4-(4-Bencil-morfolin-2-il)-3-trifluorometil-fenol: A una solución de 4-bencil-6-(4-hidroxi-2-trifluorometil-fenil)-morfolin-3-ona (26,18 g; 67,3 mmol) en THF (600 ml) se agregó gota a gota BH3·THF en THF (235,4 ml; 1,00 mol/l; 235,4 mmol), a 0°C. La mezcla resultante se agitó durante 1 hora a 0°C y a partir de entonces 18 horas a temperatura ambiente. Con posterioridad, se agregó HCl 1M acuoso (550 ml) y la mezcla se agitó hasta la mañana siguiente a temperatura ambiente. La mezcla resultante se repartió entre EtOAc y NaOH 2M acuoso (350 ml), las fases orgánicas se secaron (MgSO4), se filtraron, y se concentraron al vacío. El residuo se purificó por cromatografía en columna (SiO2, CH2Cl2/MeOH 98:2) para producir 4-(4-bencil-morfolin-2-il)-3-trifluorometil-fenol

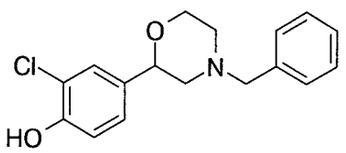
Los siguientes compuestos se obtuvieron de acuerdo con un modo similar:

4-(4-Bencil-morfolin-2-il)-3-fluoro-fenol

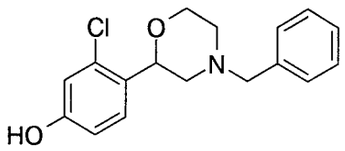
4-Bencil-2-(3-benciloxi-fenil)-morfolina

4-Bencil-2-(2-cloro-4-metoxi-fenil)-morfolina

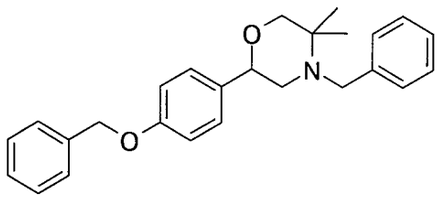
2-(4-Bromo-fenil)-tiomorfolina



4-(4-Bencil-morfolin-2-il)-2-cloro-fenol: A una solución de 4-bencil-6-(3-cloro-4-hidroxi-fenil)-morfolin-3-ona (13,05 g; 39,0 mmol) en THF (600 ml) se agregó en porciones LiAlH4 (4,44 g; 117,04 mmol) a 0°C. La mezcla resultante se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó hasta la mañana siguiente. Con posterioridad, la mezcla se enfrió hasta 0°C, y agua (4,5 ml), una solución acuosa 2M de NaOH (9,0 ml) y agua (9,0 ml) se agregaron en forma consecutiva. A partir de entonces la mezcla se agitó durante 1h. El precipitado formado se retiró por filtración sobre kieselguhr, y se lavó con EtOAc. La solución orgánica se concentró al vacío, y el residuo se purificó por cromatografía en columna (SiO2, CH2Cl2/MeOH 98:2) para producir 4-(4-bencil-morfolin-2-il)-2-cloro-fenol (9,10 g)

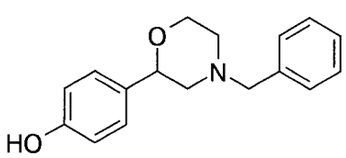


4-(4-Bencil-morfolin-2-il)-3-cloro-fenol: A una solución de 1 dodecanetiol (12,7 ml; 52,86 mmol) en DMF anhidra (50 ml), se agregó KOtBu (5,93 g; 52,86 mmol) a 0°C. Después de la incorporación completa la mezcla se dejó lentamente alcanzar la temperatura ambiente (~30 min), y a continuación se agregó 4-bencil-2-(2-cloro-4-metoxi-fenil)-morfolina (5,60 g; 17,62 mmol). La mezcla resultante se agitó a 110°C durante 6 horas. Después de enfriar hasta alcanzar la temperatura ambiente, se agregó EtOAc y la mezcla resultante se lavó con NaHCO3 al 5%, agua y salmuera; se secó (MgSO4), se filtró y se concentró al vacío. El residuo se purificó por cromatografía en columna (SiO2, CH2CL2/MeOH 99:1) para producir 4-(4-bencil-morfolin-2-il)-3-cloro-fenol (4,56 g)



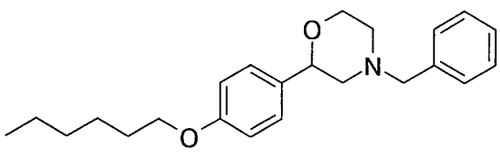
4-Bencil-2-(4-benciloxi-fenil)-5,5-dimetil-morfolina

A una solución de 4-bencil-6-(4-benciloxi-fenil)-morfolin-3-ona (7,14 g; 19,1 mmol) en THF (100 ml) se agregó ZrCl4 (4,46 g; 19,1 mmol), a -10°C. La mezcla resultante se agitó durante 30 min, a -10°C, con posterioridad, una solución de MeMgBr in Et2O (38,2 ml; 3,00 mol/l; 114,6 mmol) se agregó gota a gota, mientras se mantenía la temperatura por debajo de 10°C. Después de la incorporación completa la mezcla resultante se agitó a temperatura ambiente durante 1 hora. Después de enfriar la mezcla hasta 0°C una solución acuosa 2M de NaOH se agregó gota a gota. La suspensión resultante se filtró y el filtrado se extrajo tres veces con CH2Cl2. Las fases orgánicas combinadas se secaron (Na2SO4), se filtró, y se concentró al vacío. El residuo se purificó por cromatografía en columna (SiO2, Et2O/hexanos 1:3) para producir 4-bencil-2-(4-benciloxi-fenil)-5,5-dimetil-morfolina (3,6 g).



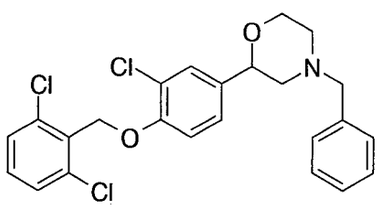
4-(4-Bencil-morfolin-2-il)-fenol: A una suspensión de 4-bencil-6-(4-bromo-fenil)-morfolina (8,70 g; 26,19 mmol) en agua (25 ml) y 1,4-dioxano (25 ml) se agregó KOH (3,23 g; 57,61 mmol), tris(dibencilidenoacetona)dipaladio(0) (479,6 mg; 0,52 mmol) y di-ter-butil-(2',4',6'-triisopropil-bifenil-2-il)-fosfano (444,8 mg; 1,05 mmol). La mezcla resultante se calentó a reflujo durante dos horas. Después de enfriar hasta alcanzar la temperatura ambiente la mezcla de reacción se concentró al vacío. El residuo se repartió entre EtOAc y solución acuosa al 5% de NaHCO3. La fase orgánica se secó (Na2SO4), se filtró y se concentró al vacío. El residuo se purificó por cromatografía en columna (SiO2, Et2O: hexanos 1:1) para producir 4-(4-bencil-morfolin-2-il)-fenol (3,67 g).

El 6-(4-Benzhidril-morfolin-2-il)-piridin-3-ol se realizó con el uso de un método similar.



4-Bencil-2-(4-hexiloxi-fenil)-morfolina: A una mezcla de 4-(4-bencil-morfolin-2-il)-fenol (1,33 g; 4,94 mmol) en agua (10 ml) y 1,4-dioxano (10 ml) se agregó KOH (0,55 g; 9,88 mmol), 1-bromohexano (1,04 ml; 7,41 mmol) y bromuro de tetrabutilamonio (0,16 g; 0,49 mmol), la mezcla resultante se calentó al reflujo hasta la mañana siguiente. Después de enfriar hasta alcanzar la temperatura ambiente la mezcla se concentró al vacío, y se repartió entre EtOAc y solución acuosa al 5% de NaHCO3. La fase orgánica se secó (Na2SO4), se filtró, y se concentró al vacío. El residuo se purificó por cromatografía en columna (SiO2, Et2O: hexanos 1:1) para producir 4-bencil-2-(4-hexiloxi-fenil)-morfolina (1,31 g).

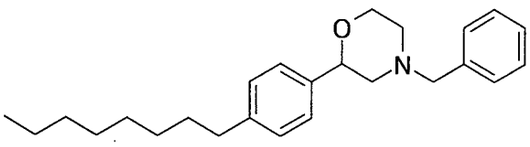
4-Bencil-2-(4-heptiloxi-fenil)-morfolina se obtuvo de acuerdo con un modo similar.



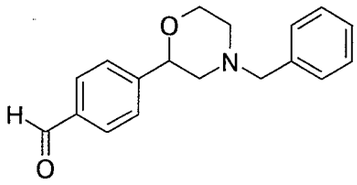
4-Bencil-2-[3-cloro-4-(2,6-dicloro-benciloxi)-fenil]-morfolina: Una mezcla de 4-(4-bencil-morfolin-2-il)-2-cloro-fenol (0,50 g; 1,56 mmol), 2,6-diclorobromuro de bencilo (0,39 g; 1,64 mmol) y Cs2CO3 (2,55 g; 7,82 mmol) en CH3CN (20 ml) se calentó al reflujo hasta

la mañana siguiente. Después de enfriar hasta alcanzar la temperatura ambiente la mezcla resultante se repartió entre EtOAc y agua. Las fases se separaron y la fase orgánica, se secó (MgSO4), se filtró, y se concentró al vacío. El residuo se purificó por cromatografía en columna (SiO2, CH2Cl2:MeOH 98:2) para producir 4-bencil-2-[3-cloro-4-(2,6-dicloro-benciloxi)-fenil]-morfolina (0,74 g)

Los siguientes compuestos se obtuvieron de acuerdo con un modo similar:
4-Bencil-2-[3-cloro-4-(2-cloro-6-fluoro-benciloxi)-fenil]-morfolina
4-Bencil-2-[3-cloro-4-(2-trifluorometil-benciloxi)-fenil]-morfolina

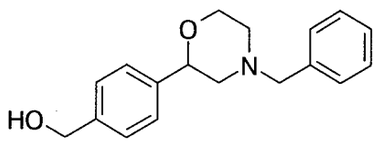


4-Bencil-2-(4-octil-fenil)-morfolina: A una solución de 1-octeno (2,12 ml, 13,5 mmol) en THF (50 ml) se agregó 9-BBN (4,3g, 17,6 mmol), a 0°C. La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó hasta la mañana siguiente. Con posterioridad, se agregó K3PO4 (7,6 g, 35,8 mmol), seguido, después de 45 minutos, de 4-bencil-6-(4-bromo-fenil)-morfolina (3,0 g, 9 mmol), paladio(II) acetato (80 mg; 4mol%), y diciclohexil-(2',6'-dimetoxi-bifenil-2-il)-fosfano (296 mg; 8 mol%). La mezcla resultante se calentó a reflujo durante 2 horas. Después de enfriar hasta alcanzar la temperatura ambiente la mezcla se concentró al vacío, se disolvió el residuo en EtOAc, y se lavó con solución acuosa al 5% de NaHCO3. La fase orgánica se secó (Na2SO4), se filtró, y se concentró al vacío. El residuo se purificó por cromatografía en columna (SiO2, Et2O: hexanos, 1:1) para producir 4-bencil-2-(4-octil-fenil)-morfolina (2,58g).

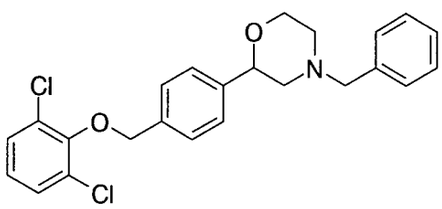


4-(4-Bencil-morfolin-2-il)-benzaldehído: A una solución de 4-bencil-6-(4-bromo-fenil)-morfolina (1,73 g; 5,21 mmol) en THF (25 ml) se agregó gota a gota n-BuLi (2,08 ml; 2,50 mol/l; 5,21 mmol), a -78°C. La mezcla resultante se agitó durante una hora, y con posterioridad una solución de N-formilmorfolina (0,90 g; 7,81 mmol) en THF (5 ml) se agregó gota a gota, a -78oC. La reacción se desactivó por medio de la incorporación de una solución acuosa al 5% de NaHCO3, a -70oC. La mezcla resultante se extrajo con

Et2O. Las fases orgánicas combinadas se secaron (Na2SO4), se filtraron, y se concentraron al vacío. El residuo se purificó por cromatografía en columna (SiO2, Et2O: hexanos 1:1) para producir 4-(4-bencil-morfolin-2-il)-benzaldehído (1,21 g).



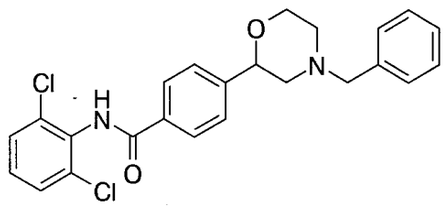
[4-(4-Bencil-morfolin-2-il)-fenil]-metanol: A una solución de 4-(4-bencil-morfolin-2-il)-benzaldehído (1,19 g; 4,23 mmol) en MeOH (25 ml) se agregó NaBH4 (0,16 g; 4,23 mmol), en pequeñas porciones, a 0°C. Después de que se completó la incorporación la mezcla se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante una hora. Con posterioridad, la mezcla se enfrió hasta 0°C, se agregó agua, y el MeOH se evaporó al vacío. A la solución acuosa se agregó a solución acuosa al 5% de NaHCO3 y EtOAc. Las fases se separaron y la fase orgánica se secó (Na2SO4), se filtró y se concentró al vacío para producir [4-(4-bencil-morfolin-2-il)-fenil]-metanol (1,16 g) que se utilizó tal como estaba.



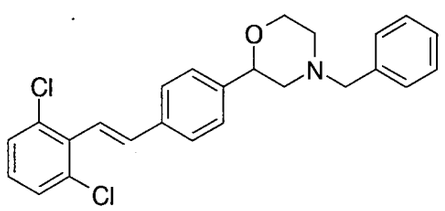
4-Bencil-2-[4-(2,6-dicloro-fenoximetil)-fenil]-morfolina: A una solución de 2,6-diclorofenol (0,68 g; 4,19 mmol) en THF (20 ml) se agregó DIAD (1,13 ml; 5,72 mmol), y trifenilfosfina (1,50 g; 5,72 mmol), a temperatura ambiente, seguido, después de 30 minutos, de [4-(4-bencil-morfolin-2-il)-fenil]-metanol (1,08 g; 3,81 mmol). Con posterioridad, la mezcla resultante se agitó a temperatura ambiente durante 1 hora, y se concentró al vacío. El residuo se purificó por cromatografía en columna (SiO2, Et2O: hexanos 1:1) para producir 4-bencil-2-[4-(2,6-dicloro-fenoximetil)-fenil]-morfolina (2,35 g) que se utilizó tal como estaba en una etapa posterior.

El siguiente compuesto se obtuvo de acuerdo con un modo similar:

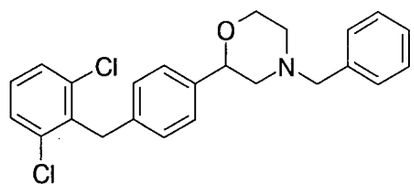
4-Bencil-2-[2-cloro-4-(2,6-dicloro-benciloxi)-fenil]-morfolina



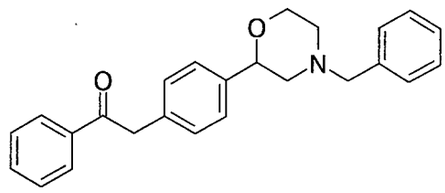
4-(4-Bencil-morfolin-2-il)-N-(2,6-dicloro-fenil)-benzamida: A una solución de 4-bencil-6-(4-bromo-fenil)-morfolina (1,01 g; 3,04 mmol) en THF (25 ml) se agregó gota a gota n-BuLi (1,2 ml; 2,5 mol/l en hexanos; 3,04 mmol), a -78°C. Después de 1 hora a -78°C, una solución de isocianato de 2,6-diclorofenilo (0,63 g; 3,34 mmol) en THF (5 ml) se agregó gota a gota. La mezcla se dejó entibiar hasta alcanzar la temperatura ambiente y a continuación se agregó NaHCO3 al 5%. Con posterioridad, la mezcla se extrajo con Et2O. La fase orgánica se secó (Na2SO4), se filtró, y se concentró al vacío. El residuo se purificó por cromatografía en columna (Et2O:hexanos 1:1) para producir 4-(4-bencil-morfolin-2-il)-N-(2,6-dicloro-fenil)-benzamida (0,68 g).



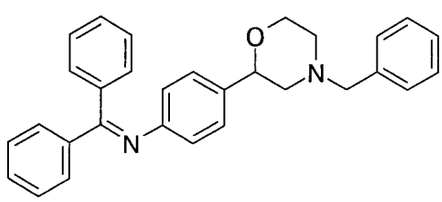
4-Bencil-2-{4-[2-(2,6-dicloro-fenil)-vinil]-fenil}-morfolina: A una suspensión de bromuro de (2,6-dicloro-bencil)-trifenil-fosfonio (2,06 g; 4,1 mmol) (Ver: A. Schmidpeter, H. Noeth, G. Jochem, H.-P. Schroedel, K. Karaghiosoff; Chem. Ber., 1995, 128, 379) en THF (25 ml) se agregó hidruro de sodio (dispersión al 60% en aceite mineral) (215 mg; 4,5 mmol), a 0°C. Después de agitar durante 1 hora, 4-(4-bencil-morfolin-2-il)-benzaldehído (1,05 g; 3,7 mmol) se agregó, a 0 °C. Con posterioridad, la mezcla resultante se calentó a reflujo durante 1 hora. Después de enfriar hasta alcanzar la temperatura ambiente, se agregó NaHCO3 al 5% y la mezcla se extrajo con Et2O. La fase orgánica se secó (Na2SO4), se filtró, y se concentró al vacío. El residuo se purificó por cromatografía en columna (SiO2, Et2O: hexanos 1:1) para producir 4-bencil-2-{4-[2-(2,6-dicloro-fenil)-vinil]-fenil}-morfolina (1,15 g).



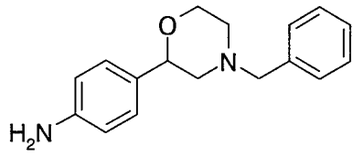
4-Bencil-2-[4-(2,6-dicloro-bencil)-fenil]-morfolina: A una mezcla de cloruro de 2,6-diclorobencilzinc (7,95 ml; 0,50 mol/l en THF; 3,97 mmol) y tetrakis(trifenilfosfina)paladio(0) (83,48 mg; 0,07 mmol) en THF (25 ml) se agregó 4-bencil-6-(4-bromo-fenil)-morfolina (1,20 g; 3,61 mmol) . La mezcla resultante se agitó a temperatura ambiente durante 2 horas, y con posterioridad se calentó bajo reflujo, durante 2 h. Después de enfriar hasta alcanzar la temperatura ambiente la mezcla se concentró al vacío. El residuo se repartió entre NaHCO3 al 5% y EtOAc .La fase orgánica se secó (Na2SO4), se filtró, y se concentró al vacío. El residuo se purificó por cromatografía en columna (SiO2, Et2O: hexanos 1:1) para producir 4-bencil-2-[4-(2,6-dicloro-bencil)-fenil]-morfolina (1,40 g).



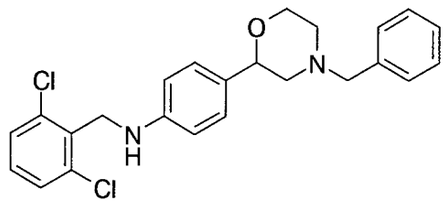
2-[4-(4-Bencil-morfolin-2-il)-fenil]-1-fenil-etanona: A una solución desgasificada de 4-bencil-2-(4-bromo-fenil)-morfolina (205 mg; 0,62 mmol) y acetofenona (87 µL; 0,74 mmol) en tolueno (4 ml) se agregó NaOtBu (148,3 mg; 1,54 mmol), 2,2'-bis(difenilfosfino)-1,1'-binaftilo (38,4 mg; 0,06 mmol) y tris(dibencilideneacetona)dipaladio(0) (28,3 mg; 0,03 mmol). La mezcla resultante se calentó hasta 110°C durante 30 min, en un microondas. Después de enfriar hasta la temperatura ambiente se agregó NaHCO3 al 5% y la mezcla se extrajo con EtOAc. Las fases orgánicas combinadas se secaron (Na2SO4), se filtraron y se concentraron al vacío. El residuo se purificó por cromatografía en columna (SiO2, Et2O / hexanos 1:1) para producir 2-[4-(4-Bencil-morfolin-2-il)-fenil]-1-fenil-etanona (110,00 mg).



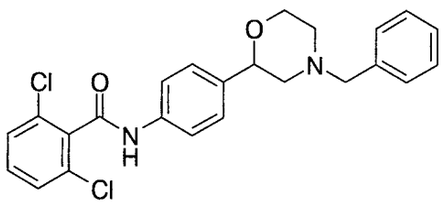
Benzhidrilideno-[4-(4-bencil-morfolin-2-il)-fenil]-amina: A una solución desgasificada de 4-bencil-6-(4-bromo-fenil)-morfolina (4,00 g; 12,04 mmol) en tolueno (50 ml) se agregó benzofenona imina (2,42 ml; 14,45 mmol), 2,2'-bis(difenilfosfino)-1,1'-binaftilo (0,60 g; 0,96 mmol), tris-(dibencilideneacetona)-dipaladio(0) (0,22 g; 0,24 mmol) y NaOtBu (1,62 g; 16,86 mmol). La mezcla resultante se calentó hasta 100°C durante 16 horas. Después de enfriar hasta alcanzar la temperatura ambiente se agregó una solución acuosa al 5% de NaHCO3, y el producto se extrajo con EtOAc. Las fases orgánicas combinadas se secaron (Na2SO4), se filtraron, y se concentraron al vacío. El residuo se purificó por cromatografía en columna (SiO2, Et2O: hexanos 1:1) para producir benzhidrilideno-[4-(4-bencil-morfolin-2-il)-fenil]-amina (3,30 g).



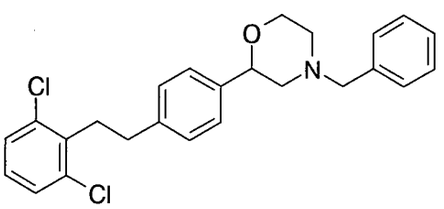
4-(4-Bencil-morfolin-2-il)-fenilamina: A una solución de benzhidrilideno-[4-(4-bencil-morfolin-2-il)-fenil]-amina (3,30 g; 7,63 mmol) en THF (50 ml) se agregó ácido clorhídrico (30,5 ml; 1,00 mol/L en agua; 30,5 mmol). La mezcla resultante se agitó hasta la mañana siguiente a temperatura ambiente. La mezcla de reacción se repartió entre HCl 1M acuoso y EtOAc. La fase acuosa se alcalinizó con NaOH 1M acuoso (pH > 10) y se extrajo con EtOAc. La fase orgánica se secó (Na2SO4), se filtró y se concentró al vacío para producir 4-(4-bencil-morfolin-2-il)-fenilamina (1,85 g).



[4-(4-Bencil-morfolin-2-il)-fenil]-(2,6-dicloro-bencil)-amina: Una mezcla de 4-(4-bencil-morfolin-2-il)-fenilamina (0,82 g; 3,06 mmol), DIPEA (1,57 ml; 9,17 mmol) y 2,6-diclorobromuro de bencilo (0,88 g; 3,67 mmol) en MeOH (25 ml), se agitó a temperatura ambiente, hasta la mañana siguiente. La mezcla resultante se repartió entre NaHCO3 al 5% y EtOAc. La fase orgánica se secó (Na2SO4), se filtró y se concentró al vacío para producir [4-(4-bencil-morfolin-2-il)-fenil]-(2,6-dicloro-bencil)-amina (1,25 g).



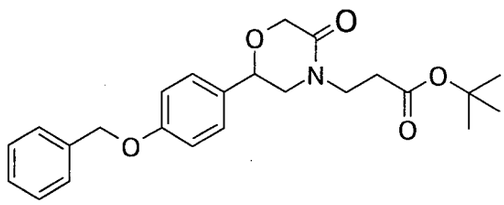
N-[4-(4-Bencil-morfolin-2-il)-fenil]-2,6-dicloro-benzamida: A una mezcla de 4-(4-bencil-morfolin-2-il)-fenilamina (0,48 g; 1,8 mmol), y N-etildiisopropilamina (0,92 ml; 5,4 mmol) en CH3CN (10 ml) se agregó cloruro de 2,6-diclorobenzoilo (0,31 ml; 2,2 mmol), a 0°C. La mezcla resultante se dejó entibiar hasta alcanzar la temperatura ambiente, se agitó durante 1 h, y se repartió entre Et2O y NaHCO3 al 5%. La fase orgánica se secó (Na2SO4), se filtró, y se concentró al vacío. El residuo se purificó por cromatografía en columna (SiO2, Et2O) para producir N-[4-(4-bencil-morfolin-2-il)-fenil]-2,6-dicloro-benzamida (0,61 g).



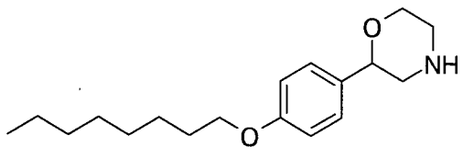
4-Bencil-2-{4-[2-(2,6-dicloro-fenil)-etil]-fenil}-morfolina: A una solución desgasificada de [2-(2,6-diclorofenil)etil]trifluoroborato de potasio (0,28 g; 1 mmol) y fosfato de potasio tribásico (0,58 g; 2,7 mmol) en tolueno (20 ml) y agua (4 ml) se agregó 4-bencil-6-(4-bromo-fenil)-morfolina (0,30 g; 0,90 mmol), paladio(II) acetato (6,1 mg; 0,03 mmol), y 2-diciclohexilfosfino-2',6'-diisopropoxi-1,1'-bifenilo (25,3 mg; 0,05 mmol). La mezcla resultante se calentó al reflujo, hasta la mañana siguiente. Después de enfriar hasta alcanzar la temperatura ambiente, la mezcla se concentró al vacío y se repartió entre EtOAc y NaHCO3 al 5%. La fase orgánica se secó (Na2SO4), se filtró, y se concentró al vacío. El residuo se purificó por cromatografía en columna (SiO2, Et2O:hexanos 1:1) para producir 4-bencil-2-{4-[2-(2,6-dicloro-fenil)-etil]-fenil}-morfolina (0,21 g).

El [2-(2,6-diclorofenil)etil]trifluoroborato de potasio requerido se preparó de la siguiente manera: A una solución de 2,6-dicloroestireno (1,58 ml; 11,6 mmol) en THF (15 ml) se agregó dímero de cloro(1,5-ciclooctadieno) Iridio(I) (38,8 mg; 0,06 mmol), 1,2-bis(difenilfosfino)etano (46,1 mg; 0,12 mmol) y pinacolborano (11,6 ml; 1M in THF; 11,6 mmol). La mezcla resultante se agitó a temperatura ambiente, hasta la mañana siguiente, con posterioridad, se concentró al vacío y se purificó por cromatografía en columna (SiO2,

Et2O:hexanos 1:3). El producto obtenido se sometió a tratamiento con MeOH (56 ml), agua (14 ml), y bifluoruro de potasio (3,43 g; 43,9 mmol), y se agitó a temperatura ambiente, hasta la mañana siguiente. Con posterioridad, los solventes se retiraron al vacío y el residuo se trató con tolueno y se concentró al vacío. Las últimas etapas se repitieron tres veces para eliminar la totalidad del agua. El sólido obtenido se sometió a tratamiento con CH3CN, y se calentó a 50°C. El precipitado se retiró por filtración sobre y se lavó con CH3CN. Las fases combinadas de CH3CN se concentraron al vacío y el residuo se sometió a tratamiento con Et2O. El precipitado formado se recolectó por filtración sobre y se secó al vacío para producir [2-(2,6-diclorofenil)etil]trifluoroborato de potasio (1,12 g), que se utilizó tal como estaba.



Éster ter-butílico del ácido 3-[2-(4-Benciloxi-fenil)-5-oxo-morfolin-4-il]-propiónico: A una mezcla de 6-(4-benciloxi-fenil)-morfolin-3-ona (13,40 g; 47,3 mmol) y NaOH en polvo (3,78 g; 94,6 mmol) en THF (250 ml) se agregó acrilato de ter-butilo (13,7 ml; 94,6 mmol). La mezcla resultante se agitó a temperatura ambiente durante 2 horas y con posterioridad se concentró al vacío. El residuo se purificó por cromatografía en columna (SiO2, Et2O) para producir éster ter-butílico del ácido 3-[2-(4-benciloxi-fenil)-5-oxo-morfolin-4-il]-propiónico (14,20 g).



2-(4-octiloxi-fenil)-morfolina: A una solución de 4-bencil-2-(4-octiloxi-fenil)-morfolina (20,22 g; 53 mmol) en MeOH (400 ml) se agregó hidróxido de paladio (0,74 g; 5,30 mmol). La mezcla se sometió a tratamiento con H2, a presión normal, hasta la mañana siguiente. La mezcla de reacción se filtró sobre Kieselguhr. La torta del filtro se lavó con una solución de amoníaco en MeOH. La evaporación del solvente produjo 2-(4-octiloxi-fenil)-morfolina (14,80 g), que se utilizó tal como estaba en una etapa posterior.

Los siguientes compuestos se obtuvieron de acuerdo con un modo similar:

3-Metil-4-morfolin-2-il-fenol

4-Morfolin-2-il-fenol

2-(4-Octil-fenil)-morfolina

2-(4-Hexiloxi-fenil)-morfolina

2-(4-Heptiloxi-fenil)-morfolina

4-Morfolin-2-il-2-trifluorometil-fenol

4-(2-Metil-morfolin-2-il)-fenol

2-Metil-4-morfolin-2-il-fenol

2-Metoxi-4-morfolin-2-il-fenol

4-(5,5-Dimetil-morfolin-2-il)-fenol

4-Morfolin-2-il-3-trifluorometil-fenol

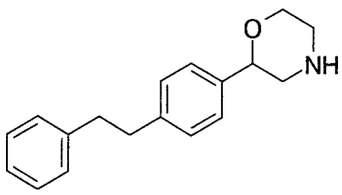
3-Fluoro-4-morfolin-2-il-fenol

éster ter-butílico del ácido 3-[2-(4-Hidroxi-fenil)-5-oxo-morfolin-4-il]-propiónico:

4-(6,6-Dimetil-morfolin-2-il)-fenol

3-Morfolin-2-il-fenol

6-Morfolin-2-il-piridin-3-ol



2-(4-Fenetil-fenil)-morfolina: Una mezcla de 4-bencil-2-{4-[2-(2,6-dicloro-fenil)-vinil]-fenil}-morfolina (0,54 g; 1,27 mmol) y hidróxido de paladio (0,04 g; 0,25 mmol) en MeOH (25 ml) se sometió a tratamiento con H2, a presión normal, hasta la mañana siguiente. La mezcla resultante se filtró sobre Kieselguhr y los solventes se evaporaron para producir 2-(4-fenetil-fenil)-morfolina (0,34 g).

(+)-2-(4-octiloxi-fenil)-morfolina y (-)-2-(4-octiloxi-fenil)-morfolina:

La 2-(4-octiloxi-fenil)-morfolina racémica se separó en ambos isómeros ópticos por HPLC preparativa quiral, a temperatura ambiente en una columna CHIRALPAK® IA 20 □m - 250 x 76 mm, con como fase móvil 99,9% CH3CN / 0,1% dietilamina (v/v) a un caudal de flujo de 270 ml/min, y con UV-detección a 240 nm. Esto produjo, después de la evaporación de los solventes (+)-2-(4-octiloxi-fenil)-morfolina (e.e. 98,3%; [□]D25 = +24 (c 1,0, MeOH)) y (-)-2-(4-octiloxi-fenil)-morfolina (e.e. 99,0%, [□]D25 = -28 (c 1,0, MeOH)).

2-[4-(2,6-Dicloro-fenoximetil)-fenil]-morfolina: A una solución de 4-bencil-2-[4-(2,6-dicloro-fenoximetil)-fenil]-morfolina (2,25 g; 3,7 mmol) en 1,2-dicloroetano (10 ml), se agregó gota a gota cloroformiato de 1-cloroetilo (0,44 ml; 4,0 mmol), a 0oC. Después de

15 minutos, se retiró el frío y con posterioridad la mezcla se calentó al reflujo hasta la mañana siguiente. Después de enfriar hasta alcanzar la temperatura ambiente la mezcla se concentró al vacío. Al residuo se agregó tolueno y la mezcla se concentró al vacío. Esta última etapa se repitió dos veces. Al residuo final se agregó MeOH (10 ml), y esta mezcla se agitó hasta la mañana siguiente a temperatura ambiente. Una vez más la mezcla se concentró al vacío. El residuo se repartió entre EtOAc y NaOH 2 M acuoso. Las fases se separaron, y la fase orgánica se secó (Na2SO4), se filtró, y se concentró al vacío para producir 2-[4-(2,6-Dicloro-fenoximetil)-fenil]-morfolina (0,98 g), que se utilizó tal como estaba en una etapa posterior.

Los siguientes compuestos se obtuvieron de acuerdo con un modo similar:

N-(2,6-Dicloro-fenil)-4-morfolin-2-il-benzamida

2-{4-[2-(2,6-Dicloro-fenil)-vinil]-fenil}-morfolina

(2,6-Dicloro-bencil)-(4-morfolin-2-il-fenil)-amina

2,6-Dicloro-N-(4-morfolin-2-il-fenil)-benzamida

2-{4-[2-(2,6-Dicloro-fenil)-etil]-fenil}-morfolina

2-[4-(2,6-dicloro-bencil)-fenil]-morfolina

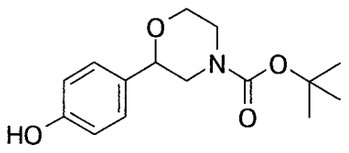
2-[3-Cloro-4-(2,6-dicloro-benciloxi)-fenil]-morfolina

2-[3-Cloro-4-(2-cloro-6-fluoro-benciloxi)-fenil]-morfolina

2-[3-Cloro-4-(2-trifluorometil-benciloxi)-fenil]-morfolina

2-[2-Cloro-4-(2,6-dicloro-benciloxi)-fenil]-morfolina

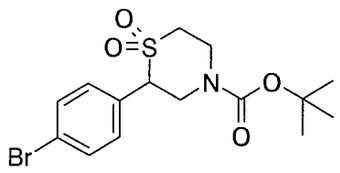
2-(4-Morfolin-2-il-fenil)-1-fenil-etanona



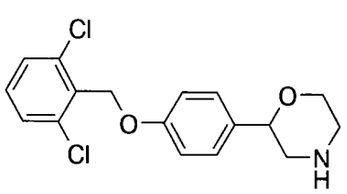
Éster ter-butílico del ácido 2-(4-Hidroxi-fenil)-morfolina-4-carboxílico: Una mezcla de 4-morfolin-2-il-fenol (0,99 g; 5,41 mmol) y dicarbonato de di-ter-butilo (1,18 g; 5,41 mmol) en CH3CN (50 ml) se agitó a temperatura ambiente durante 3 días. Con posterioridad, la mezcla resultante se concentró al vacío y el residuo se purificó por cromatografía en columna (SiO2, CH2Cl2:CH3OH 97:3) para producir éster ter-butílico del ácido 2-(4-hidroxi-fenil)-morfolina-4-carboxílico (1,15 g).

El siguiente compuesto se obtuvo de acuerdo con un modo similar:

éster ter-butílico del ácido 2-(4-Bromo-fenil)-tiomorfolina-4-carboxílico



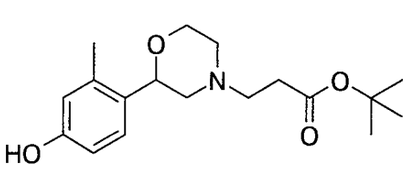
éster ter-butílico del ácido 2-(4-Bromo-fenil)-1,1-dioxo-ı□6-tiomorfolina-4-carboxílico: A una solución de éster ter-butílico del ácido 2-(4-bromo-fenil)-tiomorfolina-4-carboxílico (3,60 g; 10,05 mmol) en CH2Cl2 (100 ml) se agregó ácido 3-cloroperoxibenzoico (5,20 g; 30,14 mmol), a 0°C. La mezcla resultante se agitó hasta la mañana siguiente a temperatura ambiente, y con posterioridad, se agregó una solución acuosa saturada de tiosulfato de sodio y la mezcla se agitó durante otras 30 min Las fases se separaron y la fase acuosa se extrajo dos veces con EtOAc. Las fases combinadas de EtOAc se lavaron dos veces con una solución acuosa de Na2CO3. Las fases orgánicas combinadas se secaron (MgSO4), se filtraron y se concentraron al vacío para producir éster ter-butílico del ácido 2-(4-bromo-fenil)-1,1-dioxo-ı□6-tiomorfolina-4-carboxílico (4,06 g) que se utilizó tal como estaba en una etapa posterior.



2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolina, como clorhidrato: Se agregó cloruro de acetilo (1,35 ml, 8,9 mmol) a etanol (60 ml). La solución resultante se agregó a éster ter-butílico del ácido 2-[4-(2,6-dicloro-benciloxi)-fenil]-morfolina-4-carboxílico (1,54 g; 3,4 mmol), a temperatura ambiente. La mezcla resultante se agitó a 60°C durante 3 horas, y con posterioridad, a temperatura ambiente durante tres días. La suspensión resultante se concentró al vacío, y se trató con iPr2O. El precipitado formado se recolectó por filtración sobre y se secó al vacío para producir 2-[4-(2,6-dicloro-benciloxi)-fenil]-morfolina, como clorhidrato (1,31 g).

El siguiente compuesto se obtuvo de acuerdo con un modo similar:

1,1-dióxido de 2-(4-Bromo-fenil)-tiomorfolina



éster ter-butílico del ácido 3-[2-(4-Hidroxi-2-metil-fenil)-morfolin-4-il]-propiónico: Una mezcla de 3-metil-4-morfolin-2-il-fenol (14,26 g; 73,8 mmol) y acrilato de ter-butilo (21,4 ml; 147,6 mmol) en CH3CN (250 ml) se calentó al reflujo hasta la mañana siguiente. Después de enfriar hasta alcanzar la temperatura ambiente la mezcla se concentró al vacío, y el residuo se repartió entre EtOAc y solución acuosa al 5% de NaHCO3. La fase orgánica se secó (Na2SO4), se filtró, se concentró al vacío y se purificó por cromatografía en columna (SiO2, CH2Cl2 > Et2O / hexanos 1:1 > éter) para producir éster ter-butílico del ácido 3-[2-(4-hidroxi-2-metil-fenil)-morfolin-4-il]-propiónico (22,62 g).

Los siguientes compuestos se obtuvieron de acuerdo con un modo similar:

éster ter-butílico del ácido 3-[2-(4-Hidroxi-fenil)-morfolin-4-il]-propiónico

Isómero 1 del éster ter-butílico del ácido 3-[2-(4-octiloxi-fenil)-morfolin-4-il]-propiónico a partir de (+)-2-(4-octiloxi-fenil)-morfolina.

Isómero 2 del éster ter-butílico del ácido 3-[2-(4-octiloxi-fenil)-morfolin-4-il]-propiónico a partir de (-)-2-(4-octiloxi-fenil)-morfolina.

éster ter-butílico del ácido 3-[2-(4-Octil-fenil)-morfolin-4-il]-propiónico.

éster ter-butílico del ácido 3-[2-(4-Hexiloxi-fenil)-morfolin-4-il]-propiónico

éster ter-butílico del ácido 3-[2-(4-Heptiloxi-fenil)-morfolin-4il]-propiónico

éster ter-butílico del ácido 3-[2-(4-Hidroxi-3-trifluorometil-fenil)-morfolin-4-il]-propiónico

éster ter-butílico del ácido 3-{2-[4-(2,6-Dicloro-fenilcarbamoil)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(2,6-Dicloro-fenoximetil)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-(2-{4-[2-(2,6-Dicloro-fenil)-vinil]-fenil}-morfolin-4-il)-propiónico

éster ter-butílico del ácido 3-[2-(4-Fenetil-fenil)-morfolin-4-il]-propiónico

éster ter-butílico del ácido 3-{2-[4-(2,6-Dicloro-bencilamino)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(2,6-Dicloro-benzoilamino)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-[2-(4-Hidroxi-fenil)-2-metil-morfolin-4-il]-propiónico.

éster ter-butílico del ácido 3-(2-{4-[2-(2,6-Dicloro-fenil)-etil]-fenil}-morfolin-4-il)-propiónico.

éster ter-butílico del ácido 3-[2-(4-Hidroxi-3-metil-fenil)-morfolin-4-il]-propiónico.

éster ter-butílico del ácido 3-[2-(4-Hidroxi-3-metoxi-fenil)-morfolin-4-il]-propiónico.

éster ter-butílico del ácido 3-{2-[4-(2,6-Dicloro-bencil)-fenil]-morfolin-4-il}-propiónico.

éster ter-butílico del ácido 3-[2-(4-Hidroxi-fenil)-5,5-dimetil-morfolin-4-il]-propiónico.

éster ter-butílico del ácido 3-[2-(4-Hidroxi-2-trifluorometil-fenil)-morfolin-4-il]-propiónico

éster ter-butílico del ácido 3-[2-(2-Fluoro-4-hidroxi-fenil)-morfolin-4-il]-propiónico

éster ter-butílico del ácido 3-[6-(4-Hidroxi-fenil)-2,2-dimetil-morfolin-4-il]-propiónico

éster ter-butílico del ácido 3-{2-[3-Cloro-4-(2,6-dicloro-benciloxi)-fenil]-morfolin-4-il}-propiónico

3-{2-[3-Cloro-4-(2-cloro-6-fluoro-benciloxi)-fenil]-morfolin-4-il}- éster ter-butílico del ácido propiónico

éster ter-butílico del ácido 3-{2-[3-Cloro-4-(2-trifluorometil-benciloxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3 -[2-(3-Hidroxi-fenil)-morfolin-4-il]-propiónico

éster ter-butílico del ácido 3-{2-[2-Cloro-4-(2,6-dicloro-benciloxi)-fenil]-morfolin-4-il}-propiónico

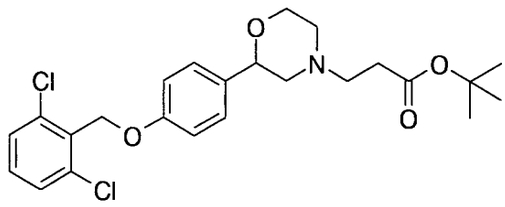
éster ter-butílico del ácido 3-[2-(4-Bromo-fenil)-tiomorfolin-4-il]-propiónico

éster ter-butílico del ácido 3-[2-(4-Bromo-fenil)-1,1-dioxo-1□6-tiomorfolin-4-il]-propiónico

éster ter-butílico del ácido 3-[2-(5-Hidroxi-piridin-2-il)-morfolin-4-il]-propiónico

éster ter-butílico del ácido 3-{2-[4-(2-Oxo-2-fenil-etil)-fenil]-morfolin-4-il}-propiónico

3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-propionitrilo usando acrilonitrilo en lugar de acrilato de ter-butilo.



éster ter-butílico del ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-propiónico: Una mezcla de éster ter-butílico del ácido 3-[2-(4-hidroxi-fenil)-morfolin-4-il]-propiónico (5,00 g; 16,3 mmol) y K2CO3 (6,74 g; 48,8 mmol) en CH3CN (100 ml) se agitó durante una hora a temperatura ambiente. Con posterioridad se agregó 2,6-diclorobromuro de bencilo (4,29 g; 17,9 mmol) y la mezcla resultante se agitó hasta la mañana siguiente a temperatura ambiente. La mezcla de reacción se repartió entre EtOAc (250 ml) y solución acuosa al 5% de NaHCO3 (100 ml). Las fases se separaron y la fase orgánica se secó (Na2SO4), se filtró y se concentró al vacío. El residuo se purificó por

cromatografía en columna (SiO2, Et2O /hexanos 1:1) para producir éster ter-butílico del ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-propiónico (7,40 g).

Los siguientes compuestos se obtuvieron de acuerdo con un modo similar:

éster ter-butílico del ácido 3-(2-(4-octiloxi-fenil)-morfolin-4-il)-propiónico

éster ter-butílico del ácido 3-{2-[4-(2-Cloro-6-fluorobenciloxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(2,6-Difluoro-benciloxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(2-Trifluorometil-benciloxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(3-Trifluorometil-benciloxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-3-trifluorometil-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-2-metil-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(2-Cloro-6-fluoro-benciloxi)-fenil]-2-metil-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(2-Trifluorometil-benciloxi)-fenil]-2-metil-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-[2-Metil-2-(4-octiloxi-fenil)-morfolin-4-il]-propiónico

éster ter-butílico del ácido 2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolina-4-carboxílico

éster ter-butílico del ácido 3-{2-[3-Metoxi-4-(2-trifluorometil-benciloxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(2-Cloro-6-fluoro-benciloxi)-3-metoxi-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-3-metoxi-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[3-Metil-4-(2-trifluorometil-benciloxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(2-Cloro-6-fluoro-benciloxi)-3-metil-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-3-metil-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(2-Cloro-5-trifluorometil-benciloxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(2-Cloro-3-trifluorometil-benciloxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(2-Cloro-6-trifluorometil-benciloxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(3-Fenil-alliloxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-5-oxo-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-[2-(4-Octiloxi-fenil)-5-oxo-morfolin-4-il]-propiónico

éster ter-butílico del ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-5,5-dimetil-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-[5,5-Dimetil-2-(4-octiloxi-fenil)-morfolin-4-il]-propiónico

éster ter-butílico del ácido 3-{6-[4-(2,6-Dicloro-benciloxi)-fenil]-2,2-dimetil-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-[2,2-Dimetil-6-(4-octiloxi-fenil)-morfolin-4-il]-propiónico

éster ter-butílico del ácido 3-{2-[4-(2-Cloro-6-fluoro-benciloxi)-2-fluoro-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[2-Fluoro-4-(2-trifluorometil-benciloxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-2-fluoro-fenil]-morfolin-4-il}-propiónico

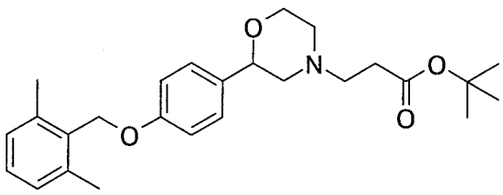
éster ter-butílico del ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-2-trifluorometil-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-[2-(4-Octiloxi-2-trifluorometil-fenil)-morfolin-4-il]-propiónico

éster ter-butílico del ácido 3-{2-[4-(2,6-Dicloro-3-etil-benciloxi)-fenil]-morfolin-4-il}-propiónico. El 2-bromometil-1,3-dicloro-4-etil-benceno requerido se preparó de la siguiente manera: A una mezcla de 2',4'-dicloroacetofenona (4,85 g; 25,66 mmol) suspendida en dietilenglicol (20 ml) se agregó KOH (2,37 g; 35,92 mmol) y hidrato de hidrazina (2,9 ml). La mezcla resultante se calentó a 100oC (durante 1 hora) y con posterioridad hasta la mañana siguiente, a 200oC. Después de enfriar hasta alcanzar la temperatura ambiente, la mezcla se repartió entre Et2O y agua. Las fases se separaron y la fase orgánica se secó (Na2SO4), se filtró, y se concentró al vacío. El residuo se purificó por cromatografía

en columna (SiO2, hexanos) para producir el producto: 2,4-dicloro-1-etilbenceno (2,24 g). A una solución 2,2,6,6-tetrametilpiperidina (2,36 ml; 14 mmol), disuelta en THF (40 ml) se agregó una solución de n-BuLi en hexanos (5,6 ml; 2,50 mol/l; 14 mmol), a -78°C. La mezcla de reacción se agitó durante 90 minutos, con lo cual se permitió que la temperatura alcance los 0oC. Con posterioridad, una solución de 2,4-dicloro-1-etilbenceno (2,23 g; 12,74 mmol), disuelta en THF (5 ml) se agregó a -78°C. La mezcla resultante se agitó durante 2,5 horas. Con posterioridad, se agregó DMF (1,48 ml; 19,11 mmol) gota a gota y la mezcla resultante se agitó durante 30 minutos. La reacción se desactivó por medio de la incorporación de una solución acuosa saturada de NH4Cl, a -50oC. La mezcla resultante se extrajo con Et2O. Las fases orgánicas combinadas se secaron (Na2SO4), se filtraron, y se concentraron al vacío para producir el 2,6-dicloro-3-etilbenzaldehído en bruto, el cual se disolvió nuevamente en MeOH (100 ml). Con posterioridad, se agregó NaBH4 (1,45 g; 38,22 mmol), en pequeñas porciones, a 0°C. Después de que se completó la incorporación la mezcla se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante una hora. Con posterioridad, la mezcla se enfrió hasta 0°C, se agregó agua, y el MeOH se evaporó al vacío. A la solución acuosa se agregó a solución acuosa al 5% de NaHCO3 y Et2O. Las fases se separaron y la fase orgánica se secó (Na2SO4), se filtró y se concentró al vacío. El residuo se purificó por cromatografía en columna (SiO2, Et2O:hexanos 1:7 seguido de 1:1) para producir (2,6-dicloro-3-etilfenil)metanol (2,11 g). A una solución de (2,6-dicloro-3-etilfenil)metanol (0,79 g; 3,85 mmol) en Et2O (25 ml) se agregó gota a gota PBr3 (0,47 ml; 5,01 mmol), a 0°C, y la mezcla resultante se agitó hasta la mañana siguiente, a temperatura ambiente. Con posterioridad, se agregó agua, a 0°C, seguido de EtOAc en NaHCO3 al 5%. Las fases se separaron y la fase orgánica se secó (MgSO4), se filtró, y se concentró al vacío para producir 2-bromometil-1,3-dicloro-4-etil-benceno (0,57 g), que se utilizó tal como estaba.

éster ter-butílico del ácido (+)-3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-propiónico y éster ter-butílico del ácido (-)-3-{2-[4-(2,6-dicloro-benciloxi)-fenil]-morfolin-4-il}-propiónico: El éster ter-butílico del ácido 3-{2-[4-(2,6-dicloro-benciloxi)-fenil]-morfolin-4-il}-propiónico racémico (7,1 gram) se separó en ambos isómeros ópticos por HPLC preparativa quiral, a 24°C sobre una columna CHIRALPAK® T304 20 □m - 270 x 110 mm, con como fase móvil 60% n-heptano / 40% isopropanol (v/v) a un caudal de flujo de 570 ml/min, y con UV-detección a 225 nm. Esto produjo, después de la evaporación de los solventes éster ter-butílico del ácido (+)-3-{2-[4-(2,6-dicloro-benciloxi)-fenil]-morfolin-4-il}-propiónico (3,38 g; e.e. >99,5%, [□]D25 = +13 (c 1,0, MeOH)), y éster ter-butílico del ácido (-)-3-{2-[4-(2,6-dicloro-benciloxi)-fenil]-morfolin-4-il}-propiónico (3,38 g; e.e. 99,0%, [□]D25 = -12 (c 1,0, MeOH)).



propiónico éster ter-butílico del ácido 3-{2-[4-(2,6-Dimetil-benciloxi)-fenil]-morfolin-4-il}-: A una solución de éster ter-butílico del ácido 3-[2-(4-hidroxi-fenil)-morfolin-4-il]-propiónico (0,45 g; 1,5 mmol) en THF (10 ml) se agregó 2,6-dimetilalcohol bencílico (0,22 g; 1,6 mmol), seguido de DIAD (0,43 ml; 2,2 mmol) y trifenilfosfina (0,58 g; 2,2 mmol). La mezcla resultante se agitó a temperatura ambiente durante 3 días. Con posterioridad, la mezcla de reacción se concentró al vacío. El residuo se purificó por cromatografía en columna (SiO2, Et2O: hexanos 2:1) para producir éster ter-butílico del ácido 3-{2-[4-(2,6-dimetil-benciloxi)-fenil]-morfolin-4-il}-propiónico (0,38 g).

Los siguientes compuestos se obtuvieron de acuerdo con un modo similar:

éster ter-butílico del ácido 3-{2-[4-(3,5-Dicloro-piridin-4-ilmetoxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-(2-{4-[1-(2,6-Dicloro-fenil)-etoxi]-fenil}-morfolin-4-il)-propiónico.

éster ter-butílico del ácido 3-{2-[4-(2,3-Dicloro-benciloxi)-fenil]-morfolin-4-il}-propiónico.

éster ter-butílico del ácido 3-{2-[4-(2,3,6-Tricloro-benciloxi)-fenil]-morfolin-4-il}-propiónico.

éster ter-butílico del ácido 3-{2-[4-(2-Cloro-6-metil-benciloxi)-fenil]-morfolin-4-il}-propiónico.

éster ter-butílico del ácido 3-{2-[4-(2,4-Dicloro-piridin-3-ilmetoxi)-fenil]-morfolin-4-il}-propiónico. El (2,4-dicloro-piridin-3-il)-metanol requerido se preparó de la siguiente manera: A una solución de 2,4-dicloropiridina (3,00 ml; 27,8 mmol) en THF (25 ml) se agregó gota a gota una solución de LDA (15,3 ml; 2,00 mol/l en THF/heptano/etilbenceno; 30,6 mmol), a -78°C. La mezcla resultante se agitó a -78°C durante 1 h. Con posterioridad, una solución de cloroformiato de etilo (3,2 ml; 33,33 mmol) en THF (5 ml), se agregó gota a gota, a -78°C y la mezcla se agitó durante 1 h adicional a la misma temperatura. A la mezcla resultante se agregó solución de NaHCO3 al 5%, gota a gota, a -78°C. La mezcla se dejó entibiar hasta alcanzar la temperatura ambiente y se extrajo con EtOAc. La fase orgánica se secó (Na2SO4) y se concentró al vacío. El residuo se purificó por cromatografía en columna (SiO2, Et2O: hexanos 1:3) para producir etil éster del ácido

2,4-dicloro-nicotínico (2,45 g). A una solución de etil éster del ácido 2,4-dicloro-nicotínico (2,35 g; 10,68 mmol) en THF (50 ml) se agregó gota a gota hidrogenuro de diisobutilaluminio (32,0 ml; 1,00 mol/l in THF, 32,0 mmol), a 4°C. Después de 15 minutos el baño de hielo se retiró y la mezcla de reacción se agitó a temperatura ambiente hasta la mañana siguiente. Con posterioridad, la mezcla resultante se concentró al vacío y se repartió entre NaHCO3 al 5% y EtOAc. Las fases se separaron y la fase orgánica se secó (Na2SO4) y se concentró al vacío. El residuo se purificó por cromatografía en columna (Et2O: hexanos 1:1) para producir (2,4-dicloro-piridin-3-il)-metanol (0,40 g).

éster ter-butílico del ácido 3-{2-[4-(2-Cloro-5-metil-benciloxi)-fenil]-morfolin-4-il}-propiónico. El (2-cloro-5-metilfenil)metanol requerido se preparó de la siguiente manera: A una solución de ácido 2-cloro-5-metilbenzoico (2,05 g; 12,2 mmol) en THF (20 ml) se agregó BH3·THF complex en THF (1 mol/l, 24,0 ml; 24,0 mmol) gota a gota y con posterioridad se agitó durante 2 horas a 60°C. A la mezcla de reacción se agregó HCL acuoso 1 M (30 ml), a 0°C, y la mezcla resultante se agitó a temperatura ambiente durante 10 minutos. La mezcla resultante se concentró al vacío y el residuo se repartió entre EtOAc y Solución al 5% de NaHCO3. La fase orgánica se secó (Na2SO4), se filtró, y se concentró al vacío para producir el producto (1,8 g), que se utilizó tal como estaba en una etapa posterior.

éster ter-butílico del ácido 3-{2-[4-(2-Cloro-5-etil-benciloxi)-fenil]-morfolin-4-il}-propiónico. El (2-cloro-5-etilfenil)metanol requerido se preparó de la siguiente manera: A una solución purgada con nitrógeno de 5-bromo-2-clorobenzoato de etilo (4,3 ml, 25,1 mmol) en THF (100 ml) se agregó cloruro de litio (2,12 g, 50,1 mmol) y Pd(dppf)Cl2 (0,82 g, 1 mmol). Con posterioridad, la mezcla se enfrió hasta -78°C, y una solución de dietilzinc en heptano (37,6 ml; 1,00 mol/l; 37,6 mmol) se agregó gota a gota. La mezcla de reacción se dejó alcanzar la temperatura ambiente hasta la mañana siguiente. La mezcla de reacción resultante se enfrió hasta -10°C y se diluyó con Et2O (300 ml). Con posterioridad, una solución 1 M acuosa de HCl (150 ml) se agregó con cuidado. Las fases se separaron, y la fase orgánica se secó (Na2SO4), se filtró, y se concentró al vacío. El residuo se purificó por cromatografía en columna (SiO2, Et2O: hexanos 5:95) para producir 2-cloro-5-etilbenzoato de etilo (4,61 g). A una solución purgada con nitrógeno de 2-cloro-5-etilbenzoato de etilo (1 g, 4,70 mmol) en THF (25 ml), se agregó hidrogenuro de diisobutil aluminio(14,11 ml; 14,11 mmol) en tolueno, a -5°C,. La mezcla de reacción se dejó alcanzar la temperatura ambiente y se agitó hasta la mañana siguiente. La mezcla de reacción resultante se enfrió hasta -10°C y se agregó una Solución al 5% de NaHCO3 (10 ml). Las fases se separaron, y la fase orgánica se secó (Na2SO4), se filtró, y se concentró al vacío. El residuo se purificó por cromatografía en columna (SiO2, Et2O:hexanos 1:3

seguido de Et2O:hexanos 1:1) para producir (2-cloro-6-etilfenil)metanol (0,59 g) que se utilizó tal como estaba.

éster ter-butílico del ácido 3-{2-[4-(2-Cloro-5-propil-benciloxi)-fenil]-morfolin-4-il}-propiónico. El (2-cloro-5-propilfenil)metanol requerido se preparó de un modo similar al que se describió para (2-cloro-5-etilfenil)metanol usando bromuro de N-propilzinc en lugar de dietilzinc.

éster ter-butílico del ácido 3-{2-[4-(2-Cloro-5-isopropil-benciloxi)-fenil]-morfolin-4-il}-propiónico. El (2-cloro-5-isopropilfenil)metanol requerido se preparó de un modo similar al que se describió para (2-cloro-5-etilfenil)metanol usando diisopropilo zinc en lugar de dietilzinc.

éster ter-butílico del ácido 3-{2-[4-(2,4,6-Tricloro-benciloxi)-fenil]-morfolin-4-il}-propiónico.

éster ter-butílico del ácido 3-{2-[4-(2,6-Dicloro-4-trifluorometil-benciloxi)-fenil]-morfolin-4-il}-propiónico. El [2,6-dicloro-4-(trifluorometil)fenil]metanol requerido se preparó de la siguiente manera: A una solución de 1,3-dicloro-5-(trifluorometil)benceno (4,73 g; 22 mmol) en THF (40 ml) se agregó n-BuLi en hexanos (8 ml; 2,50 mol/l; 20 mmol), a -78°C. La mezcla resultante se agitó durante 15 minutos y se vertió sobre hielo seco en THF. La mezcla de reacción se acidificó hasta alcanzar un pH = 3 (con solución acuosa 5 M de HCl) y se extrajo con EtOAc. La fase orgánica se secó (Na2SO4), se filtró, y se concentró al vacío. El residuo se purificó por cromatografía en columna (SiO2, CH2Cl2/MeOH 8:2) para producir ácido 2,6-dicloro-4-(trifluorometil)benzoico (1,2 g). A una solución de este ácido 2,6-dicloro-4-(trifluorometil)benzoico (1,7 g; 6,6 mmol) en THF (20 ml) se agregó gota a gota una solución de complejo de borano-THF en THF (1 mol/l, 13,3 ml; 13,3 mmol). Con posterioridad, la mezcla resultante se agitó hasta la mañana siguiente a 60°C. A la mezcla de reacción se agregó HCL acuoso 1 M (30 ml), a 0°C, y la mezcla resultante se agitó a temperatura ambiente durante 10 minutos. La mezcla resultante se concentró al vacío y el residuo se repartió entre EtOAc y solución al 5% de NaHCO3. Las fases se separaron y la fase orgánica se secó (Na2SO4), se filtró, y se concentró al vacío. El residuo se purificó por cromatografía en columna (SiO2, Et2O: hexanos 1:3 seguido de Et2O: hexanos 1:1) para producir [2,6-dicloro-4-(trifluorometil)fenil]-metanol (1,3 g), que se utilizó tal como estaba en una etapa posterior.

éster ter-butílico del ácido 3-{2-[4-(2,6-Dicloro-4-yodo-benciloxi)-fenil]-morfolin-4-il}-propiónico. El (2,6-dicloro-4-yodofenil)metanol requerido se preparó de la siguiente manera: A una solución de 3,5-dicloroyodobenceno (2,72 g; 10 mmol) en THF (25 ml) se agregó una solución de diisopropilamida de litio en THF/heptano/etilbenceno (5,5 ml; 2,00 mol/l; 11 mmol), a -78°C. La mezcla resultante se agitó durante 4,5 hora, a -78°C, y con

posterioridad una solución de DMF (1,2 ml, 15 mmol) en THF (5 ml) se agregó gota a gota, a -78oC. La mezcla de reacción resultante se agitó durante 2 horas a -40oC. Con posterioridad, la reacción se desactivó por medio de la incorporación de una solución acuosa al 5% de NH4Cl, a -20oC. La mezcla resultante se extrajo con Et2O. Las fases orgánicas combinadas se secaron (Na2SO4), se filtró, y se concentró al vacío. El residuo se purificó por cromatografía en columna (SiO2, Et2O: hexanos 1:3) para producir el 2,6-dicloro-4-benzaldehído (0,7 g, 23%). A una solución de 2,6-dicloro-4-benzaldehído (450 mg, 1,3 mmol) en MeOH (15 ml) se agregó NaBH4 (72,14 mg; 1,9 mmol), en pequeñas porciones, a 0°C. Después de que se completó la incorporación la mezcla se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante una hora. Con posterioridad, la mezcla se enfrió hasta 0°C, se agregó agua, y el MeOH se evaporó al vacío. A la solución acuosa se agregó a solución acuosa al 5% de NaHCO3 y EtOAc. Las fases se separaron y la fase orgánica se secó (Na2SO4), se filtró y se concentró al vacío. El residuo se purificó por cromatografía en columna (CH2Cl2/acetona 95:5) para producir (2,6-dicloro-4-yodofenil)metanol (0,42 g) que se utilizó tal como estaba.

éster ter-butílico del ácido 3-(2-{4-[3-(2-Fluoro-fenil)-propoxi]-fenil}-morfolin-4-il)-propiónico

éster ter-butílico del ácido 3-(2-{4-[3-(2-Trifluorometil-fenil)-propoxi]-fenil}-morfolin-4-il)-propiónico

éster ter-butílico del ácido 3-(2-{4-[3-(2-Cloro-6-fluoro-fenil)-propoxi]-fenil}-morfolin-4-il)-propiónico

éster ter-butílico del ácido 3-(2-{4-[3-(2,6-Dicloro-fenil)-propoxi]-fenil}-morfolin-4-il)-propiónico

éster ter-butílico del ácido 3-(2-{4-[3-(4-Cloro-fenil)-propoxi]-fenil}-morfolin-4-il)-propiónico

éster ter-butílico del ácido 3-(2-{4-[3-(2-Cloro-fenil)-propoxi]-fenil}-morfolin-4-il)-propiónico

éster ter-butílico del ácido 3-(2-{4-[3-(2,3-Difluoro-fenil)-propoxi]-fenil}-morfolin-4-il)-propiónico

éster ter-butílico del ácido 3-(2-{4-[3-(4-Cloro-fenil)-alliloxi]-fenil}-morfolin-4-il)-propiónico

éster ter-butílico del ácido 3-{2-[4-(3-Fenil-prop-2-iniloxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-(2-{4-[3-(4-Cloro-fenil)-prop-2-iniloxi]-fenil}-morfolin-4-il)-propiónico

ácido 3 -{2-[4-(Indan-1-iloxi)-fenil]-morfolin-4-il}-propiónico

ácido 3-{2-[4-(7-Metil-indan-1-iloxi)-fenil]-morfolin-4-il}-propiónico. El 7-metil-indan-1-ol requerido se preparó de la siguiente manera: A una solución de 7-metil-1-Indanona (0,94 g; 6,43 mmol) en EtOH (50 ml) se agregó NaBH4 (0,78 g; 20,6 mmol), a 0°C. La mezcla resultante se agitó a temperatura ambiente hasta la mañana siguiente, con posterioridad se agregó agua (5 ml) y la mezcla resultante se agitó durante 10 min La mezcla se concentró al vacío, el residuo se disolvió en EtOAc y se lavó con agua y salmuera, se secó (MgSO4) se filtró, y se concentró al vacío para producir ,7-metil-indan-1-ol (0,85 g), que se utilizó tal como estaba.

éster ter-butílico del ácido 3-{2-[4-(2,3-Dihidro-benzofuran-3-iloxi)-fenil]-morfolin-4-il}-propiónico. El 2,3-dihidro-benzofuran-3-ol requerido se preparó de acuerdo con: Ghosh, S. et al Tetrahedron, 1989, 45, 1441 – 1446.

ácido 3-{2-[4-(2,6-Dicloro-4-metil-benciloxi)-fenil]-morfolin-4-il}-propiónico. El (2,6-Dicloro-4-metil-fenil)-metanol requerido se preparó de la siguiente manera: A 1-bromo-3,5-diclorobenceno (2,50 g; 11,1 mmol) se agregó una solución de LiCl en THF (44,3 ml; 0,50 mol/l; 22,2 mmol) y Pd(dppf)Cl2 (0,32 g; 0,44 mmol). La mezcla resultante se enfrió hasta -78°C y una solución de cloruro de metilzinc en THF (11,1 ml; 2 mol/l; 22,2 mmol) se agregó gota a gota, con posterioridad la mezcla se calentó lentamente hasta 50°C durante 4 horas. Después de enfriar hasta alcanzar la temperatura ambiente, se agregaron HCl 1M acuoso y Et2O y las fases se separaron. La fase orgánica se secó (MgSO4), se filtró y se concentró al vacío. El residuo se purificó por cromatografía en columna (SiO2, hexanos/CH2Cl2 95:5) para producir 1,3-dicloro-5-metil-benceno.

A una solución de 1,3-dicloro-5-metil-benceno (0,95 g; 5,90 mmol) en THF (20 ml) se agregó gota a gota una solución de n-BuLi en hexano (2,4 ml; 2,5 mol/l; 6 mmol) a -78°C. Después de 15 min a -78°C, la mezcla resultante se vertió sobre hielo seco en THF y se dejó alcanzar la temperatura ambiente hasta la mañana siguiente. Con posterioridad la mezcla de reacción se acidificó con HCl 1M acuoso y se extrajo con CH2Cl2. Las fases orgánicas combinadas se secaron (MgSO4), se filtraron y se concentraron al vacío para producir ácido 2,6-dicloro-4-metil-benzoico (1,35 g), que se utilizó tal como estaba.

A una solución de ácido 2,6-dicloro-4-metil-benzoico (1,35 g; 6,58 mmol) en THF (13,5 ml) se agregó gota a gota una solución de BH3·THF en THF (19,8 ml; 1,00 mol/l; 19,8 mmol), a 0°C. Después de la incorporación completa la mezcla resultante se calentó al reflujo, hasta la mañana siguiente. Con posterioridad, la mezcla se enfrió hasta 0°C y se agregó HCl 1M acuoso (40 ml) seguido después de 10 min por Et2O (100 ml). Las fases se separaron; la fase acuosa se extrajo con Et2O, y las fases orgánicas combinadas se lavaron con salmuera, se secó (MgSO4), se filtró, y se concentró al vacío. El residuo se

purificó por cromatografía en columna (SiO2, Et2O/hexanos 1:2) para producir 2,6-dicloro-4-metil-fenil)-metanol (0,80 g).

éster ter-butílico del ácido 3-{2-[4-(2-Cloro-6-etil-benciloxi)-fenil]-morfolin-4-il}-propiónico; El (2-cloro-6-etil-fenil)-metanol requerido se preparó de la siguiente manera: A una solución de 2-cloro-6-etilbenzaldehído (1,8 g, 10,67 mmol), se preparó de acuerdo con la patente US2007/197621, (ver también WO2007/85556 y US6380387) en MeOH (50 ml) se agregó NaBH4 (1,21 g; 32,02 mmol), en pequeñas porciones, a 0°C. Después de que se completó la incorporación la mezcla se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante una hora. Con posterioridad, la mezcla se enfrió hasta 0°C, se agregó agua, y el MeOH se evaporó al vacío. A la solución acuosa se agregó a solución acuosa al 5% de NaHCO3 y EtOAc. Las fases se separaron y la fase orgánica se secó (Na2SO4), se filtró y se concentró al vacío. El residuo se purificó por cromatografía en columna (SiO2, Et2O: hexanos 1:7 seguido de Et2O: hexanos 3:1) para producir (2-cloro-6-etilfenil)metanol (1,2 g).

éster ter-butílico del ácido 3-{2-[4-(2-Cloro-6-isopropil-benciloxi)-fenil]-morfolin-4-il}-propiónico; El (2-cloro-6-isopropil-fenil)-metanol requerido se obtuvo a partir de a NaBH4 reducción de 2-cloro-6-isopropil-benzaldehído en MeOH, el cual se preparó de un modo similar al 2-cloro-6-etilbenzaldehído.

éster ter-butílico del ácido 3-{2-[4-(2-Cloro-6-ciclopropil-benciloxi)-fenil]-morfolin-4-il}-propiónico; El (2-cloro-6-ciclopropil-fenil)-metanol requerido se obtuvo a partir de a NaBH4 reducción de 2-cloro-6-ciclooprópil-benzaldehído en MeOH, que se preparó de un modo similar al de 2-cloro-6-etilbenzaldehído.

éster ter-butílico del ácido 3-{2-[4-(2-Cloro-6-isobutil-benciloxi)-fenil]-morfolin-4-il}-propiónico; El (2-cloro-6-isobutil-fenil)-metanol requerido se obtuvo a partir de a NaBH4 reducción de 2-cloro-6-isobutil-benzaldehído en MeOH, que se preparó de un modo similar al de 2-cloro-6-etilbenzaldehído.

éster ter-butílico del ácido 3-[2-(3-Benciloxi-fenil)-morfolin-4-il]-propiónico

éster ter-butílico del ácido 3-[2-(3-Octiloxi-fenil)-morfolin-4-il]-propiónico

éster ter-butílico del ácido 3-{2-[3-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[3-(2-Cloro-benciloxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(2,6-Dicloro-4-prop-1-inil-benciloxi)-fenil]-morfolin-4-il}-propiónico. El (2,6-dicloro-4-prop-1-inil-fenil)-metanol requerido se preparó de la siguiente manera: A una solución desgasificada de (2,6-dicloro-4-yodofenil)metanol (3,00 g; 9,90 mmol) en Et3N (80 ml), en un dispositivo de presión de microondas, se agregó CuI (0,19 g; 0,99 mmol) y PdCl2(PPh3)2 (0,35 g; 0,50 mmol). La lima de presión se enjuagó

con el nitrógeno gaseoso y se cargó con propina hasta lograr una presión de 5 bares. Con posterioridad, el recipiente se calentó en un microondas a 50°C durante 15 min, y a partir de entonces a 80°C durante 10 min Después de enfriar hasta la temperatura ambiente la presión se liberó y los elementos volátiles removed al vacío. El residuo se disolvió en CH_2Cl_2 y se lavó con agua. La fase orgánica se concentró al vacío, y el residuo se purificó por cromatografía en columna para producir (2,6-dicloro-4-prop-1-inil-fenil)-metanol (1,79 g).

éster ter-butílico del ácido 3-{2-[4-(2,6-Dicloro-4-propil-benciloxi)-fenil]-morfolin-4-il}-propiónico. El (2,6-dicloro-4-propil-fenil)-metanol requerido se preparó de la siguiente manera: Una mezcla de (2,6-dicloro-4-prop-1-inil-fenil)-metanol (800 mg; 3,72 mmol) y Níquel de Raney (20 mg) en EtOH (15 ml) se sometió a tratamiento con hidrógeno gaseoso (1 atm.) hasta la mañana siguiente, a temperatura ambiente. Con posterioridad, el catalizador se retiró por filtración sobre y el filtrado se concentró al vacío para producir (2,6-dicloro-4-propil-fenil)-metanol (790,0 mg).

éster ter-butílico del ácido 3-{2-[4-(2,6-Dicloro-4-isopropil-benciloxi)-fenil]-morfolin-4-il}-propiónico. El (2,6-dicloro-4-isopropil-fenil)-metanol requerido se preparó a partir de (2,6-dicloro-4-isopropenil-fenil)-metanol de un modo similar al que se describió para (2,6-dicloro-4-propil-fenil)-metanol. (2,6-Dicloro-4-isopropenil-fenil)-metanol se preparó de la siguiente manera: A una mezcla desgasificada de (2,6-dicloro-4-yodofenil)metanol (1,50 g; 4,95 mmol), Cs_2CO_3 (9,68 g; 29,71 mmol) y 2-isopropenil-4,4,5,5-tetrametil-1,3,2-dioxaborolano (1,85 ml; 9,90 mmol) en 1,2-dimetoxietano (20 ml) y agua (5 ml), se agregó $Pd(dppf)Cl_2$ (0,36 g; 0,50 mmol). La mezcla resultante se agitó a temperatura ambiente durante tres días, y con posterioridad se agregaron EtOAc y agua. Las fases se separaron y la fase acuosa se extrajo dos veces con EtOAc. Las fases orgánicas combinadas se secaron ($MgSO_4$), se filtró y se concentró al vacío. El residuo se purificó por cromatografía en columna (SiO_2, CH_2Cl_2/hexanos 2:1) para producir (2,6-dicloro-4-isopropenil-fenil)-metanol (0,96 g)

éster ter-butílico del ácido 3-{2-[4-(2-Cloro-6-trifluorometoxi-benciloxi)-fenil]-morfolin-4-il}-propiónico. El requerido (2-cloro-6-trifluorometoxi-fenil)-metanol se preparó de la siguiente manera: A una solución de 2,2,6,6-tetrametilpiperidina (2,35 ml; 14. mmol) en THF (25 ml) se agregó gota a gota una solución de n-BuLi en hexanos (5,60 ml; 2,50 mol/l; 14 mmol), a -78°C. La mezcla resultante se agitó durante 60 min a -78°C, y con posterioridad una solución de 3-(trifluorometoxi)clorobenceno (2,50 g; 12,72 mmol) en THF (10 ml), se agregó gota a gota, a -78°C. Después de 2,5 horas, a -78°C, DMF (1,48 ml, 19,11 mmol) se agregó gota a gota, y se continuó con la agitación durante un adicional de 30 min Después de dicho tiempo se agrego una solución acuosa saturada de NH_4Cl

se agregó seguido de la incorporación de Et2O. Después de entibiar hasta alcanzar la temperatura ambiente las fases se separaron, y la fase orgánica se lavó con agua, se secó (Na2SO4), se filtró y se concentró al vacío. El residuo se disolvió en MeOH (25 ml) y NaBH4 (1,44 g; 38,16 mmol) se agregó en porciones. Después de la incorporación completa la mezcla se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 30 minutos. Con posterioridad, agua (5 ml) se agregó y los elementos volátiles se retiraron al vacío. Se agregaron Et2O y solución acuosa al 5% de NaHCO3, y la fase orgánica se separó, se secó (Na2SO4), se filtró y se concentró al vacío para producir (2-cloro-6-trifluorometoxi-fenil)-metanol (2,10 g), que se utilizó tal como estaba.

éster ter-butílico del ácido 3-{2-[4-(2-Cloro-4-metil-benciloxi)-fenil]-morfolin-4-il}-propiónico. El (2-cloro-4-metil-fenil)-metanol requerido se preparó de la siguiente manera: A una solución de acido 2-cloro-4-metilbenzoico (2,18 g; 12,8 mmol) en THF (22 ml) se agregó gota a gota una solución de BH3·THF en THF (25,6 ml; 1,00 mol/l; 25,6 mmol), a 0°C. Luego de la incorporación completa la mezcla resultante se calentó al reflujo, durante 3 horas. Con posterioridad, la mezcla se enfrió hasta 0°C, HCl 1M acuoso (30 ml) se agregó gota a gota, y la mezcla se agitó durante 10 min Et2O (100 ml) se agregó y las fases se separaron. La fase orgánica se lavó con HCl 1M acuoso (2x), NaHCO3 al 5% (2x), y salmuera, se secó (Na2SO4), se filtró y se concentró al vacío para producir (2-cloro-4-metil-fenil)-metanol (1,80 g), que se utilizó tal como estaba.

éster ter-butílico del ácido 3-{2-[4-(2-Cloro-3-metil-benciloxi)-fenil]-morfolin-4-il}-propiónico. El (2-Cloro-3-metil-fenil)-metanol requerido se preparó de un modo similar al que se describió para (2-Cloro-4-metil-fenil)-metanol

éster ter-butílico del ácido 3-{2-[4-(2,4-Dicloro-benciloxi)-fenil]-morfolin-4-il}-propiónico.

éster ter-butílico del ácido 3-{2-[4-(4-Metoxi-benciloxi)-fenil]-morfolin-4-il}-propiónico.

éster ter-butílico del ácido 3-{2-[4-(2-Metoxi-benciloxi)-fenil]-morfolin-4-il}-propiónico.

éster ter-butílico del ácido 3-{2-[4-(4,4-Dimetil-ciclohexiloxi)-fenil]-morfolin-4-il}-propiónico.

éster ter-butílico del ácido 3-{2-[4-(2-Difluorometoxi-benciloxi)-fenil]-morfolin-4-il}-propiónico.

éster ter-butílico del ácido 3-{2-[4-(2,6-Dietil-benciloxi)-fenil]-morfolin-4-il}-propiónico. El (2,6-dietil-fenil)-metanol requerido se preparó de la siguiente manera: A una mezcla de 2,6-difluorobenzaldehído (25,00 g; 175,93 mmol) y p-TsOH (0,67 g; 3,52 mmol) en tolueno (150 ml) se agregó 1-aminobutano (16,5 ml; 167,1 mmol). La mezcla resultante se agitó a temperatura ambiente durante 24 horas, con posterioridad, se lavó con solución acuosa al

5% de NaHCO3, agua y salmuera, se secó (Na2SO4), se filtró y se concentró al vacío para producir butil-(2,6-difluoro-bencilidene)-amina (35,36 g).

A una solución de butil-(2,6-difluoro-bencilidene)-amina (1,10 g; 5,58 mmol) en THF (25 ml) se agregó gota a gota una solución de bromuro de etil magnesio en Et2O (4,1 ml; 3,00 mol/l; 12,3 mmol) a -10°C. Después de que se completó la incorporación la mezcla de reacción se agitó a temperatura ambiente durante 4 horas. La mezcla de reacción se desactivó por la incorporación gota a gota de una solución al 5% de NaHCO3, y a continuación se extrajo con EtOAc. Las fases orgánicas combinadas se secaron (Na2SO4), se filtró, y se concentró al vacío para producir butil-(2,6-dietil-bencilideno)-amina (1,10 g).

A una solución de butil-(2,6-dietil-bencilideno)-amina (1,10 g; 5,06 mmol) en agua (20 ml) se agregó H2SO4 (5,00 ml; 93,80 mmol), y la mezcla resultante se calentó a reflujo durante 2 horas. Después de enfriar hasta alcanzar la temperatura ambiente la mezcla se diluyó con EtOAc, y se lavó con agua, una solución al 5% de NaHCO3 y salmuera. La fase orgánica se secó (Na2SO4), se filtró y se concentró al vacío para producir 2,6-dietil-benzaldehído (0,72 g).

A una solución de 2,6-dietil-benzaldehído (0,68 g; 4,19 mmol) en THF (15 ml) se agregó gota a gota una solución de BH3·THF en THF (8,38 ml; 1,00 mol/l; 8,38 mmol), a 0°C. Después de la incorporación completa la mezcla se calentó a reflujo durante 3 horas. Con posterioridad, la mezcla resultante se enfrió hasta 0°C y se agregó HCl 1M acuoso (10 ml) gota a gota. La mezcla se dejó entibiar hasta la temperatura ambiente (~10 min), y se trató con Et2O. Las fases se separaron, la fase orgánica se lavó con HCl 1M acuoso (2x), NaHCO3 al 5% (2x), y salmuera, se secó (Na2SO4), se filtró, y se concentró al vacío para producir (2,6-dietil-fenil)-metanol (0,67 g), que se utilizó tal como estaba.

éster ter-butílico del ácido 3-{2-[4-(3-Trifluorometil-benciloxi)-2-trifluorometil-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(2-Cloro-6-etil-benciloxi)-2-trifluorometil-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(2-Cloro-6-trifluorometoxi-benciloxi)-2-trifluorometil-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(2-Cloro-6-isopropil-benciloxi)-2-trifluorometil-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(2-Cloro-6-fluoro-benciloxi)-2-trifluorometil-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(2-Cloro-6-trifluorometil-benciloxi)-2-trifluorometil-fenil]-morfolin-4-il}-propiónico

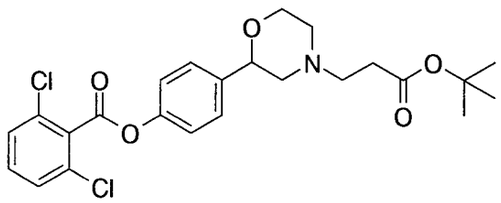
éster ter-butílico del ácido 3-{2-[4-(2-Cloro-6-ciclopropil-benciloxi)-2-trifluorometil-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[5-(2,6-Dicloro-benciloxi)-piridin-2-il]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(2-Cloro-6-difluorometoxi-benciloxi)-fenil]-morfolin-4-il}-propiónico. El (2-cloro-6-difluorometoxi-fenil)-metanol requerido se preparó de la siguiente manera: A una solución de 2-cloro-6-hidroxi-benzaldehído (1,00 g; 6,39 mmol) y KOH (7,17 g; 127,7 mmol) en CH3CN (20 ml) y agua (20 ml) se agregó bromodifluorometilo dietilfosfonato (1,25 ml; 7,03 mmol), a -15°C. Después de 30 minutos la mezcla se dejó entibiar hasta alcanzar la temperatura ambiente, se agitó durante otras 30 min y a continuación se sometió a tratamiento con HCl 1M acuoso y se extrajo con Et2O. Las fases orgánicas combinadas se secaron (Na2SO4), se filtró y se concentró al vacío. El residuo se purificó por cromatografía en columna (SiO2, Et2O/hexanos 1:3), para producir 2-cloro-6-difluorometoxi-benzaldehído (0,68 g).

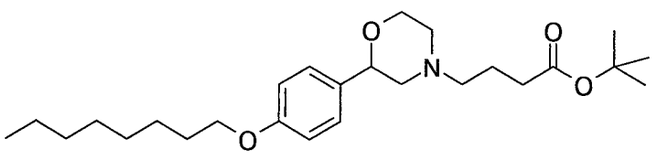
A una solución de 2-cloro-6-difluorometoxi-benzaldehído (0,65 g; 3,15 mmol) en MeOH (10 ml) se agregó NaBH4 (357,13 mg; 9,44 mmol), a -15°C. Después de la incorporación completa la mezcla se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 30 minutos. Con posterioridad, agua (5 ml) se agregó y los elementos volátiles se retiraron al vacío. El residuo se repartió entre Et2O y NaHCO3 al 5%. Las fases se separaron y la fase orgánica se secó (Na2SO4), se filtró, y se concentró al vacío para producir (2-cloro-6-difluorometoxi-fenil)-metanol (0,52 g), que se utilizó tal como estaba.

éster ter-butílico del ácido 3-{2-[4-(2-Cloro-6-difluorometoxi-benciloxi)-2-trifluorometil-fenil]-morfolin-4-il}-propiónico.



4-[4-(2-ter-butoxicarbonil-etil)-morfolin-2-il]-fenil éster del ácido 2,6-Dicloro-benzoico : A una solución de éster ter-butílico del ácido 3-[2-(4-hidroxi-fenil)-morfolin-4-il]-propiónico (0,39 g; 1,27 mmol) y N-etildiisopropilamina (0,65 ml, 3,81 mmol) en CH3CN (5 ml) se agregó cloruro de 2,6-diclorobenzoilo (0,44 ml; 3,0 mmol), a 0°C. Con posterioridad, la mezcla se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó

durante 2 días a temperatura ambiente. La mezcla resultante se repartió entre Et2O y solución acuosa al 5% de NaHCO3. Las fases se separaron y la fase orgánica se secó (Na2SO4), se filtró y se concentró al vacío. El residuo se purificó por cromatografía en columna (SiO2, Et2O para producir 4-[4-(2-ter-butoxicarbonil-etil)-morfolin-2-il]-fenil éster del ácido 2,6-dicloro-benzoico (0,51 g).



éster ter-butílico del ácido 4-[2-(4-Octiloxi-fenil)-morfolin-4-il]-butírico: 2-(4-Octiloxi-fenil)-morfolina (1,50 g; 5,2 mmol), éster ter-butílico del ácido 4-bromo-butírico (1,38 g; 6,2 mmol) (preparado de acuerdo con C. Morin, M. Vidal Tetrahedron, 1992, 48(42), 9277), yoduro de potasio (1,03 g; 6,2 mmol), K2CO3 (1,42 g; 10,29 mmol), y CH3CN (15 ml) se mezclaron y se calentaron bajo reflujo durante 2 horas. Después de enfriar hasta alcanzar la temperatura ambiente la mezcla de reacción se concentró al vacío, se disolvió en EtOAc, se lavó con solución acuosa al 5% de NaHCO3, se secó (Na2SO4) se concentró al vacío y se purificó por cromatografía en columna (SiO2, Et2O: hexanos 1:1) para producir éster ter-butílico del ácido 4-[2-(4-octiloxi-fenil)-morfolin-4-il]-butírico (1,90 g), TLC (SiO2 Rf. 0,20 EtOAc: hexanos 1:1)

Los siguientes compuestos se obtuvieron de acuerdo con un modo similar:

éster ter-butílico del ácido 4-[2-(4-Octil-fenil)-morfolin-4-il]-butírico

éster ter-butílico del ácido 4-[2-(4-Hexiloxi-fenil)-morfolin-4-il]-butírico

butírico éster ter-butílico del ácido 4-[2-(4-Heptiloxi-fenil)-morfolin-4-il]-

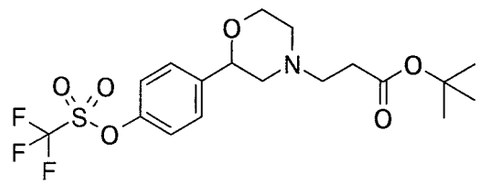
éster dietílico del ácido {3-[2-(4-Octiloxi-fenil)-morfolin-4-il]-propil}-fosfónico

éster ter-butílico del ácido 4-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-butírico

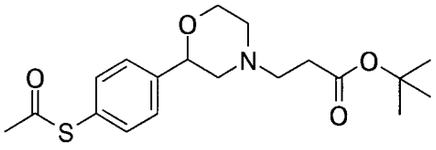
éster ter-butílico del ácido 2,2-Dimetil-3-(2-(4-octiloxi-fenil)-morfolin-4-il)-propiónico

El éster ter-butílico del ácido 3-Cloro-2,2-dimetil-propiónico requerido se preparó de la siguiente manera: A una solución de ácido 3-cloro-2,2-dimetilpropiónico (5,00 g; 36,6 mmol) en DMF (25 ml) se agregó N,N'-carbonildiimidazol (5,94 g; 36,6 mmol) y la mezcla resultante se agitó durante 1 hora a 40oC. Con posterioridad, se agregaron alcohol ter-butílico (7,1 ml; 73 mmol) y DBU (5,5 ml; 36,6 mmol) y la mezcla se agitó hasta la mañana siguiente a 40oC. Después de enfriar hasta alcanzar la temperatura ambiente, solución acuosa al 5% de NaHCO3 (50 ml) se agregó a la mezcla y se agitó durante otros 15 minutos. La mezcla de reacción se extrajo con EtOAc. La fase orgánica se secó (Na2SO4), se concentró al vacío y se purificó por cromatografía en columna (SiO2, Et2O:

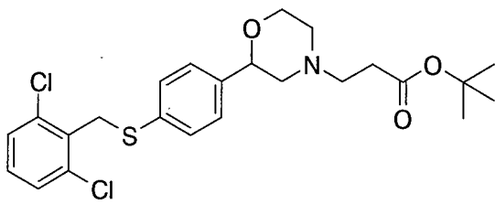
hexanos 1:1) para producir éster ter-butílico del ácido 3-cloro-2,2-dimetil-propiónico (3,34 g).



éster ter-butílico del ácido 3-[2-(4-Trifluorometanosulfoniloxi-fenil)-morfolin-4-il]-propiónico: A una solución de éster ter-butílico del ácido -[2-(4-hidroxi-fenil)-morfolin-4-il]-propiónico (2,07 g; 6,73 mmol) en CHCl3 (50 ml) se agregó Et3N (1,40 ml; 10,10 mmol), DMAP (82,3 mg; 0,67 mmol) y N-fenilbis(trifluorometano-sulfonimida) (2,89 g; 8,08 mmol). La mezcla resultante se calentó a 60°C durante 3 horas. Después de enfriar hasta alcanzar la temperatura ambiente la mezcla se lavó con Na2CO3 acuoso al 5% y agua. La fase orgánica se secó (Na2SO4), se filtró y se concentró al vacío. El residuo se purificó por cromatografía en columna (SiO2, Et2O) para producir éster ter-butílico del ácido 3-[2-(4-trifluorometanosulfoniloxi-fenil)-morfolin-4-il]-propiónico (2,30 g).



éster ter-butílico del ácido 3-[2-(4-Acetilsulfanil-fenil)-morfolin-4-il]-propiónico: A una solución desgasificada de éster ter-butílico del ácido 3-[2-(4-trifluorometanosulfoniloxi-fenil)-morfolin-4-il]-propiónico (2,55 g; 5,80 mmol) en tolueno (50 ml) se agregó Pd2dba3 (0,27 g; 0,29 mmol) y (2R)-1-[(1R)-1-[bis(1,1-dimetiletil)fosfino]-etil]-2-(diciclohexilfosfino)ferroceno (0,32 g; 0,58 mmol), seguido, después de 5 min por tioacetato de potasio (1,33 g; 11,6 mmol). La mezcla resultante se calentó al reflujo hasta la mañana siguiente. Después de enfriar hasta alcanzar la temperatura ambiente la mezcla se diluyó con CH2Cl2, se filtró y se concentró al vacío. El residuo se purificó por cromatografía en columna (SiO2, CH2Cl2/acetona 95:5) para producir éster ter-butílico del ácido 3-[2-(4-Acetilsulfanil-fenil)-morfolin-4-il]-propiónico (1,70 g)



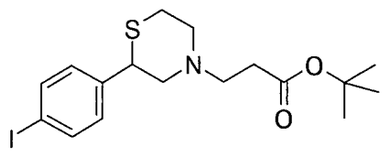
éster ter-butílico del ácido 3-{2-[4-(2,6-Dicloro-bencilsulfanil)-fenil]-morfolin-4-il}-propiónico: Una mezcla de éster ter-butílico del ácido 3-[2-(4-Acetilsulfanil-fenil)-morfolin-4-il]-propiónico (0,31 g; 0,85 mmol) y NaOH (37 mg, 0,93 mmol) en EtOH (10 ml) y agua (1 ml) se agitó durante 30 min a 0°C. Con posterioridad, se agregó 2,6-diclorobromuro de bencilo (0,22 g; 0,93 mmol), disuelto en EtOH (2,5 ml), y la mezcla se dejó entibiar hasta alcanzar la temperatura ambiente. Después de 90 min la mezcla se repartió entre EtOAc y NaHCO3 al 5%. Las fases se separaron, y la fase orgánica se lavó con NaHCO3 al 5% y salmuera, se secó (Na2SO4), se filtró y se concentró al vacío. El residuo se purificó por cromatografía en columna (SiO2, CH2Cl2/acetona 95:5) para producir éster ter-butílico del ácido 3-{2-[4-(2,6-dicloro-bencilsulfanil)-fenil]-morfolin-4-il}-propiónico (0,20 g).

Los siguientes compuestos se obtuvieron de acuerdo con un modo similar:

éster ter-butílico del ácido 3-{2-[4-(2-Cloro-bencilsulfanil)-fenil]-morfolin-4-il}-propiónico.

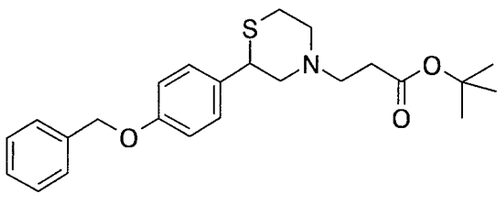
éster ter-butílico del ácido 3-{2-[4-(2-Cloro-6-fluoro-bencilsulfanil)-fenil]-morfolin-4-il}-propiónico.

éster ter-butílico del ácido 3-[2-(4-Octilsulfanil-fenil)-morfolin-4-il]-propiónico.



éster ter-butílico del ácido 3-[2-(4-Yodo-fenil)-tiomorfolin-4-il]-propiónico: A una solución de éster ter-butílico del ácido 3-[2-(4-bromo-fenil)-tiomorfolin-4-il]-propiónico (22,15 g; 57,33 mmol) 1,4-dioxano (250 ml) se agregó N,N'-dimetiletilen-diamina (3,05 ml; 28,67 mmol). A través de la mezcla resultante se burbujeó nitrógeno gaseoso durante 1 hora, y con posterioridad se agregaron CuI (1,09 g; 5,73 mmol), y NaI (21,48 g; 143,33 mmol). La mezcla resultante se calentó a 130°C en un recipiente cerrado durante 4 días. Después de enfriar hasta alcanzar la temperatura ambiente la mezcla se concentró al vacío, y el residuo se purificó por cromatografía en columna (SiO2, Et2O/hexanos 2:3)

para producir éster ter-butílico del ácido 3-[2-(4-yodo-fenil)-tiomorfolin-4-il]-propiónico (19,30 g)



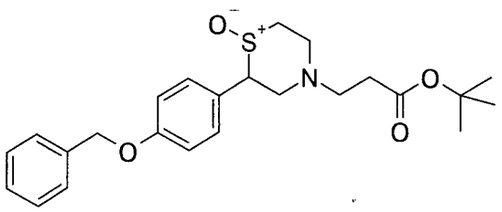
éster ter-butílico del ácido 3-[2-(4-Benciloxi-fenil)-tiomorfolin-4-il]-propiónico: (Todas las soluciones se desgasificaron) A una suspensión de 1,10-fenantrolina (183,0 mg; 1,02 mmol) en tolueno (15 ml) se agregó CuI (96,7 mg; 0,51 mmol), Cs2CO3 (3,31 g; 10,15 mmol), y una solución de éster ter-butílico del ácido 3-[2-(4-yodo-fenil)-tiomorfolin-4-il]-propiónico (2,20 g; 5,08 mmol) y alcohol bencílico (1,05 ml; 10,15 mmol) en tolueno (20 ml). La mezcla resultante se calentó durante tres días a 100°C. Después de enfriar hasta alcanzar la temperatura ambiente se agregaron EtOAc y agua. Las fases se separaron y la fase orgánica se secó (MgSO4), se filtró y se concentró al vacío. El residuo se purificó por cromatografía en columna (SiO2, EtOAc/CH2Cl2 1:6) para producir éster ter-butílico del ácido 3-[2-(4-benciloxi-fenil)-tiomorfolin-4-il]-propiónico (1,85 g).

Los siguientes compuestos se obtuvieron de acuerdo con un modo similar:

éster ter-butílico del ácido 3-{2-[4-(2-Cloro-benciloxi)-fenil]-tiomorfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-tiomorfolin-4-il}-propiónico

éster ter-butílico del ácido 3-[2-(4-Octiloxi-fenil)-tiomorfolin-4-il]-propiónico



éster ter-butílico del ácido 3-[2-(4-Benciloxi-fenil)-1-oxo-tiomorfolin-4-il]-propiónico: A una solución de éster ter-butílico del ácido 3-[2-(4-benciloxi-fenil)-tiomorfolin-4-il]-propiónico (0,85 g; 1,77 mmol) en MeOH (25 ml) se agregó gota a gota una solución de oxone® (0,54 g; 0,89 mmol) en agua (25 ml), a 0°C. La mezcla resultante se agitó durante 2 horas a 0°C, y con posterioridad, hasta la mañana siguiente a temperatura ambiente. La mezcla resultante se sometió a tratamiento con agua y una solución acuosa al 25% de NH4OH, y se extrajo con EtOAc. Las fases orgánicas combinadas se secaron (MgSO4),

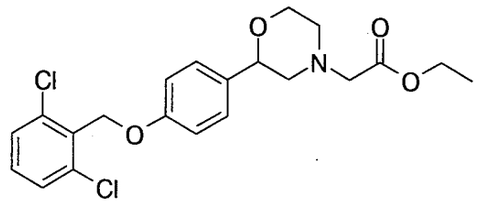
se filtraron, y se concentraron al vacío. El residuo se purificó por cromatografía en columna (SiO2, CH2Cl2/MeOH 97,5:2,5) para producir éster ter-butílico del ácido 3-[2-(4-benciloxi-fenil)-1-oxo-tiomorfolin-4-il]-propiónico (0,65 g).

Los siguientes compuestos se obtuvieron de acuerdo con un modo similar:

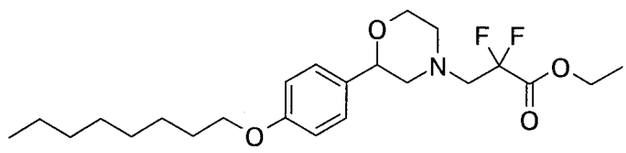
éster ter-butílico del ácido 3-{2-[4-(2-Cloro-benciloxi)-fenil]-1-oxo-tiomorfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]- 1-oxo-tiomorfolin-4-il}-propiónico

éster ter-butílico del ácido 3-[2-(4-Octiloxi-fenil)- 1-oxo-tiomorfolin-4-il]-propiónico



etil éster del ácido {2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-acético: Una mezcla de 2-[4-(2,6-dicloro-benciloxi)-fenil]-morfolina, como clorhidrato (0,65 g; 1,68 mmol), Et3N (0,58 ml; 4,2 mmol), y bromoacetato de etilo (0,24 ml; 2,19 mmol) en CH3CN (65 ml) se agitó a 85°C, hasta la mañana siguiente. Después de enfriar hasta alcanzar la temperatura ambiente la mezcla se concentró al vacío y el residuo se repartió entre agua y CH2Cl2. Las fases se separaron y la fase acuosa se extrajo once more con CH2Cl2. Las fases orgánicas combinadas se concentraron al vacío y el residuo se purificó por cromatografía en columna (SiO2, Et2O: hexanos 2:1) para producir etil éster del ácido {2-[4-(2,6-dicloro-benciloxi)-fenil]-morfolin-4-il}-acético (0,62 g).

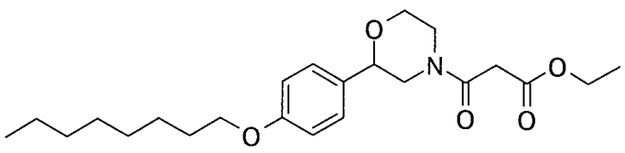


etil éster del ácido 2,2-Difluoro-3-(2-(4-octiloxi-fenil)-morfolin-4-il)-propiónico.

A una solución de 2-(4-octiloxi-fenil)-morfolina (0,75 g; 2,6 mmol) en EtOH (10 ml) se agregó 1H-benzotriazol-1-metanol (0,38 g; 2,6 mmol), y la mezcla de reacción se calentó a 50oC durante 20 minutos. Después de enfriar hasta alcanzar la temperatura ambiente, el solvente se retiró al vacío para producir 1-[2-(4-octiloxi-fenil)-morfolin-4-ilmetil]-1H-benzotriazol; que se utilizó tal como estaba.

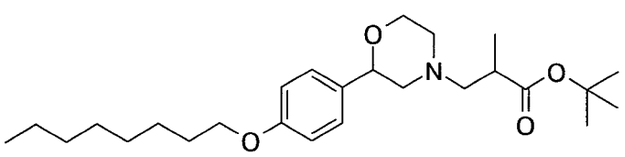
A una suspensión de polvo de zinc (0,34 g; 5,2 mmol) en THF anhidro (10 ml) se agregó clorotrimetilsilano (0,33 ml; 2,6 mmol) y bromodifluoroacetato de etilo (0,50 ml; 3,9 mmol), esta mezcla se calentó a reflujo durante 10 min y a continuación se enfrió hasta alcanzar la temperatura ambiente. A la mezcla resultante se agregó gota a gota una solución de 1-[2-(4-octiloxi-fenil)-morfolin-4-ilmetil]-1H-benzotriazol en THF (5 ml). Después de que se completa la incorporación la mezcla resultante se calienta a eflujo durante 2 horas. Después de enfriar hasta alcanzar la temperatura ambiente la mezcla de reacción se filtró sobre Kieselguhr y la torta del filtro se lavó con etanol. Los solventes se retiraron al vacío y el residuo se purificó por cromatografía en columna (SiO2, Et2O: hexanos 1:1) para producir etil éster del ácido 2,2-difluoro-3-(2-(4-octiloxi-fenil)-morfolin-4-il)-propiónico (0,58 g).

etil éster del ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-2,2-difluoro-propiónico se obtuvo de acuerdo con un modo similar.



etil éster del ácido 3-[2-(4-Octiloxi-fenil)-morfolin-4-il]-3-oxo-propiónico: A una suspensión de 2-(4-octiloxi-fenil)-morfolina (0,97 g; 3,3 mmol) y N-etildiisopropilamina (1,14 ml; 6,7 mmol) en CH3CN (10 ml) se agregó gota a gota cloruro etílico de malonilo (0,51 ml; 4,0 mmol). La mezcla resultante se agitó durante una hora a temperatura ambiente y con posterioridad se repartió entre solución acuosa al 5% de NaHCO3 y Et2O. La fase orgánica se secó (Na2SO4), se filtró, y se concentró al vacío. El residuo se purificó por cromatografía en columna (SiO2, Et2O) para producir etil éster del ácido 3-[2-(4-octiloxi-fenil)-morfolin-4-il]-3-oxo-propiónico (0,50 g).

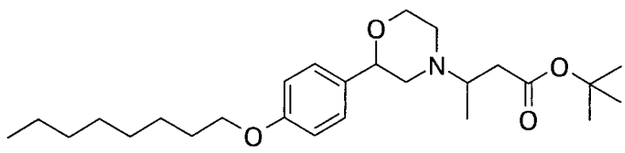
etil éster del ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-3-oxo-propiónico se obtuvo de acuerdo con un modo similar.



éster ter-butílico del ácido 2-Metil-3-[2-(4-octiloxi-fenil)-morfolin-4-il]-propiónico A una suspensión de 2-(4-octiloxi-fenil)-morfolina, como clorhidrato (0,17 g; 0,5 mmol) en DMF (5,00 ml) se agregó metacrilato de ter-butilo (0,17 ml; 1,0 mmol) y DBU (0,23 ml; 1,5 mmol) La mezcla resultante se calentó a 140°C en un matraz sellado hasta la mañana siguiente. Después de enfriar hasta alcanzar la temperatura ambiente la mezcla de

reacción se repartió entre solución acuosa al 5% de NaHCO3 y EtOAc. Las fases se separaron y la fase orgánica se secó (Na2SO4), se filtró y se concentró. El residuo se purificó por cromatografía en columna (SiO2, Et2O: hexanos 1:1) para producir éster ter-butílico del ácido 2-metil-3-[2-(4-octiloxi-fenil)-morfolin-4-il]-propiónico (0,11 g).

El éster ter-butílico del ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-2-metil-propiónico se obtuvo de acuerdo con un modo similar.



éster ter-butílico del ácido 3-[2-(4-Octiloxi-fenil)-morfolin-4-il]-butírico: Una mezcla de éster ter-butílico del ácido 2-(4-octiloxi-fenil)-morfolina (0,24 gram, 1,1 mmol), 3-bromobutírico (0,24 g; 1,1 mmol), yoduro de sodio (27,4 mg; 0,2 mmol), y DBU (0,4 ml; 2,7 mmol) en CH3CN (10 ml) se calentó en un recipiente cerrado a 120°C. Después de enfriar hasta alcanzar la temperatura ambiente la mezcla de reacción se repartió entre solución acuosa al 5% de NaHCO3 y EtOAc. Las fases se separaron y la fase orgánica se secó (Na2SO4), se filtró y se concentró. El residuo se purificó por cromatografía en columna (SiO2, Et2O) para producir éster ter-butílico del ácido 3-[2-(4-octiloxi-fenil)-morfolin-4-il]-butírico (0,15 g).

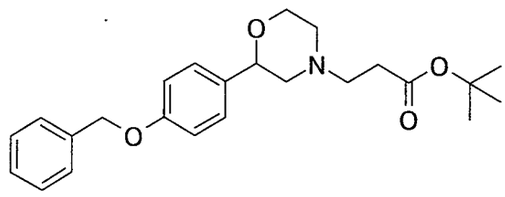
éster ter-butílico del ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-butírico se obtuvo de acuerdo con un modo similar. El éster ter-butílico del ácido 3-bromobutírico requerido se preparó de la siguiente manera: A una solución de ácido 3-bromobutírico (5,0 ml; 47,0 mmol) en tetrahidrofurano (50 ml) se agregó gota a gota anhídrido trifluoroacético (13,7 ml; 98,7 mmol) a -40°C. Después de 1 hora a -40°C se agregó alcohol ter-butílico (20 ml). La mezcla resultante se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó hasta la mañana siguiente. Con posterioridad, la mezcla de reacción se concentró al vacío. El residuo se sometió a tratamiento con solución acuosa 2M de NaOH y se extrajo con Et2O. La fase orgánica se secó (Na2SO4), y se concentró al vacío para producir éster ter-butílico del ácido 3-bromobutírico (6,05 g), que se utilizó tal como estaba.

3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-2,2-dimetil-propiónico éster metílico del ácido: A una solución de éster metílico del ácido 2,2-dimetil-3-oxo-propiónico (WHSS0374-001) (0,90 g; 5,44 mmol) en 1,2-dicloroetano (20 ml) se agregó 2-[4-(2,6-dicloro-benciloxi)-fenil]-morfolina (0,91 g, 2,7 mmol) y NaBH(OAc)3 (1,62 g; 7,62 mmol). La mezcla resultante se agitó hasta la mañana siguiente a temperatura ambiente, y con

posterioridad se trató con NaHCO3 acuoso al 5 % (10 ml) y se extrajo con CH2Cl2 (3 X 30 ml). Las fases orgánicas combinadas se secaron (Na2SO4), se filtró y se concentró al vacío. El residuo se purificó por cromatografía en columna (SiO2, Et2O/hexanos 1:1) para producir éster metílico del ácido 3-{2-[4-(2,6-dicloro-benciloxi)-fenil]-morfolin-4-il}-2,2-dimetil-propiónico (1,12 g) como un aceite incoloro transparente. El requerido éster metílico del ácido 2,2-dimetil-3-oxo-propiónico se preparó de la siguiente manera: A una solución de éster metílico del ácido 2,2-dimetil-3-hidroxipropiónico (10,00 g; 75,7 mmol) en CH2Cl2 (200 ml) se agregó cloroformiato de piridinio (28,54 g; 132,4 mmol) en pequeñas porciones, a 0°C. La mezcla de reacción se dejó entibiar lentamente hasta alcanzar la temperatura ambiente y se agitó hasta la mañana siguiente. Con posterioridad, la mezcla se diluyó con CH2Cl2, se filtró sobre kieselguhr, y se concentró al vacío. El aceite remanente se purificó por cromatografía en columna (SiO2, hexanos/Et2O 7:3) para producir éster metílico del ácido 2,2-dimetil-3-oxo-propiónico (5,59 g)

El siguiente compuesto se realizó de acuerdo con un método similar:

éster ter-butílico del ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-ciclobutanocarboxílico. El éster ter-butílico del ácido 3-oxo-ciclobutanocarboxílico requerido se preparó como se describe en: R. P. Lemieux, G. B. Schuster, J. Org. Chem., 1993, 58, 100.



éster ter-butílico del ácido 3-{2-[4-(Benciloxi)-fenil]-morfolin-4-il}-propiónico: Una mezcla de éster ter-butílico del ácido 3-[2-(4-hidroxi-fenil)-morfolin-4-il]-propiónico) (76,8 mg; 0,25 mmol), Cs2CO3 (241 mg; 0,74 mmol), y NaI (3,7 mg, 25 □mol) en CH3CN /THF (6:4; 2,5 ml) se agitó durante tres horas a temperatura ambiente. Con posterioridad, se agregó cloruro de bencilo (35 □L; 0,3 mmol) en CH3CN (1 ml) se agregó y la mezcla resultante se calentó a 60°C, durante 20h. Después de enfriar hasta alcanzar la temperatura ambiente los solventes se retiraron al vacío. El residuo se repartió entre CH2Cl2 y K2CO3 1M acuoso. Las fases se separaron y la fase acuosa se lavó con CH2Cl2. Las fases orgánicas combinadas se concentraron al vacío, y el residuo se secó con aplicación de vacío, a 40°C, hasta la mañana siguiente. El producto obtenido se utilizó como estaba en una etapa posterior.

Los siguientes compuestos se obtuvieron de acuerdo con un modo similar:

éster ter-butílico del ácido 3-{2-[4-(6-Metil-imidazo[1,2-a]piridin-2-ilmetoxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-(2-{4-[3-(2-Propil-tiazol-5-iloxi)-propoxi]-fenil}-morfolin-4-il)-propiónico

éster ter-butílico del ácido 3-{2-[4-(2-Benciloxi-etoxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(2-Fenoxi-etoxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-[2-(4-Hex-5-iniloxi-fenil)-morfolin-4-il]-propiónico

éster ter-butílico del ácido 3-{2-[4-(4-Acetoxi-butoxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-(2-{4-[3-(4-Fluoro-fenoxi)-propoxi]-fenil}-morfolin-4-il)-propiónico

éster ter-butílico del ácido 3-(2-{4-[2-(Naftalen-2-iloxi)-etoxi]-fenil}-morfolin-4-il)-propiónico

éster ter-butílico del ácido 3-[2-(4-Fenilcarbamoilmetoxi-fenil)-morfolin-4-il]-propiónico

éster ter-butílico del ácido 3-{2-[4-(4-Pirazol-1-il-benciloxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(1-Metil-1H-pirazol-3-ilmetoxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(4-Cloro-benciloxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(6-Ciano-hexiloxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-[2-(4-Fenetiloxi-fenil)-morfolin-4-il]-propiónico

éster ter-butílico del ácido 3-{2-[4-(3-Fenil-propoxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(3-Benciloxi-propoxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(7-Metoxi-heptiloxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-(2-{4-[3-(4-ter-butil-fenil)-[1,2,4]oxadiazol-5-ilmetoxi]-fenil}-morfolin-4-il)-propiónico

éster ter-butílico del ácido 3-{2-[4-(5-Oxo-hexiloxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(4-Fenil-butoxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(3-Metoxi-benciloxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(2-Cloro-benciloxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-[2-(4-Ciclohexilmetoxi-fenil)-morfolin-4-il]-propiónico

éster ter-butílico del ácido 3-{2-[4-(2-Bencenosulfonil-etoxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(3-Fenoxi-propoxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(4-[1,2,4]Triazol-1-il-benciloxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(2,3-Dihidro-benzofuran-2-ilmetoxi)-fenil]-morfolin-4-il}-propiónico

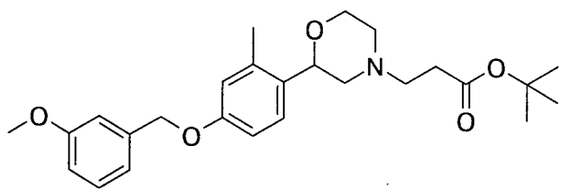
éster ter-butílico del ácido 3-{2-[4-(2-Bifenil-4-il-2-oxo-etoxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(4-Fenoxi-butoxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(2-Oxo-2-fenil-etoxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(3-Cloro-benciloxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-(2-{4-[2-(1H-Indol-3-il)-etoxi]-fenil}-morfolin-4-il)-propiónico



éster ter-butílico del ácido 3-{2-[4-(3-Metoxi-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico: A una solución de (3-metoxialcohol bencílico (0,25M, 450µl) en THF se agregó una solución de éster ter-butílico del ácido 3-[2-(4-hidroxi-2-metil-fenil)-morfolin-4-il]-propiónico (0,25M, 360 µl) en THF. A esta mezcla se agregó una solución de DIAD en THF (0,25M, 360 µl). Finalmente, se agregó trifenilfosfina con soporte de poliestireno (~190 mg, 1,2 mmol/g) seguido de THF (1 ml). La mezcla de reacción se agitó con intervalo durante 20 horas a 30 °C. Con posterioridad, se agregaron más DIAD (360□l, 0,25M en THF) y trifenilfosfina con soporte de poliestireno (95 mg, 1,2 mmol/g). La mezcla se agitó nuevamente con intervalo durante 20 horas a 30 °C. A la mezcla resultante se agregó resina de carbonato microporoso (~90mg, 3,06 mmol/g, Argonaut Technologies) y la mezcla se agitó nuevamente con intervalo durante 20 horas a 50 °C.

La mezcla se transfirió a un cartucho de Intercambio Catiónico Fuerte acondicionado con Metanol y THF (IST, 0,5g, 0,6 mmol/g), se lavó con THF (6ml) y CH3CN (8ml) consecutivamente antes de eluir con NH4OH 1N en CH3CN (6ml). La concentración al vacío produjo éster ter-butílico del ácido 3-{2-[4-(3-Metoxi-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico (~15mg), que se utilizó tal como estaba.

Los siguientes compuestos se obtuvieron de acuerdo con un modo similar:

éster ter-butílico del ácido 3-{2-[4-(5-Bromo-2-metoxi-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(2,4-Dicloro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(2,3-Dimetoxi-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-[2-(4-Ciclopentilmetoxi-2-metil-fenil)-morfolin-4-il]-propiónico

éster ter-butílico del ácido 3-{2-[4-(2,5-Dicloro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[2-Metil-4-(piridin-3-ilmetoxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[2-Metil-4-(naftalen-2-ilmetoxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(Benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(2-Metoxi-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[2-Metil-4-(6-metil-piridin-2-ilmetoxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(2-Cloro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(2,5-Dimetoxi-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(2-Bromo-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[2-Metil-4-(2-metil-benciloxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(6,6-Dimetil-biciclo[3,1,1]hept-2-ilmetoxi)-2-metil-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(2-Cloro-6-fluoro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(Bifenil-2-ilmetoxi)-2-metil-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[2-Metil-4-(2-trifluorometil-benciloxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(3,5-Dicloro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[2-Metil-4-(3-trifluorometil-benciloxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(4-Cloro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(4-Isopropil-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[2-Metil-4-(3-fenoxi-benciloxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(4-Metoxi-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[2-Metil-4-(2-fenetil-benciloxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(3,4-Dimetoxi-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(3,5-Dimetil-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(4-Benciloxi-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[2-Metil-4-(tiofen-2-ilmetoxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(3-Fluoro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(3-Benciloxi-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(4-Fluoro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico

ter-butílico del ácido 3-{2-[4-(Bifenil-4-ilmetoxi)-2-metil-fenil]-morfolin-4-il}-propiónico éster

éster ter-butílico del ácido 3-{2-[4-(2,3-Dihidro-benzo[1,4]dioxin-2-ilmetoxi)-2-metil-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[2-Metil-4-(piridin-2-ilmetoxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(4-Butoxi-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-[2-(4-Ciclohexilmetoxi-2-metil-fenil)-morfolin-4-il]-propiónico

éster ter-butílico del ácido 3-{2-[2-Metil-4-(tetrahidro-furan-2-ilmetoxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[2-Metil-4-(3-metil-benciloxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(2,3-Difluoro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[2-Metil-4-(4-trifluorometoxi-benciloxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(3-Cloro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[2-Metil-4-(tetrahidro-piran-2-ilmetoxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[2-Metil-4-(4-trifluorometil-benciloxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(3,4-Difluoro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[2-Metil-4-(2,3,4-trimetoxi-benciloxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(Ciclohex-3-enilmetoxi)-2-metil-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(4-Butil-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[2-Metil-4-(4-metil-benciloxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(3-Dimetilamino-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[2-Metil-4-(piridin-4-ilmetoxi)-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(2-Yodo-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(3,5-Dimetoxi-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(2,4-Difluoro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[2-Metil-4-(2,4,5-trimetoxi-benciloxi)-fenil]-morfolin-4-il}-propiónico

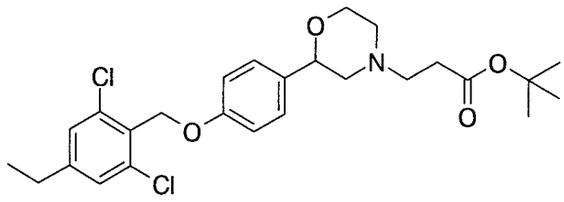
éster ter-butílico del ácido 3-{2-[4-(3-Bromo-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico

éster ter-butílico del ácido 3-{2-[4-(4-Bromo-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico

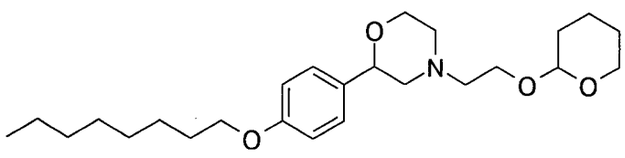
éster ter-butílico del ácido 3-{2-[4-(4-ter-butil-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico

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éster ter-butílico del ácido 3-{2-[2-Metil-4-(tetrahidro-furan-3-ilmetoxi)-fenil]-morfolin-4-il}-propiónico



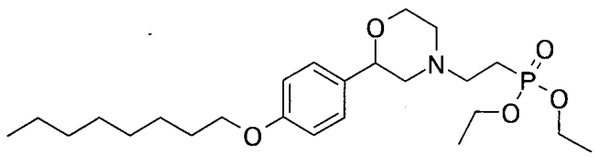
éster ter-butílico del ácido 3-{2-[4-(2,6-Dicloro-4-etil-benciloxi)-fenil]-morfolin-4-il}-propiónico: éster ter-butílico del ácido 3-{2-[4-(2,6-Dicloro-4-yodo-benciloxi)-fenil]-morfolin-4-il}-propiónico (0,34 g; 0,57 mmol), y Pd(dppf)Cl2 (14,70 mg; 0,02 mmol) se agregaron a una solución de cloruro de litio (4,59 ml; 0,50 mol/l; 2,30 mmol) en THF; 0,04 eq.). La mezcla resultante se enfrió hasta 0°C y una solución de dietilzinc in n-heptano (1,15 ml; 1,00 mol/l; 1,15 mmol) se agregó gota a gota. La mezcla se calentó hasta 60°C hasta la mañana siguiente. Después de enfriar hasta alcanzar la temperatura ambiente se agregó NH4Cl acuoso saturado. La mezcla se extrajo con EtOAc. La fase orgánica se secó (MgSO4), se filtró y se concentró al vacío. El residuo se purificó por cromatografía en columna (SiO2, EtOAc: hexanos 1:1) para producir éster ter-butílico del ácido 3-{2-[4-(2,6-dicloro-4-etil-benciloxi)-fenil]-morfolin-4-il}-propiónico (115,00 mg)



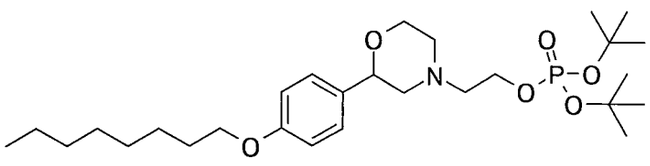
2-(4-Octiloxi-fenil)-4-[2-(tetrahidro-piran-2-iloxi)-etil]-morfolina: Una mezcla de 2-(4-octiloxi-fenil)-morfolina (1,99 g; 6,8 mmol), 2-(2-cloroetoxi)tetrahidro-2H-piran (1,21 ml; 8,2 mmol), K2CO3 (1,89 g; 13,7 mmol) y NaI (0,20 g; 1,4 mmol) en DMF (15 ml) se calentó hasta 100oC hasta la mañana siguiente. Después de enfriar hasta alcanzar la temperatura ambiente la mezcla de reacción se repartió entre solución acuosa al 5% de NaHCO3 y

Et2O. La fase orgánica se secó (Na2SO4), se filtró, y se concentró al vacío. El residuo se purificó por cromatografía en columna (SiO2, EtOAc) para producir 2-(4-octiloxi-fenil)-4-[2-(tetrahidro-piran-2-iloxi)-etil]-morfolina (2,04 g).

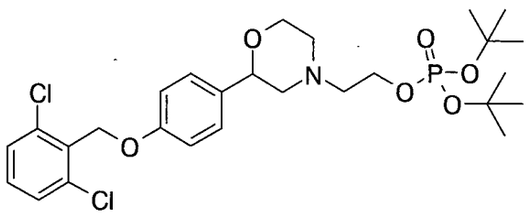
2-[4-(2,6-Dicloro-benciloxi)-fenil]-4-[2-(tetrahidro-piran-2-iloxi)-etil]-morfolina se obtuvo de acuerdo con un modo similar.



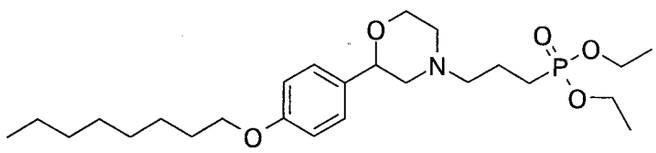
éster dietílico del ácido {2-[2-(4-Octiloxi-fenil)-morfolin-4-il]-etil}-fosfónico: Una mezcla de 2-(4-octiloxi-fenil)-morfolina (0,83 g; 2,9 mmol) y vinilfosfonato de dietilo (0,53 ml; 3,4 mmol) en CH3CN (10 ml) se calentó a reflujo durante 3 días. Después de enfriar hasta alcanzar la temperatura ambiente la mezcla se concentró al vacío y el residuo se purificó por cromatografía en columna (SiO2, EtOAc: MeOH 90:10) para producir éster dietílico del ácido {2-[2-(4-octiloxi-fenil)-morfolin-4-il]-etil}-fosfónico (0,42 g)



2-[2-(4-octiloxi-fenil)-morfolin-4-il]-etil éster de di-ter-butil éster del ácido fosfórico: A una solución de 2-[2-(4-octiloxi-fenil)-morfolin-4-il]-etanol (1,33 g; 4,0 mmol) en una mezcla de THF (15 ml) y CH2Cl2 (15 ml) se agregó una solución de tetrazol en CH3CN (17,6 ml; 0,45 mol/L; 7,9 mmol) a temperatura ambiente. La mezcla resultante se agitó durante 30 minutos y con posterioridad di-ter-butil N,N-diisopropilfosforoamidita (2,00 ml; 6,3 mmol) se agregó y se agitó hasta la mañana siguiente a temperatura ambiente. Con posterioridad, una solución acuosa de peróxido de hidrógeno (1,80 ml; 300 g/l; 15,9 mmol) se agregó y la mezcla se agitó a temperatura ambiente durante otros 15 min La reacción se desactivó por medio de la incorporación de una solución acuosa al 5% de NaHCO3 y se extrajo con EtOAc. La fase orgánica se secó (Na2SO4), se filtró y se concentró al vacío. El residuo se purificó por cromatografía en columna (SiO2, Et2O) para producir 2-[2-(4-octiloxi-fenil)-morfolin-4-il]-etil éster de di-ter-butil éster del ácido fosfórico (0,71 g).



2-{2-[4-(2,6-dicloro-benciloxi)-fenil]-morfolin-4-il}-etil éster de di-ter-butil éster del ácido fosfórico: A una solución de 2-{2-[4-(2,6-dicloro-benciloxi)-fenil]-morfolin-4-il}-etanol (0,74 g; 1,94 mmol) en una mezcla de THF (10 ml) y CH2Cl2 (10 ml) se agregó una solución de tetrazol en CH3CN ((8,60 ml; 0,45 mol/l; 3,87 mmol) a temperatura ambiente. La mezcla resultante se agitó durante 30 minutos y con posterioridad N,N-diisopropilfosforoamidita de di-ter-butilo (0,98 ml; 3,10 mmol) se agregó y se agitó hasta la mañana siguiente a temperatura ambiente. Con posterioridad, la mezcla se enfrió hasta 4°C, y se agregó una solución de ter-butilo hidroperóxido en nonano (0,31 ml; ~5,5 mol/L, 2,90 mmol). A partir de entonces la mezcla se agitó a temperatura ambiente durante otros 30 min La reacción se desactivó por medio de la incorporación de una solución acuosa al 5% de NaHCO3 y se extrajo con EtOAc. La fase orgánica se secó (Na2SO4), se filtró y se concentró al vacío. El residuo se purificó por cromatografía en columna (SiO2, EtOAc) para producir 2-{2-[4-(2,6-dicloro-benciloxi)-fenil]-morfolin-4-il}-etil éster de di-ter-butil éster del ácido fosfórico (0,66 g).



éster dietílico del ácido {2-[2-(4-Octiloxi-fenil)-morfolin-4-il]-propil}-fosfónico: Una mezcla de 2-(4-octiloxi-fenil)-morfolina (1,04 g; 3,6 mmol), dietil (3-bromopropil)fosfonato (0,82 ml; 4,3 mmol), NaI (0,11 g; 0,7 mmol), y K2CO3 (0,99 g; 7,1 mmol) en CH3CN (10 ml) se calentó a reflujo durante 2 horas. Después de enfriar hasta alcanzar la temperatura ambiente la mezcla se repartió entre solución acuosa al 5% de NaHCO3 y Et2O. La fase orgánica se secó (Na2SO4), se filtró y se concentró al vacío. El residuo se purificó por cromatografía en columna (SiO2, EtOAc : MeOH 90:10) para producir éster dietílico del ácido {2-[2-(4-octiloxi-fenil)-morfolin-4-il]-propil}-fosfónico (1,13 g).

éster dietílico del ácido (3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-propil)-fosfónico se obtuvo de acuerdo con un modo similar.

§4. SÍNTESIS DE SPECIFIC COMPUESTOS

(Ver Tablas)

Método A:

Compuesto 1 ácido (3-{2-[4-(benciloxi)-fenil]-morfolin-4-il}-propiónico): El compuesto en bruto éster ter-butílico del ácido 3-{2-[4-(benciloxi)-fenil]-morfolin-4-il}-propiónico (ver §3) se sometió a tratamiento con una mezcla de TFA, agua, y CH2Cl2 (30:3:67; 3 ml) y se agitó a temperatura ambiente durante 2h. Con posterioridad, los elementos volátiles se retiraron al vacío, y el producto en bruto se purificó por HPLC preparativa para producir sal del ácido trifluoroacético del ácido 3-{2-[4-(benciloxi)-fenil]-morfolin-4-il}-propiónico; Rt = 1,86 min (Sistema A), [M+H]+ Experimental: 342,19; Calc: 342,17. Condiciones para la LC-MS preparativa: Inyección del producto en bruto disuelto en 600µL DMSO/CH3CN 1:2; columna Waters Sunfire 19x100mm 5 µm 45°C, fase móvil agua/CH3CN/TFA 0,1% 25 ml/min, ciclo 20 min 10%-90% CH3CN, detección con UV 210-260nm.

Los siguientes compuestos se obtuvieron de manera similar:

Compuesto 2; sal del ácido trifluoroacético del ácido 3-{2-[4-(6-Metil-imidazo[1,2-a]piridin-2-ilmetoxi)-fenil]-morfolin-4-il}-propiónico Rt = 0,76 min (Sistema A), [M+H]+ Experimental: 396,23; Calc: 396,19.

Compuesto 3; sal del ácido trifluoroacético del ácido 3-(2-{4-[3-(2-Propil-tiazol-5-iloxi)-propoxi]-fenil}-morfolin-4-il)-propiónico Rt = 2,04 min (Sistema A), [M+H]+ Experimental: 435,21; Calc: 435,20.

Compuesto 4; sal del ácido trifluoroacético del ácido 3-{2-[4-(2-Benciloxi-etoxi)-fenil]-morfolin-4-il}-propiónico Rt = 1,89 min (Sistema A), [M+H]+ Experimental: 386,22; Calc: 386,20.

Compuesto 5; sal del ácido trifluoroacético del ácido 3-{2-[4-(2-Fenoxi-etoxi)-fenil]-morfolin-4-il}-propiónico Rt = 1,91 min (Sistema A), [M+H]+ Experimental: 372,21; Calc: 372,18.

Compuesto 6; sal del ácido trifluoroacético del ácido 3-[2-(4-Hex-5-iniloxi-fenil)-morfolin-4-il]-propiónico Rt = 1,77 min (Sistema A), [M+H]+ Experimental: 332,21; Calc: 332,19.

Compuesto 7; sal del ácido trifluoroacético del ácido 3-{2-[4-(4-Acetoxi-butoxi)-fenil]-morfolin-4-il}-propiónico Rt = 1,51 min (Sistema A), [M+H]+ Experimental: 366,21; Calc: 366,19.

Compuesto 8; sal del ácido trifluoroacético del ácido 3-(2-{4-[3-(4-Fluoro-fenoxi)-propoxi]-fenil}-morfolin-4-il)-propiónico Rt = 2,16 min (Sistema A), [M+H]+ Experimental: 404,22; Calc: 404,19.

Compuesto 9; sal del ácido trifluoroacético del ácido 3-(2-{4-[2-(Naftalen-2-iloxi)-etoxi]-fenil}-morfolin-4-il)-propiónico Rt = 2,35 min (Sistema A), [M+H]+ Experimental: 422,24; Calc: 422,20.

Compuesto 10; sal del ácido trifluoroacético del ácido 3-[2-(4-Fenilcarbamoilmetoxi-fenil)-morfolin-4-il]-propiónico Rt = 1,48 min (Sistema A), [M+H]+ Experimental: 385,20; Calc: 385,18.

Compuesto 11; sal del ácido trifluoroacético del ácido 3-{2-[4-(4-Pirazol-1-il-benciloxi)-fenil]-morfolin-4-il}-propiónico Rt = 1,83 min (Sistema A), [M+H]+ Experimental: 408,22; Calc: 408,19.

Compuesto 12; sal del ácido trifluoroacético del ácido 3-{2-[4-(1-Metil-1H-pirazol-3-ilmetoxi)-fenil]-morfolin-4-il}-propiónico Rt = 1,14 min (Sistema A), [M+H]+ Experimental: 346,20; Calc: 346,18.

Compuesto 13; 3-{2-[4-(4-Cloro-benciloxi)-fenil]-morfolin-4-il}-propiónico sal del ácido trifluoroacético del ácido Rt = 2,14 min (Sistema A), [M+H]+ Experimental: 376,13; Calc: 376,13.

Compuesto 14; sal del ácido trifluoroacético del ácido 3-{2-[4-(6-Ciano-hexiloxi)-fenil]-morfolin-4-il}-propiónico Rt = 1,68 min (Sistema A), [M+H]+ Experimental: 361,24; Calc: 361,21.

Compuesto 15; sal del ácido trifluoroacético del ácido 3-[2-(4-Fenetiloxi-fenil)-morfolin-4-il]-propiónico Rt = 1,93 min (Sistema A), [M+H]+ Experimental: 356,23; Calc: 356,19.

Compuesto 16; sal del ácido trifluoroacético del ácido 3-{2-[4-(3-Fenil-propoxi)-fenil]-morfolin-4-il}-propiónico Rt = 2,11 min (Sistema A), [M+H]+ Experimental: 370,24; Calc: 370,20.

Compuesto 17; sal del ácido trifluoroacético del ácido 3-{2-[4-(3-Benciloxi-propoxi)-fenil]-morfolin-4-il}-propiónico Rt = 1,97 min (Sistema A), [M+H]+ Experimental: 400,26; Calc: 400,21.

Compuesto 18; sal del ácido trifluoroacético del ácido 3-{2-[4-(7-Metoxi-heptiloxi)-fenil]-morfolin-4-il}-propiónico Rt = 2,04 min (Sistema A), [M+H]+ Experimental: 380,27; Calc: 380,24.

Compuesto 19; sal del ácido trifluoroacético del ácido 3-(2-{4-[3-(4-ter-butil-fenil)-[1,2,4]oxadiazol-5-ilmetoxi]-fenil}-morfolin-4-il)-propiónico Rt = 2,67 min (Sistema A), [M+H]+ Experimental: 466,27; Calc: 466,23.

Compuesto 20; sal del ácido trifluoroacético del ácido 3-{2-[4-(5-Oxo-hexiloxi)-fenil]-morfolin-4-il}-propiónico Rt = 1,35 min (Sistema A), [M+H]+ Experimental: 350,22; Calc: 350,20.

Compuesto 21; 3 sal del ácido trifluoroacético del ácido -{2-[4-(4-Fenil-butoxi)-fenil]-morfolin-4-il}-propiónico Rt = 2,38 min (Sistema A) , [M+H]+ Experimental: 384,25; Calc: 384,22.

Compuesto 22; sal del ácido trifluoroacético del ácido 3-{2-[4-(3-Metoxi-benciloxi)-fenil]-morfolin-4-il}-propiónico Rt = 1,75 min (Sistema A).

Compuesto 23; sal del ácido trifluoroacético del ácido 3-{2-[4-(2-Cloro-benciloxi)-fenil]-morfolin-4-il}-propiónico Rt = 1,99 min (Sistema A), [M+H]+ Experimental: 376,18; Calc: 376,13.

Compuesto 24; sal del ácido trifluoroacético del ácido 3-[2-(4-Ciclohexilmetoxi-fenil)-morfolin-4-il]-propiónico Rt = 2,26 min (Sistema A), [M+H]+ Experimental: 348,27; Calc: 348,22.

Compuesto 25; sal del ácido trifluoroacético del ácido 3-{2-[4-(2-Bencenosulfonil-etoxi)-fenil]-morfolin-4-il}-propiónico Rt = 1,45 min (Sistema A), [M+H]+ Experimental: 420,18; Calc: 420,15.

Compuesto 26; sal del ácido trifluoroacético del ácido 3-{2-[4-(3-Fenoxi-propoxi)-fenil]-morfolin-4-il}-propiónico Rt = 2,12 min (Sistema A), [M+H]+ Experimental: 386,21; Calc: 386,20.

Compuesto 27; sal del ácido trifluoroacético del ácido 3-{2-[4-(4-[1,2,4]Triazol-1-il-benciloxi)-fenil]-morfolin-4-il}-propiónico Rt = 1,46 min (Sistema A), [M+H]+ Experimental: 409,22; Calc: 409,19.

Compuesto 28; sal del ácido trifluoroacético del ácido 3-{2-[4-(2,3-Dihidro-benzofuran-2-ilmetoxi)-fenil]-morfolin-4-il}-propiónico Rt = 1,94 min (Sistema A), [M+H]+ Experimental: 384,21; Calc: 384,18.

Compuesto 29; sal del ácido trifluoroacético del ácido 3-{2-[4-(2-Bifenil-4-il-2-oxo-etoxi)-fenil]-morfolin-4-il}-propiónico Rt = 2,30 min (Sistema A), [M+H]+ Experimental: 446,23; Calc: 446,20.

Compuesto 30; sal del ácido trifluoroacético del ácido 3-{2-[4-(4-Fenoxi-butoxi)-fenil]-morfolin-4-il}-propiónico Rt = 2,25 min (Sistema A), [M+H]+ Experimental: 400,24; Calc: 400,21.

Compuesto 31; sal del ácido trifluoroacético del ácido 3-{2-[4-(2-Oxo-2-fenil-etoxi)-fenil]-morfolin-4-il}-propiónico Rt = 1,60 min (Sistema A), [M+H]+ Experimental: 370,18; Calc: 370,17.

Compuesto 32; sal del ácido trifluoroacético del ácido 3-{2-[4-(3-Cloro-benciloxi)-fenil]-morfolin-4-il}-propiónico Rt = 2,09 min (Sistema A), [M+H]+ Experimental: 376,16; Calc: 376,13.

Compuesto 33; sal del ácido trifluoroacético del ácido 3-(2-{4-[2-(1H-Indol-3-il)-etoxi]-fenil}-morfolin-4-il)-propiónico Rt = 1,99 min (Sistema A), [M+H]+ Experimental: 395,22; Calc: 395,20.

Método B:

Compuesto 34; ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-propiónico. éster ter-butílico del ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-propiónico (0,59 g; 1,27 mmol) se disolvió en una solución 4M de HCl en 1,4-dioxano (6,33 ml, 25,30 mmol) y se agitó hasta la mañana siguiente a temperatura ambiente. Con posterioridad, el solvente se retiró al vacío y el residuo se trató con iPr2O, el precipitado se recolectó por filtración sobre y se secó hasta la mañana siguiente bajo presión reducida para producir clorhidrato del ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-propiónico (0,50 g). 1H RMN (400 MHz, DMSO-d6) □ ppm 2,88 - 2,97 (2 H, m) 3,11 (1 H, t, J=11,7 Hz) 3,15 - 3,23 (1 H,m) 3,30 - 3,43 (2 H, m) 3,49 (1 H, d, J=12,0 Hz) 3,55 - 3,64 (1 H, m) 4,01 - 4,20 (2 H, m) 4,88 (1 H, d,J=12,0 Hz) 5,24 (2 H, s) 7,04 - 7,12 (2 H, m) 7,35 (2 H, d, J=8,7 Hz) 7,40 - 7,49 (1 H, m) 7,49 - 7,56 (2H, m).

Los siguientes compuestos se obtuvieron de acuerdo con un modo similar:

Compuesto 34a; clorhidrato del ácido (+)-3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-propiónico ([□]D25 = +7 (c 1,0, MeOH)). 1H RMN (400 MHz, DMSO-d6) □ ppm 2,82 - 2,96 (m, 2 H) 3,09 (d, J=0,37 Hz, 2 H) 3,34 (br. s., 2 H) 3,43 - 3,52 (m, 1 H3,95 - 4,07 (m, 1 H) 4,09 - 4,20 (m, 1 H) 4,78 - 4,88 (m, 1 H) 5,24 (s, 2 H) 7,06 - 7,14 (m, 2 H) 7,30 - 7,39 (m, 2 H) 7,43 - 7,51 (m, 1 H) 7,54 - 7,62 (m, 2 H)

Compuesto 34b; clorhidrato del ácido (-)-3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-propiónico ([□]D25 = -7 (c 1,0, MeOH)). 1H RMN (400 MHz, DMSO-d6) □ ppm 2,84 - 2,96 (m, 2 H) 3,09 (s, 2 H) 3,34 (br. s., 2 H) 3,43 - 3,52 (m, 1 H) 3,97 - 4,08 (m, 1 H) 4,09 - 4,18 (m, 1 H) 4,79 - 4,89 (m, 1 H) 5,24 (s, 2 H) 7,07 - 7,15 (m, 2 H) 7,31 - 7,38 (m, 2 H) 7,43 - 7,51 (m, 1 H) 7,54 - 7,60 (m, 2 H).

Compuesto 35; clorhidrato del ácido 3-(2-(4-Octil-fenil)-morfolin-4-il)-propiónico. 1H RMN (400 MHz, DMSO-d6) □ ppm 0,55 - 0,71 (m, 3 H) 1,04 (br, 10 H) 1,25 - 1,43 (m, 2 H) 2,23 - 2,44 (m, 2 H) 2,55 - 2,73 (m, 2 H) 2,78 - 3,04 (m, 2 H) 3,08 - 3,53 (m, 4 H) 3,67 - 4,07 (m, 2 H) 4,48 - 4,69 (m, 1 H) 6,90 - 7,25 (m, 4 H).

Compuesto 36; clorhidrato del ácido 4-[2-(4-Octil-fenil)-morfolin-4-il]-butírico. 1H RMN (600 MHz, DMSO-d6) □ ppm 0,86 (t, J=6,8 Hz, 3 H) 1,19 - 1,33 (m, 10 H) 1,52 - 1,60 (m, 2 H) 1,94 - 2,02 (m, 2 H) 2,36 (t, J=7,2 Hz, 2 H) 2,57 (t, J=7,7 Hz, 2 H) 3,03 - 3,18 (m, 4 H) 3,58 - 3,68 (m, 2 H) 4,10 - 4,19 (m, 2 H) 4,84 – 4,89 (m, 1 H) 7,22 (d, J=8,6 Hz, 2 H) 7,30 (d, J=8,6 Hz, 2 H).

Compuesto 37; clorhidrato del ácido 3-[2-(4-Hexiloxi-fenil)-morfolin-4-il]-propiónico. 1H RMN (400 MHz, DMSO-d6) □ ppm 0,84 - 0,91 (m, 3 H) 1,27 - 1,34 (m, 4 H) 1,36 - 1,46 (m, 2 H) 1,66 - 1,74 (m, 2 H) 2,84 - 2,91 (m, 2 H) 3,02 - 3,18 (m, 2 H) 3,30 - 3,40 (m, 2 H) 3,44 - 3,51 (m, 1 H) 3,52 - 3,61 (m, 1 H) 3,91 - 4,02 (m, 3 H) 4,09 - 4,17 (m, 1 H) 4,74 - 4,81 (m, 1 H) 6,95 (d, J=8,7 Hz, 2 H) 7,29 (d, J=8,7 Hz, 2 H) 11,10 -12,90 (m, 2H).

Compuesto 38; clorhidrato del ácido 4-[2-(4-Hexiloxi-fenil)-morfolin-4-il]-butírico. 1H RMN (400 MHz, DMSO-d6) □ ppm 0,63 - 0,71 (m, 3 H) 1,05 - 1,15 (m, 4 H) 1,15 - 1,25 (m, 2 H) 1,44 - 1,53 (m, 2 H) 1,70 - 1,81 (m, 2 H) 2,14 (t, J=7,1 Hz, 2 H) 2,78 - 2,95 (m, 2 H) 3,11 - 3,39 (m, 4 H) 3,75 (t, J=6,4 Hz, 2 H) 3,78 - 3,84 (m, 1 H) 3,87 - 3,96 (m, 1 H) 4,56 - 4,64 (m, 1 H) 6,75 (d, J=8,7 Hz, 2 H) 7,09 (d, J=8,7 Hz, 2 H) 10,70-11,00 (bs, 1H).

Compuesto 39; clorhidrato del ácido 3-[2-(4-Heptiloxi-fenil)-morfolin-4-il]-propiónico. 1H RMN (400 MHz, DMSO-d6) □ ppm 0,59 - 0,68 (m, 3 H) 0,96 - 1,22 (m, 8 H) 1,40 - 1,52 (m, 2 H) 2,61 - 2,72 (m, 2 H) 2,78 - 2,96 (m, 2 H) 3,02 - 3,39 (m, 4 H) 3,67 - 3,81 (m, 3 H) 3,84 - 3,94 (m, 1 H) 4,57 (d, J=10,8 Hz, 1 H) 6,71 (d, J=8,7 Hz, 2 H) 7,05 (d, J=8,7 Hz, 2 H) 10,67 - 12,94 (m, 2 H).

Compuesto 40; clorhidrato del ácido 4-[2-(4-Heptiloxi-fenil)-morfolin-4-il]-butírico. 1H RMN (400 MHz, DMSO-d6) □ ppm 0,87 (t, J=7,0 Hz, 3 H) 1,22 - 1,35 (m, 6 H) 1,36 - 1,44 (m, 2 H) 1,66 - 1,74 (m, 2 H) 1,94 - 2,05 (m, 2 H) 2,34 (t, J=7,4 Hz, 2 H) 2,99 - 3,17 (m, 4 H) 3,43 - 3,57 (m, 2 H) 3,95 (t, J=6,4 Hz, 2 H) 4,03 - 4,14 (m, 2 H) 4,87 (d, J=10,2 Hz, 1 H) 6,94 (d, J=8,7 Hz, 2 H) 7,29 (d, J=8,7 Hz, 2 H) 10,80 - 11,20 (bs, 1 H) 12,00 – 12,40 (bs, 1 H).

Compuesto 41; clorhidrato del ácido 3-(2-(4-Octiloxi-fenil)-morfolin-4-il)-propiónico. 1H RMN (400 MHz, DMSO-d6) □ ppm 1,22 - 1,36 (8 H, m) 1,37 - 1,46 (2 H, m) 1,66 - 1,77 (2 H, m)2,85 - 2,92 (2 H, m) 3,08 (1 H, t, J=11,7 Hz) 3,13 - 3,21 (1 H, m) 3,29 - 3,41 (2 H, m) 3,48 (1 H, d)3,56 (1 H, d, J=12,3 Hz) 3,95 (2 H, t, J=6,5 Hz) 4,01 (1 H, t, J=12,2 Hz) 4,07 - 4,17 (1 H, m) 4,80 (1 H,d, J=10,8 Hz) 6,92 (2 H, dt, J=8,5, 0,7 Hz) 7,28 (2 H, d, J=9,0 Hz).

Compuesto 41a; clorhidrato del ácido (+)-3-[2-(4-Octiloxi-fenil)-morfolin-4-il]-propiónico a partir del Isómero 2 de éster ter-butílico del ácido 3-[2-(4-octiloxi-fenil)-morfolin-4-il]-propiónico, [□]D25 = +5 (c 1,0, MeOH); 1H RMN (400 MHz, DMSO-d6) □ ppm 0,81 - 0,92 (m, 3 H) 1,19 - 1,47 (m, 10 H) 1,64 - 1,77 (m, 2 H) 2,83 - 2,96 (m, 2 H) 3,03 - 3,21 (m, 2 H) 3,29 - 3,40 (m, 2 H) 3,48 (d, J=12,34 Hz, 1 H) 3,56 (d, J=12,34 Hz, 1 H) 3,95 (t, J=6,47 Hz, 2 H) 3,98 - 4,08 (m, 1 H) 4,08 - 4,18 (m, 1 H) 4,75 - 4,87 (m, 1 H) 6,88 - 6,97 (m, 2 H) 7,28 (d, J=8,73 Hz, 2H)

Compuesto 41b; clorhidrato del ácido (-)-3-[2-(4-Octiloxi-fenil)-morfolin-4-il]-propiónico a partir del Isómero 1 del éster ter-butílico del ácido 3-[2-(4-octiloxi-fenil)-morfolin-4-il]-propiónico, [□]D25 = -5 (c 1,0, MeOH); 1H RMN (400 MHz, DMSO-d6) □ ppm 0,57 - 0,76 (m, 3 H) 0,93 - 1,31 (m, 10 H) 1,40 - 1,58 (m, 2 H) 2,61 - 2,80 (m, 2 H) 2,80 - 3,01 (m, 2 H) 3,13 (t, J=7,83 Hz, 2 H) 3,20 - 3,45 (m, 2 H) 3,65 - 4,01 (m, 4 H) 4,63 (m, 1 H) 6,65 - 6,87 (m, 2 H) 7,09 (d, J=8,73 Hz, 2 H)

Compuesto 42; clorhidrato del ácido 4-[2-(4-Octiloxi-fenil)-morfolin-4-il]-butírico 1H RMN (600 MHz, DMSO-d6) □ ppm 0,86 (t, J=6,8 Hz, 3 H) 1,21 - 1,34 (m, 8 H) 1,36 - 1,44 (m, 2 H) 1,66 - 1,74 (m, 2 H) 1,95 - 2,05 (m, 2 H) 2,36 (t, J=7,2 Hz, 2 H) 3,03 - 3,19 (m, 4 H) 3,47 - 3,59 (m, 2 H) 3,95 (t, J=6,4 Hz, 2 H) 4,02 - 4,20 (m, 2 H) 4,86 (d, J=10,2 Hz, 1 H) 6,93 (d, J=8,7 Hz, 2 H) 7,30 (d, J=8,7 Hz, 2 H) 11,23 – 11,40 (bs, 1 H).

Compuesto 43; clorhidrato del ácido 2,2-Dimetil-3-(2-(4-octiloxi-fenil)-morfolin-4-il)-propiónico. 1H RMN (400 MHz, DMSO-d6) □ ppm 0,64 (t, J=6,32 Hz, 3 H) 0,86 - 1,25 (m, 17 H) 1,42 - 1,53 (m, J=6,96, 6,96, 6,85, 6,62 Hz, 2 H) 3,68 - 3,99 (m, 4 H) 4,73 (d, J=10,53 Hz, 1 H) 6,72 (d, 2 H) 7,06 (d, J=7,83 Hz, 2 H).

Compuesto 44; clorhidrato del ácido 3-[2-(4-octiloxi-fenil)-morfolin-4-il]-butírico 1H RMN (400 MHz, DMSO-d6) □ ppm 0,79 - 0,86 (m, 4 H) 1,17 - 1,42 (m, 16 H) 1,63 - 1,72 (m, 2 H) 3,93 (t, J=6,47 Hz, 3 H) 4,11 - 4,19 (m, 1 H) 4,65 - 4,73 (m, 1 H) 6,91 (d, J=8,73 Hz, 2 H) 7,31 (d, J=8,43 Hz, 2 H).

Compuesto 45; clorhidrato del ácido 2-Metil-3-[2-(4-octiloxi-fenil)-morfolin-4-il]-propiónico 1H RMN (400 MHz, DMSO-d6) □ ppm 0,67 (t, J=6,47 Hz, 2 H) 1,05 (dd, J=7,22, 3,91 Hz, 4 H) 1,03 (br. s., 2 H) 1,09 (br. s., 3 H) 1,19 (d, J=7,52 Hz, 2 H) 1,50 (qd, J=6,92, 6,62 Hz, 1 H) 2,31 (br. s., 3 H) 2,85 - 2,93 (m, 2 H) 2,95 (br. s., 1 H) 3,18 (br. s., 7 H) 3,26 (br. s., 2 H) 3,29 (br. s., 1 H) 3,37 (s, 1 H) 3,76 (t, J=6,47 Hz, 1 H) 3,90 (br. s., 1 H) 6,75 (d, J=8,43 Hz, 1 H) 7,08 (dd, J=8,43, 6,32 Hz, 1 H).

Compuesto 46; clorhidrato del ácido 3-{2-[4-(2-Cloro-6-fluorobenciloxi)-fenil]-morfolin-4-il}-propiónico 1H RMN (400 MHz, DMSO-d6) □ ppm 1,42 (s, 1 H) 2,82 - 2,98 (m, 2 H) 3,02 - 3,20 (m, 2 H) 3,26 - 3,40 (m, 2 H) 3,47 (d, J=12,04 Hz, 1 H) 3,93 - 4,07 (m, 1 H) 4,08 - 4,21 (m, 1 H) 4,75 - 4,91 (m, 1 H) 5,16 (dd, J=1,35, 0,75 Hz, 2 H) 7,02 - 7,17 (m, 1 H) 7,28 - 7,39 (m, 2 H) 7,40 - 7,46 (m, 1 H) 7,48 - 7,57 (m, 1 H).

Compuesto 47; clorhidrato del ácido 3-{2-[4-(2-Trifluorometil-benciloxi)-fenil]-morfolin-4-il}-propiónico 1H RMN (400 MHz, DMSO-d6) □ ppm 1,41 (s, 1 H) 2,81 - 2,96 (m, 2 H) 3,01 - 3,20 (m, 2 H) 3,24 - 3,39 (m, 2 H) 3,47 (d, J=12,64 Hz, 1 H) 3,53 - 3,64 (m, 1 H) 3,92 - 4,06 (m, 1 H) 4,08 - 4,19 (m, 1 H) 4,80 (d, J=11,14 Hz, 1 H) 5,24 (s, 2 H) 7,00 - 7,09 (m, 2 H) 7,28 - 7,38 (m, 2 H) 7,54 - 7,64 (m, 1 H) 7,68 - 7,84 (m, 2 H).

Compuesto 48; clorhidrato del ácido 3-{2-[4-(2,6-Difluoro-benciloxi)-fenil]-morfolin-4-il}-propiónico 1H RMN (400 MHz, DMSO-d6) □ ppm 1,41 (s, 1 H) 2,85 - 2,99 (m, 2 H) 3,03 - 3,22 (m, 2 H) 3,25 - 3,40 (m, 2 H) 3,47 (d, J=12,04 Hz, 1 H) 3,95 - 4,08 (m, 1 H) 4,10 - 4,19 (m, 1 H) 4,78 - 4,91 (m, 1 H) 5,13 (s, 2 H) 7,08 (d, J=8,73 Hz, 2 H) 7,15 - 7,25 (m, 2 H) 7,34 (d, J=8,73 Hz, 2 H) 7,48 - 7,60 (m, 1 H).

Compuesto 49; clorhidrato del ácido 3-{2-[4-(3-Trifluorometil-benciloxi)-fenil]-morfolin-4-il}-propiónico 1H RMN (400 MHz, DMSO-d6) □ ppm 2,83 - 2,94 (1 H, m) 3,02 -

3,19 (1 H, m) 3,26 - 3,37 (1 H, m)3,47 (1 H, d, J=12,4 Hz) 3,57 (1 H, dd, J=12,4, 0,8 Hz) 3,93 - 4,05 (1 H, m, J=12,3, 12,3, 1,3, 1,0 Hz)4,07 - 4,18 (1 H, m) 4,80 (1 H, d) 5,23 (1 H, s) 7,07 (1 H, d) 7,33 (1 H, d) 7,64 (1 H, t) 7,68 - 7,74 (1H, m) 7,77 (1 H, d, J=7,6 Hz) 7,82 (1 H, s).

Compuesto 50; clorhidrato del ácido 3-{2-[4-(2,6-Dimetil-benciloxi)-fenil]-morfolin-4-il}-propiónico 1H RMN (400 MHz, DMSO-d6) □ ppm 2,32 (s, 6 H) 2,83 - 2,94 (m, 2 H) 3,02 - 3,21 (m, 2 H) 3,26 - 3,40 (m, 3 H) 3,41 - 3,51 (m, 1 H) 3,51 - 3,61 (m, 1 H) 3,91 - 4,06 (m, 1 H) 4,06 - 4,19 (m, 1 H) 4,82 (dd, J=9,85, 1,01 Hz, 1 H) 5,05 (s, 2 H) 6,74 - 6,81 (m, 0 H) 7,04 - 7,11 (m, 2 H) 7,17 (dd, J=8,34, 6,06 Hz, 2 H) 7,29 - 7,37 (m, 2 H).

Compuesto 51; clorhidrato del ácido 3-{2-[4-(3,5-Dicloro-piridin-4-ilmetoxi)-fenil]-morfolin-4-il}-propiónico: 1H RMN (400 MHz, DMSO-d6) □ ppm 2,81 - 2,98 (m, 2 H) 3,01 - 3,22 (m, 2 H) 3,24 - 3,42 (m, 2 H) 3,42 - 3,70 (m, 2 H) 3,92 - 4,19 (m, 2 H) 4,85 (dd, J=11,17, 1,13 Hz, 1 H) 5,25 (s, 2 H) 7,03 - 7,14 (m, 2 H) 7,26 - 7,41 (m, 2 H) 8,61 - 8,79 (m, 2 H)

Compuesto 52; clorhidrato del ácido 3-{2-[4-(2,4-Dicloro-piridin-3-ilmetoxi)-fenil]-morfolin-4-il}-propiónico: 1H RMN (400 MHz, DMSO-d6) □ ppm 2,83 - 2,98 (2 H, m) 3,01 - 3,22 (2 H, m) 3,23 - 3,53 (3 H, m) 3,52 - 3,65 (1 H, m) 3,94 - 4,07 (1 H, m) 4,08 - 4,21 (1 H, m) 4,84 (1 H, dt, J=11,1, 0,7 Hz) 5,21 - 5,31(2 H, m) 7,04 - 7,18 (2 H, m) 7,29 - 7,44 (2 H, m) 7,74 (1 H, d, J=5,3 Hz) 8,45 (1 H, d, J=5,3 Hz).

Compuesto 53; clorhidrato del ácido 3-{2-[4-(2,6-Dicloro-fenilcarbamoil)-fenil]-morfolin-4-il}-propiónico 1H RMN (400 MHz, DMSO-d6) □ ppm 2,85 - 2,98 (1 H, m) 3,02 - 3,25 (1 H, m) 3,35 (1 H, t, J=8,1 Hz) 3,51 (1 H, d, J=12,6 Hz) 3,67 - 3,77 (1 H, m) 4,07 (1 H, t, J=12,4 Hz) 4,15 - 4,26 (1 H, m) 4,96 - 5,07 (1 H, m) 7,41 (1 H, t, J=8,1 Hz) 7,51 - 7,64 (2 H, m) 8,06 (1 H, d, J=8,3 Hz).

Compuesto 54; clorhidrato del ácido 3-{2-[4-(2,6-Dicloro-fenoximetil)-fenil]-morfolin-4-il}-propiónico 1H RMN (400 MHz, DMSO-d6) □ ppm 2,86 - 2,99 (2 H, m) 3,00 - 3,25 (2 H, m) 3,24 - 3,42 (2 H, m) 3,50 (1 H, d, J=12,1 Hz) 3,65 (1 H, d, J=12,6 Hz) 4,00 - 4,12 (1 H, m) 4,12 - 4,24 (1 H, m) 4,89 - 4,99 (1 H, m) 5,03 (2 H, s) 7,22 (1 H, t, J=8,1 Hz) 7,36 - 7,49 (2 H, m) 7,49 - 7,63 (3 H, m).

Compuesto 55; clorhidrato del ácido 3-(2-{4-[2-(2,6-Dicloro-fenil)-vinil]-fenil}-morfolin-4-il)-propiónico 1H RMN (400 MHz, DMSO-d6) □ ppm 2,85 - 2,95 (1 H, m) 3,07 (1 H, t, J=11,5 Hz) 3,12 - 3,21 (1 H, m) 3,35 (1 H, t, J=7,8 Hz) 3,43 - 3,55 (1 H, m) 3,60 - 3,70 (1 H, m) 3,97 - 4,07 (1 H, m) 4,14 - 4,22 (1 H, m) 4,90 (1 H, dd, J=11,0, 0,6 Hz) 7,07 - 7,14 (1 H, m) 7,16 - 7,24 (1 H, m) 7,34 (1 H, t, J=8,1 Hz) 7,43 (1 H, d, J=8,3 Hz) 7,55 (1 H, d, J=8,1 Hz) 7,68 (1 H, d, J=8,3 Hz).

Compuesto 56; clorhidrato del ácido 3-[2-(4-Fenetil-fenil)-morfolin-4-il]-propiónico 1H RMN (400 MHz, DMSO-d6) □ ppm: 2,80 - 3,23 (7 H, m), 3,24 - 3,80 (4 H, m), 3,96 - 4,29 (2 H, m), 4,80 - 5,04 (1 H, m), 7,10 - 7,52 (9 H, m).

Compuesto 57; clorhidrato del ácido 3-{2-[4-(2,6-Dicloro-bencilamino)-fenil]-morfolin-4-il}-propiónico 1H RMN (400 MHz, DMSO-d6) □ ppm 2,86 - 2,98 (2 H, m) 3,01 - 3,18 (2 H, m) 3,26 - 3,36 (2 H, m)3,40 - 3,53 (2 H, m) 3,94 - 4,05 (1 H, m) 4,05 - 4,14 (1 H, m) 4,35 - 4,43 (2 H, m) 4,72 (1 H, dt, J=10,9, 1,1 Hz) 6,72 (2 H, d, J=8,6 Hz) 7,07 - 7,20 (2 H, m) 7,12 (1 H, d, J=8,8 Hz) 7,35 - 7,45 (1 H, m) 7,51 (1 H, d, J=7,8 Hz).

Compuesto 58; clorhidrato del ácido 3-{2-[4-(2,6-Dicloro-benzoilamino)-fenil]-morfolin-4-il}-propiónico 1H RMN (400 MHz, DMSO-d6) □ ppm 2,87 - 2,97 (2 H, m) 2,99 - 3,22 (2 H, m) 3,27 - 3,42 (3 H, m)3,49 (1 H, d, J=11,9 Hz) 3,60 (1 H, dd, J=11,9, 1,0 Hz) 3,98 - 4,10 (1 H, m) 4,10 - 4,23 (1 H, m) 4,88(1 H, dd, J=11,0, 0,6 Hz) 7,38 (2 H, d, J=8,6 Hz) 7,46 - 7,55 (1 H, m) 7,55 - 7,63 (1 H, m) 7,72 (1 H, d,J=8,6 Hz).

Compuesto 59; clorhidrato del ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-2-metil-morfolin-4-il}-propiónico 1H RMN (400 MHz, DMSO-d6) □ ppm 1,21 – 1,84 (m, 3 H) 2,95 (m, 2 H) 3,02 - 3,42 (m, 6 H) 3,70 - 4,20 (m, 2 H) 5,24 (s, 2 H) 7,10 (d, J=7,6 Hz, 2 H) 7,43 - 7,52 (m, 3 H) 7,56 - 7,60 (m, 2 H) 11,41 (br. s., 1 H) 12,85 (br. s.,1 H).

Compuesto 60; 3-{2-[4-(2-Cloro-6-fluoro-benciloxi)-fenil]-2-metil-morfolin-4-il}-propiónico clorhidrato del ácido 1H RMN (400 MHz, DMSO-d6) □ ppm 1,21 - 1,93 (m, 3 H) 2,86 - 3,01 (m, 2 H) 3,02 - 3,44 (m, 6 H) 3,60 - 4,20 (m, 2 H) 5,16 (s, 2 H) 7,09 (d, J=7,8 Hz, 2 H) 7,34 (t, J=8,8 Hz, 1 H) 7,41 - 7,49 (m, 3 H) 7,49 - 7,56 (m, 1 H) 11,36 (br. s., 1 H) 12,72 (br. s., 1 H).

Compuesto 61; clorhidrato del ácido 3-{2-[4-(2-Trifluorometil-benciloxi)-fenil]-2-metil-morfolin-4-il}-propiónico 1H RMN (400 MHz, DMSO-d6) □ ppm 1,21 - 1,90 (m, 3 H) 2,86 - 3,00 (m, 2 H) 3,02 - 3,46 (m, 6 H) 3,52 - 4,22 (m, 2 H) 7,04 (d, J=7,3 Hz, 2 H) 7,44 (d, J=8,6 Hz, 2 H) 7,60 (t, J=7,3 Hz, 1 H) 7,69 - 7,85 (m, 3 H) 11,33 (m, 1 H) 12,71 (br. s., 1 H).

Compuesto 62; clorhidrato del ácido 3-[2-Metil-2-(4-octiloxi-fenil)-morfolin-4-il]-propiónico 1H RMN (400 MHz, DMSO-d6) □ ppm 0,80 - 0,92 (m, 3 H) 1,20 - 1,89 (m, 13 H) 1,71 (quin, J=6,9 Hz, 2 H) 2,85 - 2,99 (m, 2 H) 3,00 - 3,43 (m, 6 H) 3,53 - 4,16 (m, 2 H) 3,95 (t, J=6,4 Hz, 2 H) 6,94 (d, J=8,7 Hz, 2 H) 7,39 (d, J=8,7 Hz, 2 H) 11,23 (br. s., 1 H) 12,72 (br. s., 1 H).

Compuesto 63; clorhidrato del ácido 4-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-butírico 1H RMN (400 MHz, DMSO-d6) □ ppm 1,92 – 2,04 (m, 2 H) 2,35 (t, J=7,20 Hz, 2 H) 3,02 – 3,18 (m , 4 H) 3,45 – 3,64 (m, 2 H) 4,00 – 4,18 (m, 2 H) 4,83 – 4,91 (m, 1 H)

5,23 (s, 2 H) 7,07 – 7,13 (m, 2 H) 7,32 – 7,38 (m, 2 H) 7,45 – 7,51 (m, 1 H) 7,58 (d, J=7 Hz, 2 H) 11,3 (br. s, 1 H) 12,3 (br. s, 1 H).

Compuesto 64; clorhidrato del ácido 3-(2-{4-[1-(2,6-Dicloro-fenil)-etoxi]-fenil}-morfolin-4-il)-propiónico 1H RMN (400 MHz, DMSO-d6) □ ppm 1,71 (d, J=6,6 Hz, 3 H) 2,82 - 2,91 (m, 2 H) 2,96 - 3,13 (m, 2 H) 3,21 - 3,35 (m, 2 H) 3,39 - 3,56 (m, 2 H) 3,96 (t, J=12,0 Hz, 1 H) 4,08 (d, J=11,1 Hz, 1 H) 4,74 (d, J=10,6 Hz, 1 H) 6,04 (q, J=6,6 Hz, 1 H) 6,84 (d, J=8,7 Hz, 2 H) 7,24 (d, J=8,7 Hz, 2 H) 7,31 (t, J=8,1 Hz, 1 H) 7,44 (d, J=8,1 Hz, 2 H) 11,51 (br. s., 1 H) 12,69 (br. s., 1 H).

Compuesto 65; clorhidrato del ácido 3-(2-{4-[2-(2,6-Dicloro-fenil)-etil]-fenil}-morfolin-4-il)-propiónico 1H RMN (400 MHz, DMSO-d6) □ ppm 2,76 - 2,83 (m, 2 H) 2,85 - 2,93 (m, 2 H) 3,01 - 3,20 (m, 4 H) 3,34 (t, J=8,0 2 H) 3,45 - 3,66 (m, 2 H) 3,95 - 4,05 (m, 1 H) 4,16 (d, J=11,6 Hz 1 H) 4,84 (d, J=10,1 Hz 1 H) 7,27 - 7,36 (m, 5 H) 7,48 (d, J=8,1 Hz, 2 H) 11,31 (br. s., 1 H) 12,67 (br. s., 1 H).

Compuesto 66; clorhidrato del ácido 3-{2-[3-Metoxi-4-(2-trifluorometil-benciloxi)-fenil]-morfolin-4-il}-propiónico. Punto de fusión 170–172°C.

Compuesto 67; clorhidrato del ácido 3-{2-[4-(2-Cloro-6-fluoro-benciloxi)-3-metoxi-fenil]-morfolin-4-il}-propiónico. Punto de fusión 169–171°C.

Compuesto 68; clorhidrato del ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-3-metoxi-fenil]-morfolin-4-il}-propiónico. Punto de fusión 214–216°C.

Compuesto 139: clorhidrato del ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-2-metil-propiónico 1H RMN (400 MHz, DMSO-d6) □ ppm 1,20 - 1,26 (m, 3 H) 3,01 - 3,22 (m, 4 H) 3,41 - 3,63 (m, 3 H) 3,97 - 4,08 (m, 1 H) 4,09 - 4,16 (m, 1 H) 4,81 - 4,90 (m, 1 H) 5,24 (s, 2 H) 7,10 (d, J=8,6 Hz, 2H) 7,31 - 7,37 (m, 2 H) 7,45 - 7,51 (m, 1 H) 7,57 (d, J=8,3 Hz, 2 H) 10,2 – 10,9 (bs, 1H) 12,5 – 13,1 (bs, 1H).

Compuesto 140: clorhidrato del ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-butírico 1H RMN (400 MHz, DMSO-d6) □ ppm 1,34 (d, J=6,6 Hz, 3 H) 2,54 - 2,64 (m, 1 H) 3,03 - 3,24 (m, 2 H) 3,33 - 3,76 (m, 4H) 4,01 - 4,22 (m, 2 H) 4,86 - 4,94 (m, 1 H) 5,23 (s, 2 H) 7,10 (d, J=8,6 Hz, 2 H) 7,38 (d, J=8,6 Hz, 2 H) 7,45 – 7,51 (m, 1 H) 7,57 (d, J=8,3 Hz, 2 H) 10,9 – 11,4 (bs, 1H) 12,5 – 13,0 (bs, 1H).

Compuesto 142: Clorhidrato del éster mono-(2-{2-[4-(2,6-dicloro-benciloxi)-fenil]-morfolin-4-il}-etil) del ácido fosfórico 1H RMN (400 MHz, DMSO-d6) □ ppm 3,03 - 3,19 (m, 2 H) 3,30 - 3,41 (m, 2 H) 3,43 - 3,51 (m, 1 H) 3,52 - 3,65 (m, 1 H) 3,94 - 4,05 (m, 1 H) 4,09 - 4,24 (m, 3 H) 4,82 (d, J=10,6 Hz, 1 H) 5,23 (s, 2 H) 7,10 (d, J=8,6 Hz, 2 H) 7,34 (d, J=8,6 Hz, 2 H) 7,44 - 7,51 (m, 1 H) 7,57 (d, J=8,3 Hz, 2 H) 10,1 – 11,5 (bs, 1H).

Compuesto 143: clorhidrato del ácido 3 -{2-[3-Metil-4-(2-trifluorometil-benciloxi)-fenil]-morfolin-4-il}-propiónico Punto de fusión 191–194°C.

Compuesto 144: clorhidrato del ácido 3-{2-[4-(2-Cloro-6-fluoro-benciloxi)-3-metil-fenil]-morfolin-4-il}-propiónico Punto de fusión 194–196°C.

Compuesto 145: clorhidrato del ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-3-metil-fenil]-morfolin-4-il}-propiónico Punto de fusión 198–200°C.

Compuesto 147: clorhidrato del ácido 3-{2-[4-(2,3-Dicloro-benciloxi)-fenil]-morfolin-4-il}-propiónico. Mp222–227°C.

Compuesto 148: clorhidrato del ácido 3-{2-[4-(2-Cloro-5-trifluorometil-benciloxi)-fenil]-morfolin-4-il}-propiónico Punto de fusión 218,5–222°C.

Compuesto 152: clorhidrato del ácido 3-{2-[4-(2-Cloro-3-trifluorometil-benciloxi)-fenil]-morfolin-4-il}-propiónico. Punto de fusión 223 - 228°C.

Compuesto 153: clorhidrato del ácido 3-{2-[4-(2-Cloro-6-trifluorometil-benciloxi)-fenil]-morfolin-4-il}-propiónico. Punto de fusión 185,5 – 190,5°C.

Compuesto 154: clorhidrato del ácido 3 -{2-[4-(2,3,6-Tricloro-benciloxi)-fenil]-morfolin-4-il}-propiónico. Punto de fusión 213 - 216°C.

Compuesto 155: clorhidrato del ácido 3-{2-[4-(2-Cloro-6-metil-benciloxi)-fenil]-morfolin-4-il}-propiónico. Punto de fusión 215 - 218°C.

Compuesto 156: 3-{2-[4-(2-Cloro-5-metil-benciloxi)-fenil]-morfolin-4-il}-propiónico clorhidrato del ácido. Punto de fusión 209 - 213°C.

Compuesto 157: clorhidrato del ácido 3-{2-[4-(2-Cloro-5-etil-benciloxi)-fenil]-morfolin-4-il}-propiónico. Punto de fusión 198 - 202°C.

Compuesto 158: clorhidrato del ácido 3-{2-[4-(2-Cloro-5-propil-benciloxi)-fenil]-morfolin-4-il}-propiónico. Punto de fusión 199 - 203°C.

Compuesto 159: 3-{2-[4-(2-Cloro-5-isopropil-benciloxi)-fenil]-morfolin-4-il}-propiónico clorhidrato del ácido. Punto de fusión 203 - 207°C.

Compuesto 160: clorhidrato del ácido 3-{2-[4-(2,4,6-Tricloro-benciloxi)-fenil]-morfolin-4-il}-propiónico. Punto de fusión 215 - 218°C.

Compuesto 161: clorhidrato del ácido 3-{2-[4-(2,6-Dicloro-4-trifluorometil-benciloxi)-fenil]-morfolin-4-il}-propiónico. Punto de fusión 221 - 226°C.

Compuesto 162: clorhidrato del ácido 3-{2-[4-(2,6-Dicloro-4-yodo-benciloxi)-fenil]-morfolin-4-il}-propiónico. Punto de fusión 210 - 215°C.

Compuesto 163: clorhidrato del ácido 3-(2-{4-[3-(2-Fluoro-fenil)-propoxi]-fenil}-morfolin-4-il)-propiónico 1H RMN (400 MHz, DMSO-d6) □ ppm 1,96 - 2,05 (m, 2 H) 2,76 - 2,81 (m, 2 H) 2,83 - 2,96 (m, 2 H) 3,04 - 3,17 (m, 2 H) 3,28 - 3,37 (m, 2 H) 3,47 (d, J=12,2 Hz, 1 H) 3,56 (d, J=12,2 Hz, 1 H) 3,94 - 4,04 (m, 3 H) 4,08 - 4,16 (m, 1 H) 4,78 (d, J=10,6 Hz 1 H) 6,95 (J=8,6 Hz, 2 H) 7,10 - 7,17 (m, 2 H) 7,22 - 7,34 (m, 4 H) 11,0-11,6 (bs, 1 H) 12,1-12,9 (bs, 1 H).

Compuesto 164: clorhidrato del ácido 3-{2-[4-(2,6-Dicloro-4-etil-benciloxi)-fenil]-morfolin-4-il}-propiónico. Punto de fusión 198 - 202°C.

Compuesto 165: clorhidrato del ácido 3 -{2-[4-(2,6-Dicloro-4-metil-benciloxi)-fenil]-morfolin-4-il}-propiónico. Punto de fusión 197 - 204°C.

Compuesto 166: ácido 3-[2-(4-Benciloxi-fenil)-5-oxo-morfolin-4-il]-propiónico. 1H RMN (400 MHz, CDCl3) □ ppm 2,71 - 2,79 (m, 2 H) 3,41 - 3,49 (m, 1 H) 3,56 - 3,72 (m, 3 H) 4,28 - 4,45 (m, 2 H) 4,70 - 4,76 (m, 1 H) 5,07 (s, 2 H) 6,98 (d, J=8,8 Hz, 2 H) 7,27 - 7,45 (m, 7 H).

Compuesto 167: ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-5-oxo-morfolin-4-il}-propiónico. 1H RMN (400 MHz, CDCl3) □ ppm 2,67 - 2,83 (m, 2 H) 3,43 - 3,51 (m, 1 H) 3,57 - 3,66 (m, 1 H) 3,67 - 3,75 (m, 2 H) 4,29 - 4,47 (m, 2 H) 4,72 - 4,79 (m, 1 H) 5,27 (s, 2 H) 7,03 (d, J=8,8 Hz, 2 H) 7,22 - 7,29 (m, 1 H) 7,30 - 7,40 (m, 4 H)

Compuesto 168: ácido 3-[2-(4-Octiloxi-fenil)-5-oxo-morfolin-4-il]-propiónico 1H RMN (400 MHz, CDCl3) □ ppm 0,85 - 0,93 (m, 3 H) 1,22 - 1,39 (m, 8 H) 1,39 - 1,50 (m, 2 H) 1,72 - 1,82 (m, 2 H) 2,67 - 2,81 (m, 2 H) 3,41 - 3,48 (m, 1 H) 3,61 (t, J=12,3 Hz, 1 H) 3,69 (t, J=6,6 Hz, 2 H) 3,94 (t, J=6,6 Hz, 2 H) 4,27 - 4,45 (m, 2 H) 4,69 – 4,74 (m, 1H) 6,89 (d, J=8,8 Hz, 2 H) 7,28 (d, J=8,8 Hz, 2 H).

Compuesto 169: clorhidrato del ácido 3-(2-{4-[3-(2-Trifluorometil-fenil)-propoxi]-fenil}-morfolin-4-il)-propiónico 1H RMN (400 MHz, DMSO-d6) □ ppm 1,97 - 2,07 (m, 2 H) 2,84 - 2,95 (m, 4 H) 3,04 – 3,19 (m, 2 H) 3,29 - 3,38 (m, 2 H) 3,47 (d, J=11,9 Hz, 1 H) 3,53 - 3,60 (m, 1 H) 3,94 – 4,08 (m, 3 H) 4,09 - 4,17 (m, 1 H) 4,80 (d, J=9,3 Hz, 1 H) 6,96 (d, J=8,7 Hz, 2 H) 7,30 (d, J=8,7 Hz, 2 H) 7,39 - 7,46 (m, 1 H) 7,52 (d, J=7,8 Hz, 1 H) 7,58 - 7,65 (m, 1 H) 7,68 (d, J=7,8 Hz, 1 H) 11,2 (bs, 1 H) 12,8 (bs, 1 H).

Compuesto 170: clorhidrato del ácido 3-(2-{4-[3-(2-Cloro-6-fluoro-fenil)-propoxi]-fenil}-morfolin-4-il)-propiónico 1H RMN (400 MHz, DMSO-d6) □ ppm 1,90 - 2,02 (m, 2 H) 2,83 - 2,95 (m, 4 H) 3,04 – 3,18 (m, 2 H) 3,33 (t, J=7,9 Hz, 2 H) 3,47 (d, J=11,9 Hz, 1 H) 3,57 (d, J=11,9 Hz, 1 H) 3,95 - 4,05 (m, 3 H) 4,13 (d, J=11,9 Hz, 1 H) 4,78 (d, J=10,0 Hz, 1 H) 6,96 (J=8,6 Hz, 2 H) 7,16 - 7,23 (m, 1 H) 7,27 - 7,35 (m, 4 H) 10,9 - 11,4 (bs, 1 H) 12,1 - 12,9 (bs, 1 H).

Compuesto 171: clorhidrato del ácido 3-(2-{4-[3-(2,6-Dicloro-fenil)-propoxi]-fenil}-morfolin-4-il)-propiónico 1H RMN (400 MHz, DMSO-d6) □ ppm 1,92 - 2,01 (m, 2 H) 2,84 - 2,91 (m, 2 H) 3,01 - 3,16 (m, 3 H) 3,28 – 3,38 (m, 2 H) 3,47 (d, J=12,2 Hz, 2 H) 3,58 (d, J=12,2 Hz, 1 H) 3,93 - 4,01 (m, 1 H) 4,03 - 4,08 (m, 2 H) 4,13 (d, J=12,1 Hz, 1 H) 4,77 (d, J=10,4 Hz, 1 H) 6,95 (d, J=8,9 Hz, 2 H) 7,25 - 7,33 (m, 3 H) 7,46 (d, J=8,1 Hz, 2 H) 10,8 - 11,4 (bs, 1 H) 12,2 - 12,9 (bs, 1 H).

Compuesto 172: clorhidrato del ácido 3-(2-{4-[3-(4-Cloro-fenil)-propoxi]-fenil}-morfolin-4-il)-propiónico 1H RMN (400 MHz, DMSO-d6) □ ppm 1,95 - 2,05 (m, 2 H) 2,69 - 2,76 (m, 2 H) 2,84 - 2,94 (m, 2 H) 3,04 - 3,16 (m, 2 H) 3,28 - 3,37 (m, 2 H) 3,47 (d, J=12,3 Hz, 1 H) 3,56 (d, J=12,3, 1 H) 3,92 - 4,04 (m, 3 H) 4,15 (d, J=12,3 Hz, 1 H) 4,80 (d, J=9,6 Hz, 1 H) 6,95 (d, J=8,7 Hz, 2 H) 7,24 - 7,36 (m, 6 H) 10,9 - 11,9 (bs, 1 H) 12,2 - 12,9 (bs, 1 H).

Compuesto 173: clorhidrato del ácido 3-(2-{4-[3-(2-Cloro-fenil)-propoxi]-fenil}-morfolin-4-il)-propiónico 1H RMN (400 MHz, DMSO-d6) □ ppm 1,97 - 2,09 (m, 2 H) 2,83 - 2,95 (m, 4 H) 3,04 - 3,17 (m, 2 H) 3,33 (t, J=7,9 Hz, 2 H) 3,47 (d, J=12,1 Hz, 1 H) 3,56 (d, J=12,1 Hz, 1 H) 3,96 - 4,05 (m, 3 H) 4,13 (d, J=12,1 Hz, 1 H) 4,79 (d, J=10,0 Hz, 1 H) 6,96 (J=8,6 Hz, 2 H) 7,20 - 7,31 (m, 4 H) 7,33 - 7,37 (m, 1 H) 7,40 - 7,45 (m, 1 H) 11,0-11,4 (bs, 1 H) 12,1-12,9 (bs, 1 H).

Compuesto 174: clorhidrato del ácido 3-(2-{4-[3-(2,3-Difluoro-fenil)-propoxi]-fenil}-morfolin-4-il)-propiónico 1H RMN (400 MHz, DMSO-d6) □ ppm 1,98 - 2,08 (m, 2 H) 2,82 - 2,88 (m, 2 H) 2,88 - 2,94 (m, 2 H) 3,01 - 3,16 (m, 2 H) 3,28 – 3,38 (m, 2 H) 3,47 (d, J=12,2 Hz, 1 H) 3,58 (d, J=12,2 Hz, 1 H) 3,93 - 4,08 (m, 3 H) 4,13 (d, J=12,1 Hz, 1 H) 4,82 (d, J=10,4 Hz, 1 H) 6,95 (d, J=8,9 Hz, 2 H) 7,11 - 7,18 (m, 2 H) 7,22 - 7,32 (m, 3 H) 11,2-11,9 (bs, 1 H) 12,2 - 12,9 (bs, 1 H).

Compuesto 175: clorhidrato del ácido 3-{2-[3-Cloro-4-(2,6-dicloro-benciloxi)-fenil]-morfolin-4-il}-propiónico Punto de fusión 179 - 181°C.

Compuesto 176: clorhidrato del ácido 3-{2-[3-Cloro-4-(2-cloro-6-fluoro-benciloxi)-fenil]-morfolin-4-il}-propiónico Punto de fusión 178 - 180°C.

Compuesto 177; clorhidrato del ácido 3-{2-[3-Cloro-4-(2-trifluorometil-benciloxi)-fenil]-morfolin-4-il}-propiónico. Punto de fusión 199 - 201°C.

Compuesto 178; clorhidrato del ácido 3-{2-[4-(2-Cloro-6-fluoro-benciloxi)-2-fluoro-fenil]-morfolin-4-il}-propiónico Punto de fusión 189 - 190°C.

Compuesto 179; clorhidrato del ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-2-fluoro-fenil]-morfolin-4-il}-propiónico Punto de fusión 174,5 - 178°C.

Compuesto 180; clorhidrato del ácido 3-{2-[2-Fluoro-4-(2-trifluorometil-benciloxi)-fenil]-morfolin-4-il}-propiónico Punto de fusión 201 – 201,5°C.

Compuesto 181; clorhidrato del ácido 3-{2-[4-(2,6-Dicloro-3-etil-benciloxi)-fenil]-morfolin-4-il}-propiónico 1H RMN (400 MHz, DMSO-d6) □ ppm 1,19 (t, J=7,5 Hz, 3 H) 2,75 (q, J=7,5 Hz, 2 H) 2,83 - 2,95 (m, 2 H) 2,99 - 3,18 (m, 2 H) 3,30 -3,38 (m, 2 H) 3,48 (d, J=12,7 Hz, 1 H) 3,57 - 3,65 (m, 1 H) 3,95 – 4,04 (m, 1 H) 4,10 - 4,17 (m, 1 H) 4,81 (d, J=11,9 Hz, 1 H) 5,26 (s, 2 H) 7,11 (d, J=8,7 Hz, 2 H) 7,34 (d, J=8,7 Hz, 2 H) 7,46 (d, J=8,4 Hz, 1 H) 7,52 (d, J=8,4 Hz, 1 H) 10,9 - 11,9 (bs, 1 H) 12,2 - 12,9 (bs, 1 H).

Compuesto 182; clorhidrato del ácido 3-{2-[4-(2-Cloro-6-etil-benciloxi)-fenil]-morfolin-4-il}-propiónico 1H RMN (400 MHz, DMSO-d6) □ ppm 1,17 (t, J=7,5 Hz, 3 H) 2,72 (q, J=7,5 Hz, 2 H) 2,83 - 2,95 (m, 2 H) 3,05 - 3,18 (m, 2 H) 3,29 - 3,38 (m, 2 H) 3,48 (d, J=11,9 Hz, 1 H) 3,55 – 3,65 (m, 1 H) 3,96 - 4,04 (m, 1 H) 4,11 - 4,18 (m, 1 H) 4,82 (d, J=11,9 Hz, 1 H) 5,17 (s, 2 H) 7,10 (d, J=8,7 Hz, 2 H) 7,27 - 7,39 (m, 5 H) 11,1 - 11,9 (bs, 1 H) 12,2 - 12,9 (bs, 1 H).

Compuesto 183; clorhidrato del ácido 3-{2-[4-(2-Cloro-6-isopropil-benciloxi)-fenil]-morfolin-4-il}-propiónico 1H RMN (400 MHz, DMSO-d6) □ ppm 1,21 (d, J=6,8 Hz, 6 H) 2,84 - 2,96 (m, 2 H) 3,08 - 3,22 (m, 3 H) 3,29 - 3,38 (m, 2 H) 3,48 (d, J=12,8 Hz, 1 H) 3,58 (d, J=12,8 Hz, 1 H) 3,95 - 4,02 (m, 1 H) 4,10 - 4,18 (m, 1 H) 4,82 (d, J=10,1 Hz, 1 H) 5,21 (s, 2 H) 7,10 (d, J=8,7 Hz, 2 H) 7,31 - 7,44 (m, 5 H) 11,0 - 11,8 (bs, 1 H) 12,2 - 12,9 (bs, 1 H).

Compuesto 184; clorhidrato del ácido 3-{2-[4-(2-Cloro-6-ciclopropil-benciloxi)-fenil]-morfolin-4-il}-propiónico 1H RMN (400 MHz, DMSO-d6) □ ppm 0,64 - 0,76 (m, 2 H) 0,87 - 0,96 (m, 2 H) 2,02 - 2,11 (m, 1 H) 2,85 - 2,97 (m, 2 H) 3,06 - 3,18 (m, 2 H) 3,32 - 3,41 (m, 2 H) 3,48 (d, J=12,4 Hz, 1 H) 3,55 – 3,61 (m, 1 H) 3,97 - 4,03 (m, 1 H) 4,10 - 4,14 (m, 1 H) 4,83 (d, J=10,6 Hz, 1 H) 5,33 (s, 2 H) 7,10 dd, J=6,9 1,6 Hz, 1 H) 7,12 (d, J=8,8 Hz, 2 H) 7,30 – 7,37 (m, 4 H) 11,1 – 11,8 (bs, 1 H) 12,4 – 13,0 (bs, 1 H).

Compuesto 185; clorhidrato del ácido 3 -{2-[4-(2-Cloro-6-isobutil-benciloxi)-fenil]-morfolin-4-il}-propiónico 1H RMN (400 MHz, DMSO-d6) □ ppm 0,85 (d, J=6,6 Hz, 6 H) 1,78 - 1,90 (m, 1 H) 2,58 (d, J=7,2 Hz, 2 H) 2,84 - 2,92 (m, 2 H) 3,06 - 3,18 (m, 2 H) 3,32 - 3,41 (m, 2 H) 3,41 - 3,53 (m, 2 H) 3,97 - 4,07 (m, 1 H) 4,10 - 4,18 (m, 1 H) 4,83 (d, J=10,5 Hz, 1 H) 5,13 (s, 2 H) 7,06 (d, J=8,8 Hz, 2 H) 7,23 (dd, J=7,1, 1,8 Hz, 1 H) 7,30 - 7,41 (m, 4 H) 11,1 – 11,8 (bs, 1 H) 12,4 – 12,9 (bs, 1 H).

Compuesto 186; clorhidrato del ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-5,5-dimetil-morfolin-4-il}-propiónico 1H RMN (400 MHz, DMSO-d6) □ ppm 1,37 - 1,47 (m, 6 H) 2,91 - 3,03 (m, 3 H) 3,12 - 3,23 (m, 1 H) 3,51 - 3,64 (m, 2 H) 3,79 - 3,88 (m, 1 H) 3,92 - 4,01 (m, 1 H) 4,93 (d, J=11,9 Hz, 1 H) 5,24 (s, 2 H) 7,11 (d, J=8,8 Hz, 2 H) 7,38 (d, J=8,8 Hz, 2 H) 7,45 - 7,52 (m, 1 H) 7,58 (d, J=7,8 Hz, 2 H) 10,9 - 11,3 (bs, 1 H) 12,6 – 13,1 (bs, 1 H).

Compuesto 187; clorhidrato del ácido 3-[5,5-Dimetil-2-(4-octiloxi-fenil)-morfolin-4-il]-propiónico 1H RMN (400 MHz, DMSO-d6) □ ppm 0,81 - 0,89 (m, 3 H) 1,17 - 1,47 (m, 16 H) 1,63 – 1,75 (m, 2 H) 2,91 - 3,04 (m, 3 H) 3,12 - 3,23 (m, 1 H) 3,47 - 3,64 (m, 2 H) 3,74 - 3,84 (m, 1 H) 3,91 - 4,03 (m, 3 H) 4,93 (d, J=11,9 Hz, 1 H) 6,95 (d, J=8,8 Hz, 2 H) 7,33 (d, J=8,8 Hz, 2 H) 11,1 (bs, 1 H) 12,8 (bs, 1 H).

Compuesto 188; clorhidrato del ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-2-trifluorometil-fenil]-morfolin-4-il}-propiónico Punto de fusión 195 -197°C.

Compuesto 189; clorhidrato del ácido 3-[2-(4-Octiloxi-2-trifluorometil-fenil)-morfolin-4-il]-propiónico Punto de fusión 178,5 -180,5°C.

Compuesto 190; clorhidrato del ácido 3-{6-[4-(2,6-Dicloro-benciloxi)-fenil]-2,2-dimetil-morfolin-4-il}-propiónico 1H RMN (400 MHz, DMSO-d6) □ ppm 1,27 (s, 3 H) 1,53 (s, 3 H) 2,85 - 2,97 (m, 4 H) 3,29 - 3,35 (m, 2 H) 3,46 - 3,53 (m, 2 H) 4,93 (d, J=11,9 Hz, 1 H) 5,24 (s, 2 H) 7,10 (d, J=8,8 Hz, 2 H) 7,33 (d, J=8,8 Hz, 2 H) 7,44 - 7,52 (m, 1 H) 7,57 (d, J=7,8 Hz, 2 H) 10,5 – 10,9 (bs, 1 H) 12,5 – 13,0 (bs, 1 H).

Compuesto 191; clorhidrato del ácido 3-[2,2-Dimetil-6-(4-octiloxi-fenil)-morfolin-4-il]-propiónico 1H RMN (400 MHz, DMSO-d6) □ ppm 0,86 (t, J=6,8 Hz, 3 H) 1,19 - 1,45 (m, 13 H) 1,54 (s, 3 H) 1,64 - 1,75 (m, 2 H) 2,84 - 3,02 (m, 4 H) 3,24 - 3,36 (m, 2 H) 3,39 - 3,51 (m, 2 H) 3,95 (t, J=6,5 Hz, 2 H) 4,92 (d, J=10,6 Hz, 1 H) 6,94 (d, J=8,5 Hz, 2 H) 7,27 (d, J=8,5 Hz, 2 H) 10,9 – 11,4 (bs, 1 H) 12,5 – 13,0 (bs, 1 H).

Compuesto 192; 3-{2-[4-(2,6-Dicloro-4-propil-benciloxi)-fenil]-morfolin-4-il}-propiónico clorhidrato del ácido. Punto de fusión 101 - 103°C.

Compuesto 193; clorhidrato del ácido 3-{2-[4-(2,6-Dicloro-4-isopropil-benciloxi)-fenil]-morfolin-4-il}-propiónico. Punto de fusión 108 - 110°C.

Compuesto 194; clorhidrato del ácido 3-{2-[4-(2,6-Dicloro-4-prop-1-inil-benciloxi)-fenil]-morfolin-4-il}-propiónico. Punto de fusión 220 - 224°C.

Compuesto 195; clorhidrato del ácido 3-{2-[4-(2-Cloro-6-trifluorometoxi-benciloxi)-fenil]-morfolin-4-il}-propiónico. 1H RMN (400 MHz, DMSO-d6) □ ppm 2,85 - 2,97 (m, 2 H) 3,06 - 3,18 (m, 2 H) 3,29 - 3,38 (m, 1 H) 3,48 (d, J=11,9 Hz, 1 H) 3,59 (d, J=11,9, 1 H) 3,95 - 4,07 (m, 1 H) 4,09 - 4,18 (m, 1 H) 4,83 (d, J=10,6 Hz, 1 H) 5,16 (s, 2 H) 7,09 (d, J=8,8 Hz, 2 H) 7,35 (d, J=8,8 Hz, 2 H) 7,48 -7,52 (m, 2 H) 7,58 - 7,68 (m, 2 H) 11,2 – 11,9 (bs, 1 H) 12,4 – 13,0 (bs, 1 H).

Compuesto 196; clorhidrato del ácido 3-{2-[4-(2-Cloro-4-metil-benciloxi)-fenil]-morfolin-4-il}-propiónico. 1H RMN (400 MHz, DMSO-d6) □ ppm 2,32 (s, 3 H) 2,83 - 2,92 (m, 2 H) 3,04 - 3,17 (m, 2 H) 3,28 - 3,40 (m, 2 H) 3,47 (d, J=10,6 Hz, 1 H) 3,57 (d, J=10,6 Hz, 1 H) 3,94 - 4,05 (m, 1 H) 4,08 - 4,16 (m, 1 H) 4,83 (d, J=10,2 Hz, 1 H) 5,12 (s, 2 H) 7,04 (d, J=8,8 Hz, 2 H) 7,18 (d, J=7,8 Hz, 1 H) 7,27 - 7,39 (m, 3 H) 7,46 (d, J=7,8 Hz, 1 H) 11,2 – 12,0 (bs, 1 H) 12,3 – 13,0 (bs, 1 H).

Compuesto 197; clorhidrato del ácido 3-{2-[4-(2-Cloro-3-metil-benciloxi)-fenil]-morfolin-4-il}-propiónico. 1H RMN (400 MHz, DMSO-d6) □ ppm 2,38 (s, 3 H) 2,81 - 2,89 (m, 2 H) 3,04 – 3,18 (m, 2 H) 3,30 - 3,52 (m, 3 H) 3,55 - 3,61 (m, 1 H) 3,92 – 4,02 (m, 1 H) 4,13 (d, J=12,6 Hz, 1 H) 4,78 (d, J=10,2 Hz, 1 H) 5,17 (s, 2 H) 7,06 (d, J=8,8 Hz, 2 H) 7,27 - 7,43 (m, 5 H) 10,8 – 11,5 (bs, 1 H) 12,3 – 13,0 (bs, 1 H).

Compuesto 198; clorhidrato del ácido 3-{2-[4-(2,4-Dicloro-benciloxi)-fenil]-morfolin-4-il}-propiónico. 1H RMN (400 MHz, DMSO-d6) □ ppm 2,85 - 2,97 (m, 2 H) 3,04 - 3,17 (m, 2 H) 3,28 - 3,38 (m, 2 H) 3,42 - 3,51 (m, 1 H) 3,52 - 3,62 (m, 1 H) 3,96 - 4,06 (m, 1 H) 4,09 - 4,17 (m, 1 H) 4,83 (d, J=10,4 Hz, 1 H) 5,16 (s, 2 H) 7,06 (d, J=8,8 Hz, 2 H) 7,32 (d, J=8,8 Hz, 2 H) 7,49 (dd, J=8,3, 2,1 Hz, 1 H) 7,61 (d, J=8,3 Hz, 1 H) 7,70 (d, J=2,1 Hz, 1 H) 11,2 – 12,0 (bs, 1 H) 12,3 – 12,9 (bs, 1 H).

Compuesto 199; clorhidrato del 4-[4-(2-carboxi-etil)-morfolin-2-il]-fenil éster del ácido2,6-Dicloro-benzoico. 1H RMN (400 MHz, DMSO-d6) □ ppm 2,89 - 2,96 (m, 2 H) 3,09 - 3,22 (m, 2 H) 3,30 - 3,41 (m, 2 H) 3,51 (d, J=12,0 Hz, 1 H) 3,70 (d, J=12,0 Hz, 1 H) 4,01 - 4,11 (m, 1 H) 4,15 - 4,23 (m, 1 H) 4,96 (d, J=10,5 Hz, 1 H) 7,36 (d, J=8,7 Hz, 2 H) 7,55 (d, J=8,7 Hz, 2 H) 7,61 - 7,73 (m, 3 H)) 11,2 – 11,9 (bs, 1 H) 12,1 – 12,7 (bs, 1 H).

Compuesto 200; clorhidrato del ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-ciclobutanocarboxílico. 1H RMN (400 MHz, DMSO-d6) □ ppm 2,40 - 2,53 (m, 2 H) 2,81 – 3,00 (m, H) 3,32 - 3,50 (m, 4 H) 3,54 - 3,66 (m, 1 H) 3,89 - 4,01 (m, 1 H) 4,10 - 4,20 (m, 1 H) 4,75 (d, J=10,8 Hz, 1 H) 5,20 (s, 2 H) 7,10 (d, J=8,8 Hz, 2 H) 7,37 (d, J=8,8 Hz, 2 H)7,45 - 7,50 (m, 1 H) 7,55 - 7,59 (m, 2 H) 11,1(bs, 1 H) 12,6 (bs, 1 H).

Compuesto 201; clorhidrato del ácido 3-{2-[4-(2,6-Dicloro-bencilsulfanil)-fenil]-morfolin-4-il}-propiónico. 1H RMN (400 MHz, DMSO-d6) □ ppm 2,84 - 2,96 (m, 2 H) 3,05 - 3,09 (m, 1 H) 3,11 - 3,18 (m, 1 H) 3,33 (t, J=7,9 Hz, 1 H) 3,49 (d, J=11,0 Hz, 1 H) 3,64 (d, J=11,0 Hz, 1 H) 3,97 - 4,06 (m, 1 H) 4,12 - 4,20 (m, 1 H) 4,41 (s, 2 H) 4,87 (1 H) 4,86 (d, J=10,4 Hz, 1 H) 7,31 - 7,39 (m, 3 H) 7,42 - 7,52 (m, 4 H) 11,0 – 12,0 (bs, 1 H) 12,3 – 13,0 (bs, 1 H).

Compuesto 202; clorhidrato del ácido 3-{2-[4-(2-Cloro-bencilsulfanil)-fenil]-morfolin-4-il}-propiónico. 1H RMN (400 MHz, DMSO-d6) □ ppm 2,84 - 2,96 (m, 2 H) 3,00 - 3,18 (m, 2 H) 3,28 - 3,37 (m, 2 H) 3,47 (d, J=12,0 Hz, 1 H) 3,61 (d, J=12,0 Hz, 1 H) 3,96 - 4,07 (m, 1 H) 4,10 - 4,18 (m, 1 H) 4,32 (s, 2 H) 4,86 (d, J=11,4 Hz, 1 H) 7,23 - 7,35 (m, 4 H) 7,37 - 7,43 (m, 3 H) 7,43 - 7,48 (m, 1 H) 11,2 – 11,9 (bs, 1 H) 12,3 – 12,9 (bs, 1 H).

Compuesto 203; clorhidrato del ácido 3-{2-[4-(2-Cloro-6-fluoro-bencilsulfanil)-fenil]-morfolin-4-il}-propiónico. 1H RMN (400 MHz, DMSO-d6) □ ppm 2,84 - 2,91 (m, 2 H) 3,01 – 3,18 (m, 2 H) 3,30 - 3,38 (m, 2 H) 3,48 (d, J=12,0 Hz, 1 H) 3,63 (d, J=12,0 Hz, 1 H) 3,93 – 4,05 (m, 1 H) 4,12 – 4,19 (m, 1 H) 4,29 (s, 2 H) 4,80 – 4,88 (m, 1 H) 7,17 - 7,24 (m, 1 H) 7,32 - 7,45 (m, 6 H)) 11,0 – 11,6 (bs, 1 H) 12,1 – 12,7 (bs, 1 H).

Compuesto 204; clorhidrato del ácido 3-[2-(4-Octilsulfanil-fenil)-morfolin-4-il]-propiónico. 1H RMN (400 MHz, DMSO-d6) □ ppm 0,81 - 0,89 (m, 3 H) 1,19 - 1,31 (m, 8 H) 1,32 - 1,43 (m, 2 H) 1,51 - 1,61 (m, 2 H) 2,86 - 2,92 (m, 2 H) 2,94 - 2,99 (m, 2 H) 3,01 - 3,18 (m, 2 H) 3,27 - 3,37 (m, 2 H) 3,46 (d, J=12,1 Hz, 1 H) 3,60 (d, J=12,1 Hz, 1 H) 3,96 -

4,06 (m, 1 H) 4,10 - 4,18 (m, 1 H) 4,84 (d, J=10,4 Hz, 1 H) 7,28 - 7,36 (m, 4 H) 11,0 –12,9 (bs, 2 H).

Compuesto 205; clorhidrato del ácido 3-{2-[4-(4,4-Dimetil-ciclohexiloxi)-fenil]-morfolin-4-il}-propiónico 1H RMN (400 MHz, DMSO-d6) □ ppm 0,93 (d, J=3,3 Hz, 6 H) 1,22 – 1,32 (m., 2 H) 1,39 – 1,47 (m., 2 H) 1,50 – 1,61 (m., 2 H) 1,75 – 1,84 (m., 2 H) 2,82 - 2,90 (m, 2 H) 3,02 - 3,16 (m, 2 H) 3,26 - 3,59 (m, 4 H) 3,94 (t, J=11,4, 1 H) 4,12 (d, J=11,4 Hz, 1 H) 4,30 – 4,39 (m, 1 H) 4,73 (d, J=11,4 Hz, 1 H) 6,95 (d, J=8,7 Hz, 2 H) 7,27 (d, J=8,7 Hz, 2 H) 10,9 (bs, 1 H) 12,9 (bs, 1 H).

Compuesto 206; clorhidrato del ácido 3-{2-[4-(2-Difluorometoxi-benciloxi)-fenil]-morfolin-4-il}-propiónico 1H RMN (400 MHz, DMSO-d6) □ ppm 2,84 - 2,92 (m, 2 H) 3,04 - 3,16 (m, 2 H) 3,28 – 3,38 (m, 2 H) 3,43 - 3,51 (m, 1 H) 3,53 - 3,61 (m, 1 H) 3,97 (t, J=11,4, 1 H) 4,13 (dd, J=11,4, 2,4 Hz, 1 H) 4,78 (d, J=11,4 Hz, 1 H) 5,12 (s, 2 H) 7,02 - 7,09 (m, 2 H) 7,25 (t, J=75 Hz, 1 H) 7,24 - 7,35 (m, 4 H) 7,42 - 7,48 (m, 1 H) 7,57 (dd, J=7,6, 1,9 Hz, 1 H) 11,1 (bs, 1 H) 12,9 (bs, 1 H).

Compuesto 207; clorhidrato del ácido 3-{2-[4-(3-Trifluorometil-benciloxi)-2-trifluorometil-fenil]-morfolin-4-il}-propiónico Punto de fusión 209 - 211°C.

Compuesto 208; 3-{2-[4-(2-Cloro-6-etil-benciloxi)-2-trifluorometil-fenil]-morfolin-4-il}-propiónico clorhidrato del ácido Punto de fusión 214 - 215°C.

Compuesto 209; clorhidrato del ácido 3-{2-[4-(2-Cloro-6-trifluorometoxi-benciloxi)-2-trifluorometil-fenil]-morfolin-4-il}-propiónico Punto de fusión 179 - 182°C.

Compuesto 210; clorhidrato del ácido 3-{2-[4-(2-Cloro-6-isopropil-benciloxi)-2-trifluorometil-fenil]-morfolin-4-il}-propiónico Punto de fusión 206 - 210°C.

Compuesto 211; clorhidrato del ácido 3-{2-[4-(2-Cloro-6-fluoro-benciloxi)-2-trifluorometil-fenil]-morfolin-4-il}-propiónico Punto de fusión 171,5 – 172,5°C.

Compuesto 212; clorhidrato del ácido 3-{2-[4-(2-Cloro-6-trifluorometil-benciloxi)-2-trifluorometil-fenil]-morfolin-4-il}-propiónico Punto de fusión 200 - 201°C.

Compuesto 213; clorhidrato del ácido 3-{2-[4-(2-Cloro-6-ciclopropil-benciloxi)-2-trifluorometil-fenil]-morfolin-4-il}-propiónico Punto de fusión 203 - 204°C.

Compuesto 214; clorhidrato del ácido 3-{2-[4-(2,6-Dietil-benciloxi)-fenil]-morfolin-4-il}-propiónico 1H RMN (400 MHz, DMSO-d6) □ ppm 1,15 (t, J=7,5 Hz, 6 H) 1,88 (d, J=11,3 Hz, 1 H) 2,01 – 2,10 (m., 3 H) 2,45 – 2,55 (m., 2 H) 2,66 (q, J=7,4 Hz, 4 H) 2,71 – 2,75 (m., 1 H) 2,80 – 2,85 (m., 1 H) 3,58 – 3,67 (m., 1 H) 3,87 – 3,92 (m., 1 H) 4,37 – 4,42 (m., 1 H) 5,01 (s, 2 H) 7,01 (d, J=8,7 Hz, 2 H) 7,11 (d, J=7,8 Hz, 2 H) 7,23 - 7,31 (m, 3 H).

Compuesto 215; clorhidrato del ácido 3-{2-[2-Cloro-4-(2,6-dicloro-benciloxi)-fenil]-morfolin-4-il}-propiónico 1H RMN (400 MHz, DMSO-d6) □ ppm 2,87 – 2,93 (m, 2 H) 3,04 – 3,20 (m, 2 H) 3,30 – 3,38 (m, 2 H) 3,46 – 3,55 (m, 2 H) 4,02 – 4,11 (m, 1 H) 4,12 – 4,20

(m, 1 H) 5,19 – 5,25 (m, 1 H) 5,27 (s, 2 H) 7,15 (dd, J=8,8, 2,6 Hz, 1 H) 7,28 (d, J=2,6 Hz, 1 H) 7,46 - 7,53 (m, 2 H) 7,59 (d, J=8,8 Hz, 2 H) 11,8 – 12,9 (bs, 2 H).

Compuesto 216: clorhidrato del ácido 3-{2-[4-(2,6-Dicloro-bencil)-fenil]-morfolin-4-il}-propiónico: 1H RMN (400 MHz, DMSO-d6) □ ppm 2,83 - 2,93 (m, 2 H) 2,97 - 3,20 (m, 2 H) 3,22 - 3,39 (m, 2 H) 3,47 (d, J=12,38 Hz, 1 H) 3,55 - 3,66 (m, 1 H) 3,94 - 4,06 (m, 1 H) 4,08 - 4,19 (m, 1 H) 4,28 (s, 2 H) 4,78 - 4,89 (m, 1 H) 7,15 (d, J=8,34 Hz, 2 H) 7,26 - 7,40 (m, 3 H) 7,53 (d, J=8,08 Hz, 2 H).

Compuesto 217: clorhidrato del ácido 3-{2-[4-(2-Cloro-6-difluorometoxi-benciloxi)-fenil]-morfolin-4-il}-propiónico: 1H RMN (400 MHz, DMSO-d6) □ ppm 2,88 - 2,95 (m, 2 H) 3,05 - 3,18 (m, 2 H) 3,28 – 3,39 (m, 2 H) 3,42 - 3,51 (m, 1 H) 3,53 - 3,62 (m, 1 H) 3,97 (t, J=11,4, 1 H) 4,13 (d, J=11,4 Hz, 1 H) 4,84 (d, J=11,4 Hz, 1 H) 5,13 (s, 2 H) 7,08 (d, J=8,7 Hz 2 H) 7,33 (t, J=85 Hz, 1 H) 7,26 - 7,37 (m, 3 H) 7,47 (d, J=7,6 Hz, 1 H) 7,56 (d, J=7,6, 1,9 Hz, 1 H) 11,8 (bs, 1 H) 12,8 (bs, 1 H).

Compuesto 218: clorhidrato del ácido 3-{2-[4-(2-Cloro-6-difluorometoxi-benciloxi)-2-trifluorometil-fenil]-morfolin-4-il}-propiónico: Punto de fusión 192 – 193°C.

Compuesto 230; clorhidrato del ácido 3-[2-(3-Benciloxi-fenil)-morfolin-4-il]-propiónico Punto de fusión 222 - 225°C.

Compuesto 231; clorhidrato del ácido 3-[2-(3-Octiloxi-fenil)-morfolin-4-il]-propiónico Punto de fusión 218 - 220°C.

Compuesto 232; clorhidrato del ácido 3-{2-[3-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-propiónico Punto de fusión 229 - 230°C.

Compuesto 233; clorhidrato del ácido 3-{2-[3-(2-Cloro-benciloxi)-fenil]-morfolin-4-il}-propiónico Punto de fusión 233 - 234°C.

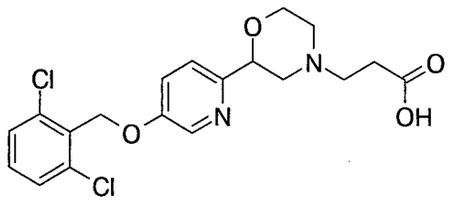
Compuesto 234; ácido 3 -[2-(4-Benciloxi-fenil)-tiomorfolin-4-il]-propiónico 1H RMN (400 MHz, DMSO-d6) □ ppm 1,91 – 1,99 (m, 2 H) 2,11 - 2,19 (m, 1 H) 2,25 - 2,33 (m, 1 H) 2,47 - 2,54 (m, 3 H) 2,72 - 2,83 (m, 1 H) 2,91 - 3,04 (m, 2 H) 3,81 - 3,88 (m, 1 H) 5,01 (s, 2 H) 6,88 (d, J=8,8 Hz, 2 H) 7,18 - 7,39 (m, 7 H).

Compuesto 235; clorhidrato del ácido 3-{2-[4-(2-Cloro-benciloxi)-fenil]-tiomorfolin-4-il}-propiónico Punto de fusión 178 – 182°C

Compuesto 236; clorhidrato del ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-tiomorfolin-4-il}-propiónico 1H RMN (400 MHz, DMSO-d6) □ ppm 2,89 - 2,99 (m, 3 H) 3,10 – 3,20 (m, 1 H) 3,33 - 3,54 (m, 4 H) 3,71 – 3,83 (m, 2 H) 4,54 – 4,60 (m, 1 H) 5,23 (s, 2 H) 7,11 (d, J=8,7 Hz, 2 H) 7,32 (d, J=8,7 Hz, 2 H) 7,46 - 7,52 (m, 1 H) 7,55 - 7,59 (m, 2 H) 11,4 (bs, 1 H) 12,8 (bs, 1 H).

Compuesto 237; ácido 3-[2-(4-Octiloxi-fenil)-tiomorfolin-4-il]-propiónico 1H RMN (400 MHz, DMSO-d6) □ ppm 0,84 - 0,90 (m, 3 H) 1,23 - 1,34 (m, 8 H) 1,35 - 1,42 (m, 2 H) 1,64

- 1,73 (m, 2 H) 2,26 - 2,34 (m, 1 H) 2,35 - 2,41 (m, 2 H) 2,41 – 2,48 (m, 1 H) 2,57 – 2,63 (m, 1 H) 2,64 – 2,70 (m, 2 H) 2,81 – 2,89 (m, 1 H) 3,02 – 3,14 (m, 2 H) 3,89 – 3,96 (m, 3 H) 6,86 (d, J=8,8 Hz, 2 H) 7,26 (d, J=8,8 Hz, 2 H).



Compuesto 238; clorhidrato del ácido 3-{2-[5-(2,6-Dicloro-benciloxi)-piridin-2-il]-morfolin-4-il}-propiónico 1H RMN (400 MHz, DMSO-d6) □ ppm 2,88 - 2,97 (m, 2 H) 3,11 - 3,26 (m, 2 H) 3,32 - 3,44 (m, 2 H) 3,52 (d, J=11,9 Hz, 1 H) 3,74 (d, J=11,9 Hz, 1 H) 4,06 - 4,21 (m, 2 H) 5,01 (d, J=11,9 Hz, 1 H) 5,34 (s, 2 H) 7,38 (bs, 1 H) 7,47 - 7,55 (m, 2 H) 7,56 - 7,61 (m, 2 H) 7,69 (dd, J=8,7, 3,0 Hz, 1 H) 8,40 (d, J=3,0 Hz, 1 H) 11,8 (bs, 1 H).

Compuesto 239; clorhidrato del ácido 3-{2-[4-(2-Oxo-2-fenil-etil)-fenil]-morfolin-4-il}-propiónico 1H RMN (400 MHz, DMSO-d6) □ ppm 2,84 – 2,92 (m, 2 H) 3,00 – 3,18 (m, 2 H) 3,28 – 3,38 (m, 2 H) 3,42 – 3,51 (m, 1 H) 3,58 – 3,66 (m, 1 H) 3,94 – 4,04 (m, 1 H)) 4,11 – 4,19 (m, 1 H) 4,42 (s, 2 H) 4,79 – 4,87 (m, 1 H) 7,28 – 7,37 (m., 4 H) 7,54 (t, J=7,6 Hz, 2 H) 7,65 (t, J=7,0 Hz, 1 H) 8,05 (t, J=7,6 Hz, 2 H) 11,2 (bs, 1 H) 12,8 (bs, 1 H)

Método C:

Compuesto 69; ácido 3-{2-[4-(3-Metoxi-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico: éster ter-butílico del ácido 3-{2-[4-(3-Metoxi-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico se disolvió en una solución 4M de HCl en 1,4-dioxano (1 ml, 4 mmol) y se agitó hasta la mañana siguiente a temperatura ambiente. Con posterioridad, el solvente se retiró al vacío. El residuo se purificó por HPLC preparativa para producir ácido 3-{2-[4-(3-Metoxi-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico Rt = 1,00 min (Sistema B). Condiciones para la LC-MS preparativa: Inyección del producto en bruto disuelto en 2700□L DMSO/CH3CN 1:2; columna Waters SunFire Prep OBD C18 Columna 5 µm 30 x 100 mm, fase móvil agua/CH3CN/HCOOH 0,1% 40 ml/min, ciclo 8,5 min 5%-100% CH3CN, detección con UV 225nm.

Los siguientes compuestos se obtuvieron de acuerdo con un modo similar: Compuesto 70; ácido 3-{2-[4-(5-Bromo-2-metoxi-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico Rt = 1,26 min (Sistema B).

Compuesto 71; ácido 3-{2-[4-(2,4-Dicloro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico Rt = 1,61 min (Sistema B).

Compuesto 72; ácido 3-{2-[4-(2,3-Dimetoxi-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico Rt = 0,99 min (Sistema B).

Compuesto 73; ácido 3-[2-(4-Ciclopentilmetoxi-2-metil-fenil)-morfolin-4-il]-propiónico Rt = 1,05 min (Sistema B).

Compuesto 74; ácido 3-{2-[4-(2,5-Dicloro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico Rt = 1,10 min (Sistema B).

Compuesto 75; ácido 3-{2-[2-Metil-4-(piridin-3-ilmetoxi)-fenil]-morfolin-4-il}-propiónico Rt = 0,68 min (Sistema B).

Compuesto 76; ácido 3-{2-[2-Metil-4-(naftalen-2-ilmetoxi)-fenil]-morfolin-4-il}-propiónico Rt = 1,10 min (Sistema B).

Compuesto 77; 3-{2-[4-(Benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico ácido Rt = 1,01 min (Sistema B).

Compuesto 78; ácido 3-{2-[4-(2-Metoxi-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico Rt = 0,92 min (Sistema B).

Compuesto 79; ácido 3-{2-[2-Metil-4-(6-metil-piridin-2-ilmetoxi)-fenil]-morfolin-4-il}-propiónico Rt = 0,71 min (Sistema B).

Compuesto 80; ácido 3-{2-[4-(2-Cloro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico Rt = 1,04 min (Sistema B).

Compuesto 81; ácido 3 -{2-[4-(2,5-Dimetoxi-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico Rt = 0,93 min (Sistema B).

Compuesto 82; ácido 3-{2-[4-(2-Bromo-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico Rt = 1,05 min (Sistema B).

Compuesto 83; ácido 3-{2-[2-Metil-4-(2-metil-benciloxi)-fenil]-morfolin-4-il}-propiónico Rt = 1,04 min (Sistema B).

Compuesto 84; ácido 3-{2-[4-(6,6-Dimetil-biciclo[3,1,1]hept-2-ilmetoxi)-2-metil-fenil]-morfolin-4-il}-propiónico Rt = 1,21 min (Sistema B).

Compuesto 85; ácido 3-{2-[4-(2-Cloro-6-fluoro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico Rt = 1,03 min (Sistema B).

Compuesto 86; ácido 3-{2-[4-(Bifenil-2-ilmetoxi)-2-metil-fenil]-morfolin-4-il}-propiónico Rt = 1,13 min (Sistema B).

Compuesto 87; ácido 3-{2-[2-Metil-4-(2-trifluorometil-benciloxi)-fenil]-morfolin-4-il}-propiónico Rt = 1,06 min (Sistema B).

Compuesto 88; ácido 3-{2-[4-(3,5-Dicloro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico Rt = 1,13 min (Sistema B).

Compuesto 89; ácido 3-{2-[2-Metil-4-(3-trifluorometil-benciloxi)-fenil]-morfolin-4-il}-propiónico Rt = 1,09 min (Sistema B).

Compuesto 90; ácido 3-{2-[4-(4-Cloro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico Rt = 1,06 min (Sistema B).

Compuesto 91; ácido 3-{2-[4-(4-Isopropil-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico Rt = 1,14 min (Sistema B).

Compuesto 92; ácido 3-{2-[2-Metil-4-(3-fenoxi-benciloxi)-fenil]-morfolin-4-il}-propiónico Rt = 1,15 min (Sistema B).

Compuesto 93; 3-{2-[4-(4-Metoxi-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico ácido Rt = 0,92 min (Sistema B).

Compuesto 94; ácido 3-{2-[2-Metil-4-(2-fenetil-benciloxi)-fenil]-morfolin-4-il}-propiónico Rt = 1,19 min (Sistema B).

Compuesto 95; ácido 3-{2-[4-(3,4-Dimetoxi-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico Rt = 0,86 min (Sistema B).

Compuesto 96; ácido 3-{2-[4-(3,5-Dimetil-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico Rt = 1,08 min (Sistema B).

Compuesto 97; ácido 3-{2-[4-(4-Benciloxi-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico Rt = 1,05 min (Sistema B).

Compuesto 98; ácido 3-{2-[2-Metil-4-(tiofen-2-ilmetoxi)-fenil]-morfolin-4-il}-propiónico Rt = 0,90 min (Sistema B).

Compuesto 99; ácido 3-{2-[4-(3-Fluoro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico Rt = 1,03 min (Sistema B).

Compuesto 100; 3-{2-[4-(3-Benciloxi-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico ácido Rt = 1,15 min (Sistema B).

Compuesto 101; ácido 3-{2-[4-(4-Fluoro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico Rt = 1,01 min (Sistema B).

Compuesto 102; ácido 3-{2-[4-(Bifenil-4-ilmetoxi)-2-metil-fenil]-morfolin-4-il}-propiónico Rt = 1,14 min (Sistema B).

Compuesto 103; ácido 3-{2-[4-(2,3-Dihidro-benzo[1,4]dioxin-2-ilmetoxi)-2-metil-fenil]-morfolin-4-il}-propiónico Rt = 1,03 min (Sistema B).

Compuesto 104; ácido 3-{2-[2-Metil-4-(piridin-2-ilmetoxi)-fenil]-morfolin-4-il}-propiónico Rt = 0,75 min (Sistema B).

Compuesto 105; ácido 3-{2-[4-(4-Butoxi-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico Rt = 1,05 min (Sistema B).

Compuesto 106; ácido 3-[2-(4-Ciclohexilmetoxi-2-metil-fenil)-morfolin-4-il]-propiónico Rt = 1,10 min (Sistema B).

Compuesto 107; ácido 3-{2-[2-Metil-4-(tetrahidro-furan-2-ilmetoxi)-fenil]-morfolin-4-il}-propiónico Rt = 0,83 min (Sistema B).

Compuesto 108; ácido 3-{2-[2-Metil-4-(3-metil-benciloxi)-fenil]-morfolin-4-il}-propiónico Rt = 1,05 min (Sistema B).

Compuesto 109; ácido 3-{2-[4-(2,3-Difluoro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico Rt = 1,03 min (Sistema B).

Compuesto 110; ácido 3-{2-[2-Metil-4-(4-trifluorometoxi-benciloxi)-fenil]-morfolin-4-il}-propiónico Rt = 1,12 min (Sistema B).

Compuesto 111; ácido 3-{2-[4-(3-Cloro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico Rt = 1,05 min (Sistema B).

Compuesto 112; ácido 3-{2-[2-Metil-4-(tetrahidro-piran-2-ilmetoxi)-fenil]-morfolin-4-il}-propiónico Rt = 0,91 min (Sistema B).

Compuesto 113; ácido 3-{2-[2-Metil-4-(4-trifluorometil-benciloxi)-fenil]-morfolin-4-il}-propiónico Rt = 1,08 min (Sistema B).

Compuesto 114; 3 ácido -{2-[4-(3,4-Difluoro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico Rt = 1,05 min (Sistema B).

Compuesto 115; ácido 3-{2-[2-Metil-4-(2,3,4-trimetoxi-benciloxi)-fenil]-morfolin-4-il}-propiónico Rt = 0,91 min (Sistema B).

Compuesto 116; ácido 3-{2-[4-(Ciclohex-3-enilmetoxi)-2-metil-fenil]-morfolin-4-il}-propiónico Rt = 1,07 min (Sistema B).

Compuesto 117; ácido 3-{2-[4-(4-Butil-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico Rt = 1,22 min (Sistema B).

Compuesto 118; ácido 3-{2-[2-Metil-4-(4-metil-benciloxi)-fenil]-morfolin-4-il}-propiónico Rt = 1,05 min (Sistema B).

Compuesto 119; ácido 3-{2-[4-(3-Dimetilamino-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico Rt = 0,86 min (Sistema B).

Compuesto 120; ácido 3-{2-[2-Metil-4-(piridin-4-ilmetoxi)-fenil]-morfolin-4-il}-propiónico Rt = 0,66 min (Sistema B).

Compuesto 121; ácido 3-{2-[4-(2-Yodo-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico Rt = 1,07 min (Sistema B).

Compuesto 122; ácido 3-{2-[4-(3,5-Dimetoxi-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico Rt = 1,00 min (Sistema B).

Compuesto 123; ácido 3-{2-[4-(2,4-Difluoro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico Rt = 1,03 min (Sistema B).

Compuesto 124; ácido 3-{2-[2-Metil-4-(2,4,5-trimetoxi-benciloxi)-fenil]-morfolin-4-il}-propiónico Rt = 0,88 min (Sistema B).

Compuesto 125; ácido 3-{2-[4-(3-Bromo-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico Rt = 1,08 min (Sistema B).

Compuesto 126; ácido 3-{2-[4-(4-Bromo-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico Rt = 1,07 min (Sistema B).

Compuesto 127; ácido 3-{2-[4-(4-ter-butil-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico Rt = 1,18 min (Sistema B).

Compuesto 128; ácido 3-{2-[4-(2,5-Difluoro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico Rt = 1,02 min (Sistema B).

Compuesto 129; ácido 3-{2-[2-Metil-4-(tetrahidro-furan-3-ilmetoxi)-fenil]-morfolin-4-il}-propiónico Rt = 0,83 min (Sistema B).

Método D:

Compuesto 130; sal del ácido trifluoroacético del ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico: éster ter-butílico del ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico (1,23 g; 2,6 mmol) se disolvió en CH2Cl2 (15 ml). TFA (5 ml) se agregó y la mezcla resultante se agitó hasta la mañana siguiente a temperatura ambiente. La mezcla de reacción se concentró al vacío, y el residuo se sometió a tratamiento con iPr2O. El precipitado se recolectó por filtración sobre para producir sal del ácido trifluoroacético del ácido 3-{2-[4-(2,6-dicloro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico. 1H RMN (400 MHz, DMSO-d6) □ ppm 2,27 - 2,38 (2 H, m), 2,83 (2 H, t, J=7,6 Hz), 3,07 (1 H, t, J=11,7Hz), 3,13 - 3,28 (1 H, m), 3,39 (2 H, t, J=7,7 Hz), 3,48 - 3,69 (2 H, m), 3,83 - 3,98 (1 H, m), 4,18 (1 H, d), 4,90 (1 H, d, J=10,6 Hz), 5,22 (2 H, d), 6,88 - 7,01 (2 H, m), 7,34 (1 H, d, J=8,3 Hz), 7,43 - 7,52 (1 H, m), 7,58 (2 H, d).

El siguiente compuesto se obtuvo de acuerdo con un modo similar:

Compuesto 131; sal del ácido trifluoroacético del ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-3-trifluorometil-fenil]-morfolin-4-il}-propiónico. 1H RMN (400 MHz, DMSO-d6) □ ppm 2,73 - 2,90 (m, 2 H) 3,07 - 3,26 (m, 2 H) 3,28 - 3,45 (m, 2 H) 3,51 (d, J=12,1 Hz, 1 H) 3,71 (d, J=12,1 Hz, 1 H) 3,90 (t, J=12,1 Hz, 1 H) 4,20 (d, J=10,7 Hz, 1 H) 4,81 (d, J=10,7 Hz, 1 H) 5,38 (s, 2 H) 7,47 - 7,53 (m, 1 H) 7,56 - 7,63 (m, 3 H) 7,65 - 7,75 (m, 2 H) 10,84 (br. s., 1 H) 12,42 (br. s., 1 H).

Método E:

Compuesto 132; ácido {2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-acético: Una mezcla de etil éster del ácido {2-[4-(2,6-dicloro-benciloxi)-fenil]-morfolin-4-il}-acético (0,62 g; 1,5 mmol), NaOH 2M acuoso (5 ml) y etanol (25 ml) se agitó durante 3 horas a temperatura ambiente. Con posterioridad, se agregó HCl 1M acuoso (9,8 ml) y la mezcla se concentró al vacío. El residuo se sometió a tratamiento con NH4Cl saturado y CH2Cl2. El precipitado formado se recolectó por filtración sobre, se lavó con pequeñas cantidades de agua y etanol, y se secó al vacío para producir {2-[4-(2,6-dicloro-benciloxi)-fenil]-morfolin-4-il}-acético ácido (0,41 g). 1H RMN (400 MHz, DMSO-d6) □ ppm 2,23 (t, J= 10 Hz, 1 H) 2,40 (dt, J=10 Hz J=3 Hz, 1 H) 2,76 – 2,83 (m , 1 H) 2,86 – 2,93 (m, 1 H) 3,13 – 3,25 (m, 2 H) 3,67 (dt, J= 11 Hz J=2 Hz, 1 H) 3,87 – 3,95 (m, 1 H) 4,46 (dd, J=10 Hz J=2

Hz, 1H) 5,21 (s, 2 H) 6,99 – 7,06 (m, 2 H) 7,26 – 7,32 (m, 2 H) 7,44 – 7,50 (m, 1 H) 7,57 (d, J=7 Hz, 2 H) 12,3 (br. s, 1 H).

Los siguientes compuestos se obtuvieron de acuerdo con un modo similar:

Compuesto 219; ácido 3-{2-[4-(Indan-1-iloxi)-fenil]-morfolin-4-il}-propiónico Punto de fusión 124 – 129,5°C.

Compuesto 220; ácido 3-{2-[4-(7-Metil-indan-1-iloxi)-fenil]-morfolin-4-il}-propiónico Punto de fusión 134 – 139°C.

Compuesto 221; 3-{2-[4-(2,3-Dihidro-benzofuran-3-iloxi)-fenil]-morfolin-4-il}-propiónico ácido. Punto de fusión 141,5 – 144,5°C.

Compuesto 222; ácido 3-(2-{4-[3-(4-Cloro-fenil)-alliloxi]-fenil}-morfolin-4-il)-propiónico 1H RMN (400 MHz, CDCl3) □ ppm 2,33 (t, J=11,7 Hz, 1 H) 2,47 - 2,59 (m, 3 H) 2,74 - 2,86 (m, 2 H) 2,98 - 3,10 (m, 2 H) 3,87 (td, J=11,9, 2,4 Hz, 1 H) 4,13 (dd, J=11,9, 2,4 Hz, 1 H) 4,55 (dd, J=10,5, 2,5 Hz, 1 H) 4,69 (dd, J=5,7, 1,6 Hz, 2 H) 6,32 - 6,42 (m, 1 H) 6,68 (d , J=16,0 1 H) 6,95 (d, J=8,8 Hz, 2 H) 7,23 - 7,36 (m, 6 H).

Compuesto 223; ácido 3-{2-[4-(3-Fenil-prop-2-iniloxi)-fenil]-morfolin-4-il}-propiónico 1H RMN (400 MHz, CDCl3) □ ppm 2,33 (t, J=11,7 Hz, 1 H) 2,47 - 2,60 (m, 3 H) 2,74 - 2,86 (m, 2 H) 2,98 - 3,11 (m, 2 H) 3,87 (td, J=11,9, 2,5 Hz, 1 H) 4,13 (dd, J=11,9, 2,4 Hz, 1 H) 4,55 (dd, J=10,5, 2,5 Hz, 1 H) 4,91 (s, 2 H) 7,03 (d, J=8,8 Hz, 2 H) 7,25 - 7,36 (m, 5 H) 7,40 - 7,46 (m, 2 H).

Compuesto 224; 3-(2-{4-[3-fenil-alliloxi]-fenil}-morfolin-4-il)-propiónico ácido 1H RMN (400 MHz, CDCl3) □ ppm 2,32 (t, J=11,7 Hz, 1 H) 2,47 - 2,59 (m, 3 H) 2,75 - 2,87 (m, 2 H) 2,98 - 3,11 (m, 2 H) 3,87 (td, J=11,9, 2,5 Hz, 1 H) 4,14 (dd, J=10,5, 2,4 Hz, 1 H) 4,55 (dd, J=10,5, 2,4 Hz, 1 H) 4,70 (dd, J=5,7, 1,6 Hz, 2 H) 6,36 - 6,44 (m, 1 H) 6,69 (d , J=15,9 1 H) 6,95 (d, J=8,8 Hz, 2 H) 7,22 - 7,43 (m, 7 H).

Compuesto 225; ácido 3-(2-{4-[3-(4-Cloro-fenil)-prop-2-iniloxi]-fenil}-morfolin-4-il)-propiónico 1H RMN (400 MHz, CDCl3) □ ppm 2,28 - 2,36 (m, 1 H) 2,47 - 2,59 (m, 3 H) 2,73 - 2,86 (m, 2 H) 3,01 (d, J=11,5 Hz, 1 H) 3,08 (d, J=11,5 Hz, 1 H) 3,86 - 3,91 (m, 1 H) 4,11 – 4,16 (m, 1 H) 4,53 - 4,58 (m, 1 H) 4,89 (s, 2 H) 7,03 (d, J=8,7 Hz, 2 H) 7,25 - 7,37 (m, 6 H).

Compuesto 226; ácido 3-{2-[4-(4-Metoxi-benciloxi)-fenil]-morfolin-4-il}-propiónico. 1H RMN (400 MHz, DMSO-d6) □ ppm 2,03 - 2,12 (m, 1 H) 2,20 – 2,28 (m, 1 H) 2,41 – 2,48 (m, 2 H) 2,63 - 2,71 (m, 2 H) 2,82 - 2,87 (m, 1 H) 2,88 - 2,96 (m, 1 H) 3,58 - 3,71 (m, 1 H) 3,75 (s, 3 H) 3,89 - 3,96 (m, 1 H) 4,35 - 4,44 (m, 1 H) 5,00 (s, 2 H) 6,88 - 6,99 (m, 4 H) 7,25 (d, J=8,7 Hz, 2 H) 7,37(d, J=8,7 Hz, 2 H) 12,3 (bs, 1 H).

Compuesto 227; ácido 3-{2-[4-(2-Metoxi-benciloxi)-fenil]-morfolin-4-il}-propiónico. 1H RMN (400 MHz, DMSO-d6) □ ppm 1,90 - 1,98 (m, 1 H) 2,08 - 2,17 (m, 1 H) 2,36 - 2,44 (m,

2 H) 2,54 - 2,61 (m, 2 H) 2,73 - 2,79 (m, 1 H) 2,82 - 2,88 (m, 1 H) 3,55 - 3,65 (m, 1 H) 3,82 (s, 3 H) 3,87 - 3,93 (m, 1 H) 4,35 - 4,40 (m, 1 H) 5,03 (s, 2 H) 6,91 - 6,99 (m, 3 H) 7,05 (d, J=7,8 Hz, 1 H) 7,27 (d, J=8,7 Hz, 2 H) 7,30 - 7,40 (m, 2 H) 12,1 –12,6 (bs, 1 H).

Método F:

Compuesto 133; ácido 3 -[2-(4-Octiloxi-fenil)-morfolin-4-il]-3-oxo-propiónico: A una solución de etil éster del ácido 3-[2-(4-octiloxi-fenil)-morfolin-4-il]-3-oxo-propiónico (0,46 g; 1,1 mmol) en tetrahidrofurano (4 ml) y agua (1 ml) se agregó hidróxido de litio (54,3 mg; 2,3 mmol) y la mezcla se agitó a 70°C durante 3 horas. Después de enfriar hasta alcanzar la temperatura ambiente la mezcla resultante se cargó sobre una PE-AX columna [ISOLUTE (Biotage AB); 0,58 mmol/g, 10g]. La columna se lavó con CH3CN y a continuación el requerido compuesto se eluyó con 20 % v/v TFA en CH3CN. Las fracciones que contienen compuesto se concentraron al vacío para producir ácido 3-[2-(4-octiloxi-fenil)-morfolin-4-il]-3-oxo-propiónico (0,40 g) 1H RMN (400 MHz, DMSO-d6) □ ppm 0,83 - 0,89 (m, 3 H) 1,22 - 1,34 (m, 8 H) 1,39 (d, J=7,52 Hz, 2 H) 1,65 - 1,73 (m, 2 H) 3,75 (d, J=1,20 Hz, 1 H) 3,91 - 3,99 (m, 3 H) 4,27 (br. s., 1 H) 6,89 (dd, J=8,58, 3,16 Hz, 2 H) 7,28 (dd, J=8,43, 3,91 Hz, 2 H)

Compuesto 151: ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-3-oxo-propiónico se obtuvo de acuerdo con un modo similar. 1H RMN (400 MHz, CLOROFORMO-d) □ ppm 2,71 - 2,79 (m, 2 H) 3,41 - 3,49 (m, 1 H) 3,56 - 3,72 (m, 3 H) 4,28 - 4,45 (m, 2 H) 4,70 - 4,76 (m, 1 H) 5,07 (s, 2 H) 6,98 (d, J=8,8 Hz, 2 H) 7,27 - 7,45 (m, 7 H).

Método G:

Compuesto 134; sal de trietilamonio del ácido 2,2-Difluoro-3-[2-(4-octiloxi-fenil)-morfolin-4-il]-propiónico: A una solución de etil éster del ácido 2,2-difluoro-3-[2-(4-octiloxi-fenil)-morfolin-4-il]-propiónico (0,55 g; 1,3 mmol) en THF (5 ml) y agua (1 ml) se agregó Hidróxido de litio (0,06 g; 2,6 mmol) y se agitó a 70°C durante 3 horas. Después de enfriar hasta alcanzar la temperatura ambiente la mezcla de reacción se cargó sobre una columna SCX-3 [ISOLUTE (Biotage AB); 0,61 mmol/g, 15g]. La columna se lavó con CH3CN (4 x 15 ml) y con posterioridad el requerido compuesto se eluyó con CH3CN + 10% Et3N (2 x 15 ml). Las fracciones que contienen compuesto se concentraron al vacío para producir ácido 2,2-Difluoro-3-[2-(4-octiloxi-fenil)-morfolin-4-il]-propiónico como la sal de trietilamonio (0,45 g). 1H RMN (400 MHz, Cloroformo-d) □ ppm 0,85 - 0,92 (m, 1 H) 0,88 (s, 1 H) 1,13 (d, J=6,32 Hz, 5 H) 1,30 (t, J=7,37 Hz, 10 H) 1,43 (qd, J=7,22, 6,92 Hz, 1 H) 1,72 - 1,79 (m, J=7,30, 7,30, 7,07, 6,62 Hz, 1 H) 2,99 - 3,04 (m, 1 H) 3,06 (s, 1 H) 3,09 (br. s., 1 H) 3,09 - 3,15 (m, 2 H) 3,11 (d, J=7,52 Hz, 2 H) 3,77 - 3,85 (m, 1 H) 3,92 (t, J=6,62 Hz, 2 H) 6,84 (d, J=8,73 Hz, 1 H) 7,24 (d, J=8,73 Hz, 1 H).

Compuesto 150; sal de trietilamonio del ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-2,2-difluoro-propiónico: se obtuvo de acuerdo con un modo similar. 1H RMN (400 MHz, DMSO-d6) □ ppm 2,18 (t, J=10,8 Hz, 1 H) 2,32 - 2,42 (m, 1 H) 2,77 - 2,94 (m, 4 H) 3,56 - 3,65 (m, 1 H) 3,82 - 3,90 (m, 1 H) 4,34 - 4,41 (m, 1 H) 5,21 (s, 2 H) 7,02 (d, J=8,6 Hz, 2 H) 7,27 (d, J=8,6 Hz, 2 H) 7,44 - 7,50 (m, 1 H) 7,56 (d, J=8,3 Hz, 2 H) 10,4 (bs, 1 H).

Método H:

Compuesto 135; 2-[2-(4-Octiloxi-fenil)-morfolin-4-il]-etanol: A una solución de 2-(4-octiloxi-fenil)-4-[2-(tetrahidro-piran-2-iloxi)-etil]-morfolina (1,85 g; 4,4 mmol) en MeOH (10 ml) se agregó ácido p-toluensulfónico monohidrato (0,84 g; 4,4 mmol) y la mezcla resultante se agitó a temperatura ambiente durante 3 horas. La mezcla de reacción se repartió entre solución acuosa al 5% de NaHCO3 y EtOAc. La fase orgánica se secó (Na2SO4), se filtró, y se concentró al vacío para producir 2-[2-(4-octiloxi-fenil)-morfolin-4-il]-etanol (1,44 g). 1H RMN (400 MHz, CDCl3) □ ppm 0,85 - 0,92 (m, 3 H) 1,23 - 1,37 (m, 7 H) 1,39 - 1,48 (m, 2 H) 1,71 - 1,81 (m, 2 H) 2,05 (s, 1 H) 2,15 - 2,24 (m, 1 H) 2,36 (td, J=11,44, 3,31 Hz, 1 H) 2,53 - 2,62 (m, 2 H) 2,79 (dd, J=11,44, 1,50 Hz, 1 H) 3,32 (d, J=1,50 Hz, 1 H) 3,61 - 3,68 (m, 2 H) 3,76 - 3,88 (m, 1 H) 3,94 (t, J=6,62 Hz, 2 H) 4,03 (dd, J=11,44, 1,81 Hz, 1 H) 4,48 (dd, J=10,23, 2,11 Hz, 1 H) 6,84 - 6,89 (m, 2 H) 7,24 - 7,30 (m, 2 H)

Compuesto 141; 2-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-etanol se obtuvo de acuerdo con un modo similar. 1H RMN (400 MHz, DMSO-d6) □ ppm 3,06 - 3,28 (m, 4 H) 3,48 - 3,66 (m, 2 H) 3,81 (t, J=4,6 Hz, 2 H) 3,98 - 4,09 (m, 1 H) 4,10 - 4,19 (m, 1 H) 4,86 (d, J=10,6 Hz, 1 H) 5,24 (s, 2 H) 5,42 (bs., 1 H) 7,11 (d, J=8,6 Hz, 2 H) 7,34 (d, J=8,6 Hz, 2 H) 7,45 - 7,51 (m, 1 H) 7,57 (d, J=8,3 Hz, 2 H) 10,9 (s, 1H)

Método I:

Compuesto 136; ácido {3-[2-(4-Octiloxi-fenil)-morfolin-4-il]-propil}-fosfónico: A una solución de éster dietílico del ácido {3-[2-(4-Octiloxi-fenil)-morfolin-4-il]-propil}-fosfónico (1,06 g; 2,26 mmol) en CH2Cl2 (10 ml) se agregó bromotrimetilsilano (2,38 ml; 18,06 mmol) y la mezcla de reacción se agitó a temperatura ambiente hasta la mañana siguiente. Con posterioridad la mezcla se concentró al vacío, redisuelto en MeOH (10 ml), y se agitó durante 2 horas a temperatura ambiente. La mezcla resultante se concentró al vacío y se trató con iPr2O. El precipitado se recolectó por filtración sobre y se secó con aplicación de vacío para dar ácido {3-[2-(4-Octiloxi-fenil)-morfolin-4-il]-propil}-fosfónico (0,82 g; 69,8%) 1H RMN (400 MHz, DMSO-d6) □ppm 0,75 (t, 3 H) 1,06 - 1,25 (m, 8 H) 1,24 - 1,35 (m, 2 H) 1,42 - 1,68 (m, 4 H) 1,73 - 1,94 (m, 2 H) 2,83 - 3,04 (m, 2 H) 3,10 (t, 2 H) 3,37 (d, J=12,04 Hz, 1 H) 3,43 (d, J=12,04 Hz, 1 H) 3,72 - 3,91 (m, 3 H) 4,04 (d,

J=12,34 Hz, 1 H) 4,64 (d, J=10,83 Hz, 1 H) 6,83 (d, J=8,43 Hz, 2 H) 7,20 (d, J=8,43 Hz, 2 H).

Los siguientes compuestos se obtuvieron de acuerdo con un modo similar:

Compuesto 137; ácido {2-[2-(4-Octiloxi-fenil)-morfolin-4-il]-etil}-fosfónico 1H RMN (400 MHz, DMSO-d6) □ ppm 0,79 - 0,90 (m, 3 H) 1,15 - 1,45 (m, 9 H) 1,62 - 1,74 (m, 2 H) 2,04 - 2,20 (m, 2 H) 3,03 - 3,23 (m, 2 H) 3,25 - 3,39 (m, 2 H) 3,57 (d, J=11,74 Hz, 1 H) 3,67 (d, J=12,04 Hz, 1 H) 3,84 - 3,99 (m, 3 H) 4,09 - 4,22 (m, 1 H) 4,72 (d, J=10,53 Hz, 1 H) 6,94 (d, J=8,43 Hz, 2 H) 7,29 (d, J=8,73 Hz, 2 H).

Compuesto 146; ácido (3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-propil)-fosfónico; 1H RMN (400 MHz, DMSO-d6) □ ppm 1,57 – 1,69 (m, 2 H) 1,86 – 2,00 (m, 2H) 3,05 - 3,27 (m, 4 H) 3,47 - 3,65 (m, 2 H) 3,90 (d, J=12,8 Hz, 1 H) 4,18 (d, J=12,8 Hz 1 H) 4,72 (d, J=10,9 Hz, 1 H) 5,24 (s, 2H) 7,11 (d, J=8,6 Hz, 2 H) 7,37 (d, J=8,6 Hz, 2 H) 7,45 – 7,52 (m, 1H) 7,58 (d, J=8,3 Hz, 2H) 9,80 -10,20 (bs, 1H).

Método J:

Compuesto 138; mono-{2-[2-(4-octiloxi-fenil)-morfolin-4-il]-etil} éster del ácido fosfórico: Una solución de 2-[2-(4-octiloxi-fenil)-morfolin-4-il]-etil éster de di-ter-butil éster del ácido fosfórico (0,69 g; 1,31 mmol) en TFA (3 ml) y CH2Cl2 (3 ml) se agitó a temperatura ambiente durante 1 hora. Con posterioridad, la mezcla de reacción se concentró al vacío y el residuo se trató con iPr2O. El precipitado se recolectó por filtración sobre y se secó al vacío hasta la mañana siguiente para producir sal del ácido mono-{2-[2-(4-octiloxi-fenil)-morfolin-4-il]-etil} éster del ácido fosfórico (0,42 g) 1H RMN (400 MHz, DMSO-d6) □ ppm 0,63 - 0,79 (m, 3 H) 0,98 - 1,32 (m, 9 H) 1,45 - 1,58 (m, 2 H) 2,86 - 3,07 (m, 2 H) 3,13 - 3,28 (m, 2 H) 3,29 - 3,47 (m, 2 H) 3,68 - 3,83 (m, 3 H) 3,89 - 4,06 (m, 3 H) 4,57 (d, J=10,53 Hz, 1 H) 6,77 (d, J=8,43 Hz, 2 H) 7,10 (d, J=8,43 Hz, 2 H).

Método K:

Compuesto 149; 2-[4-(2,6-Dicloro-benciloxi)-fenil]-4-(1(2)H-tetrazol-5-ilmetil)-morfolina, como clorhidrato: A 2-[4-(2,6-dicloro-benciloxi)-fenil]-morfolina, como clorhidrato (0,30 g; 0,80 mmol) se agregó NaOH 2 M acuoso y EtOAc. Las fases se separaron y la fase orgánica se secó (Na2SO4), se filtró, y se concentró al vacío. La 2-[4-(2,6-dicloro-benciloxi)-fenil]-morfolina obtenida se mezcló con NaI (24,0 mg; 0,16 mmol), 5-clorometil-1(2)H-tetrazol (0,11 g; 0,96 mmol), K2CO3 (0,33 g; 2,40 mmol), y CH3CN (10 ml) en un frasco de pírex cerrado. La mezcla resultante se calentó a 100°C, hasta la mañana siguiente. Después de enfriar hasta alcanzar la temperatura ambiente la mezcla se concentró al vacío, y el residuo se purificó por cromatografía en columna (SiO2, EtOAc: MeOH 1:1) para producir 2-[4-(2,6-dicloro-benciloxi)-fenil]-4-(1(2)H-tetrazol-5-ilmetil)-morfolina La base libre se disolvió en una solución 4M de HCl in 1,4-dioxano (4 ml, 16

mmol) y se agitó a temperatura ambiente, durante una hora. Con posterioridad la mezcla se concentró al vacío y el residuo se trató con iPr2O. El precipitado se recolectó por filtración sobre y se secó con aplicación de vacío para producir 2-[4-(2,6-Dicloro-benciloxi)-fenil]-4-(1(2)H-tetrazol-5-ilmetil)-morfolina, como clorhidrato (0,13 g). 1H RMN (400 MHz, DMSO-d6) □ ppm 1,96 (t, J=10,9 Hz, 1 H) 2,13 - 2,21 (m, 1 H) 2,73 - 2,79 (m, 1 H) 2,84 - 2,90 (m, 1 H) 3,55 - 3,64 (m, 3 H) 3,84 - 3,91 (m, 1 H) 4,34 - 4,39 (m, 1 H) 5,21 (s, 2 H) 7,00 (d, J=8,6 Hz, 2 H) 7,24 (d, J=8,6 Hz, 2 H) 7,44 - 7,50 (m, 1 H) 7,56 (d, J=8,3 Hz, 2 H).

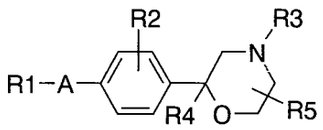
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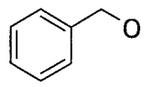
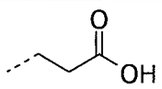
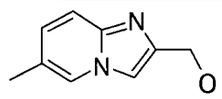
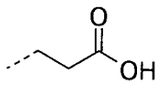
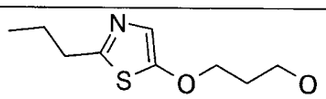
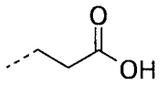
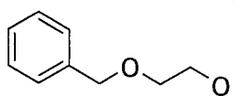
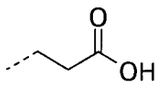
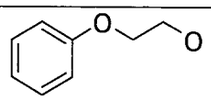
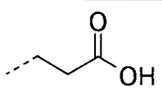
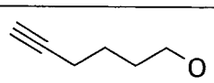
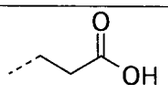
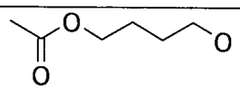
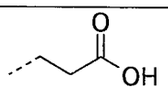
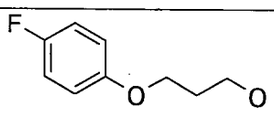
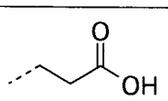
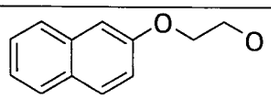
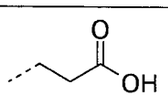
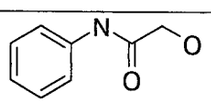
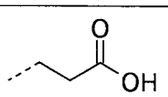
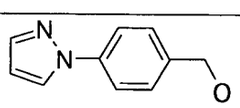
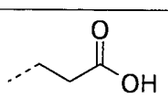
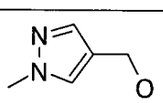
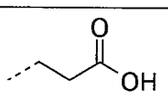
Compuesto 228; 2-[4-(2,6-Dicloro-benciloxi)-fenil]-4-[2-(2H-tetrazol-5-il)-etil]-morfolina, como clorhidrato: A una solución de 3-{2-[4-(2,6-dicloro-benciloxi)-fenil]-morfolin-4-il}-propionitrilo (0,30 g; 0,77 mmol) en xileno (10 ml) se agregó cloruro de tributilestaño (0,46 ml; 1,7 mmol) y NaN3 (110 mg; 1,7 mmol). La mezcla resultante se calentó a 120°C durante dos días. Después de enfriar hasta alcanzar la temperatura ambiente la mezcla se sometió a tratamiento con metanol (10 ml) y se concentró al vacío. El residuo se purificó por cromatografía en columna (EtOAc: metanol 90:10 hasta 50:50) para producir 2-[4-(2,6-dicloro-benciloxi)-fenil]-4-[2-(2H-tetrazol-5-il)-etil]-morfolina como la base libre (0,30 g), La base libre se sometió a tratamiento con una solución de HCl en 1,4-dioxano, después de agitar a temperatura ambiente durante 4 horas, la sal se precipitó. La sal se recolectó por filtración sobre, se lavó con Et2O y se secó al vacío para producir 2-[4-(2,6-dicloro-benciloxi)-fenil]-4-[2-(2H-tetrazol-5-il)-etil]-morfolina, como clorhidrato (0,30 g). 1H RMN (400 MHz, DMSO-d6) □ ppm 3,15 - 3,29 (m, 2 H) 3,53 - 3,75 (m, 6 H) 4,06 - 4,22 (m, 2 H) 4,94 (d, J=11,0 Hz, 1 H) 5,24 (s, 2 H) 7,11 (d, J=8,6 Hz, 2 H) 7,36 (d, J=8,6 Hz, 2 H) 7,45 - 7,52 (m, 1 H) 7,58 (d, J=8,3 Hz, 2 H) 12,31 (bs, 1 H).

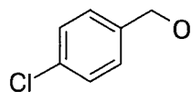
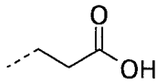
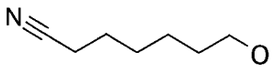
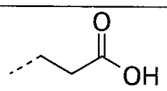
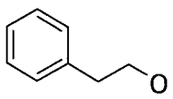
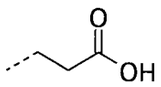
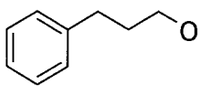
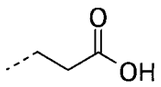
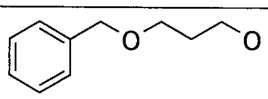
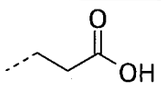
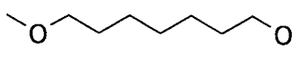
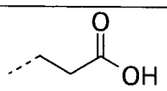
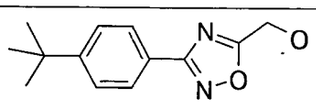
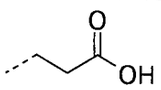
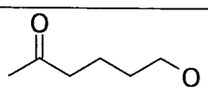
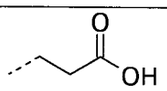
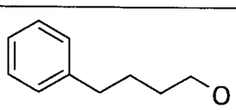
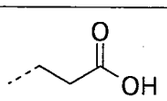
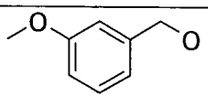
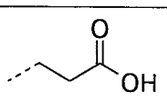
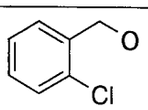
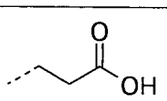
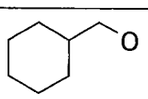
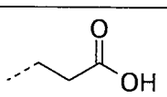
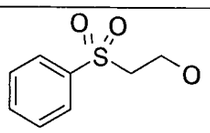
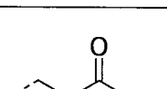
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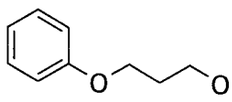
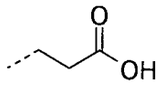
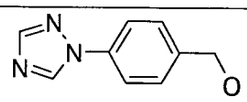
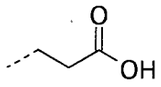
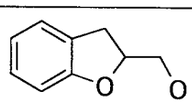
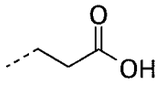
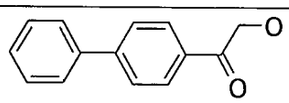
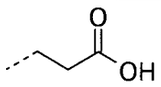
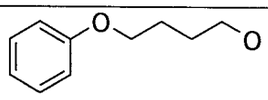
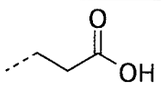
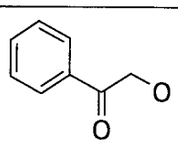
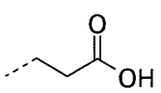
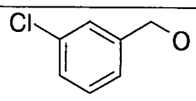
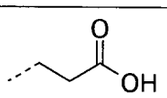
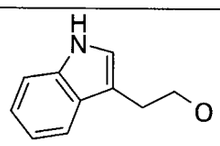
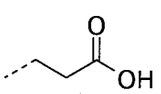
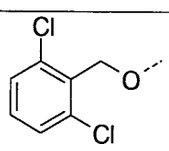
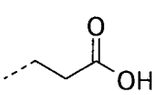
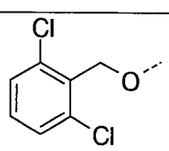
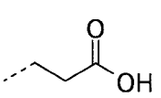
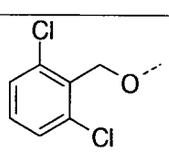
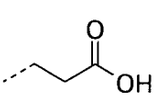
Compuesto 229; ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-2,2-dimetil-propiónico: A una suspensión de éster metílico del ácido 3-{2-[4-(2,6-dicloro-benciloxi)-fenil]-morfolin-4-il}-2,2-dimetil-propiónico (1,05 g; 2,32 mmol) en THF (21 ml) y agua (5,25 ml) se agregó LiOH (111,2 mg; 4,64 mmol). La mezcla resultante se agitó durante dos días a 50°C. Después de enfriar hasta alcanzar la temperatura ambiente la mezcla de reacción se neutralizó (pH 7) con HCl 1M acuoso (4,64 ml), se diluyó con agua (50 ml) y se extrajo con CH2Cl2 (3 X 50 ml). Las fases orgánicas combinadas se secaron (Na2SO4), se filtraron y se concentraron al vacío. El residuo sólido se trituró con iPr2O (10 ml) y se recolectó por filtración sobre para producir ácido 3-{2-[4-(2,6-dicloro-benciloxi)-fenil]-morfolin-4-il}-2,2-dimetil-propiónico (0,72 g) como un polvo blanco.

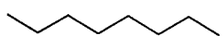
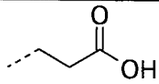
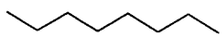
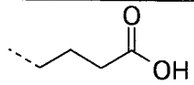
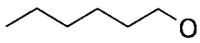
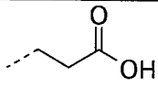
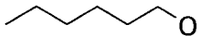
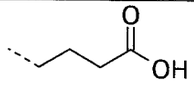
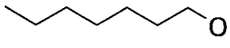
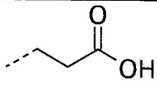
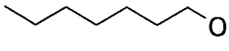
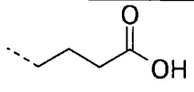
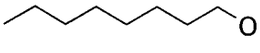
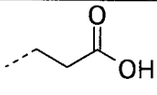
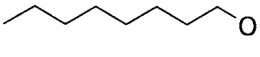
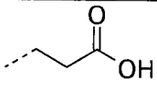
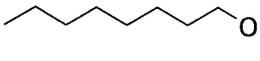
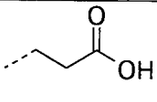
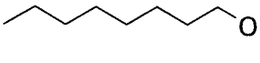
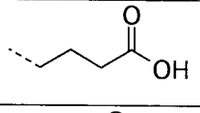
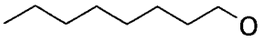
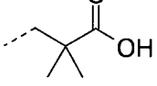
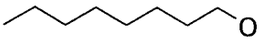
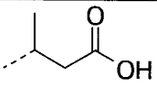
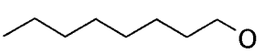
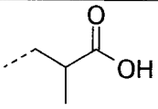
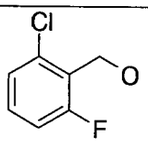
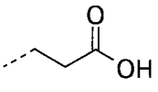
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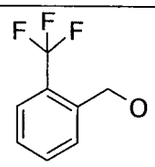
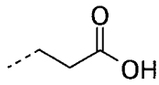
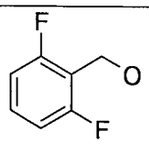
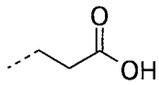
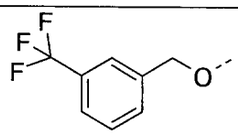
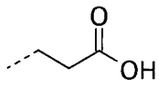
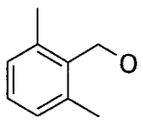
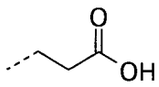
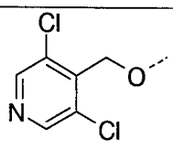
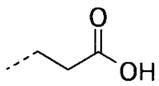
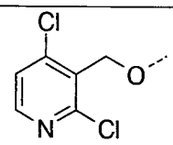
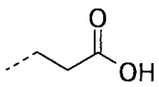
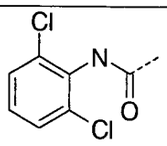
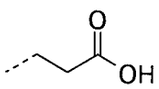
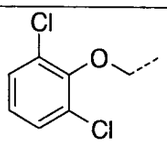
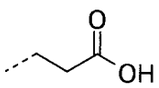
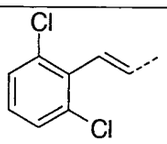
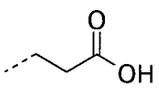
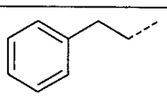
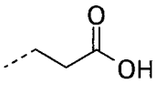


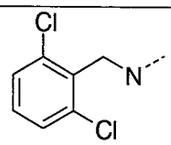
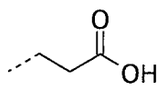
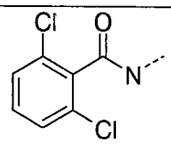
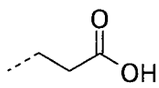
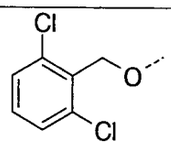
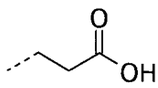
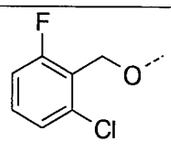
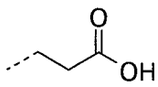
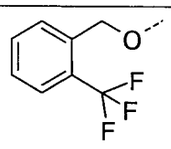
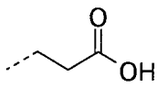
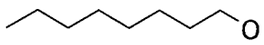
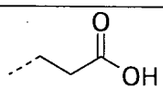
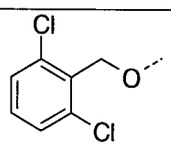
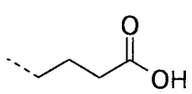
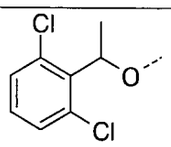
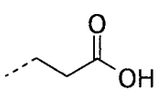
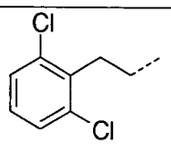
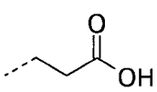
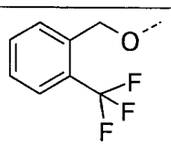
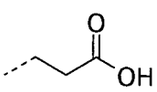
Comp no.	R1-A	R2	R3	R4	R5	Met.
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4		H		H	H	A
5		H		H	H	A
6		H		H	H	A
7		H		H	H	A
8		H		H	H	A
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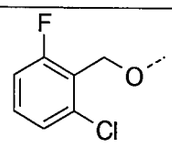
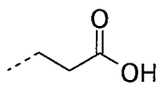
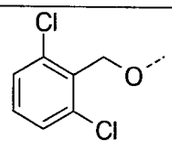
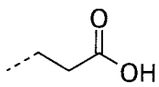
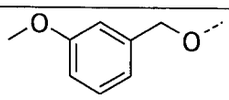
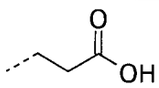
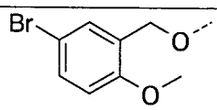
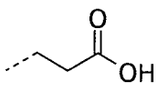
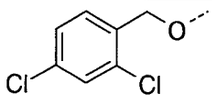
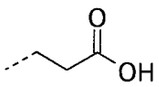
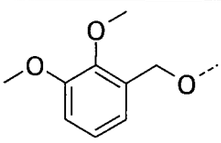
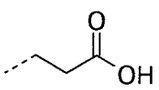
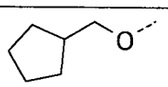
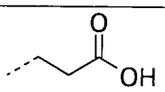
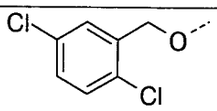
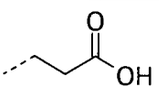
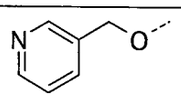
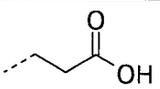
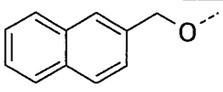
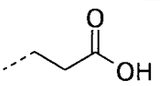
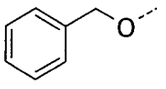
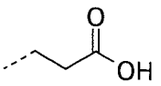
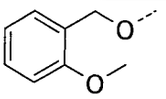
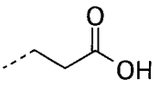
Comp no.	R1-A	R2	R3	R4	R5	Met.
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15		H		H	H	A
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17		H		H	H	A
18		H		H	H	A
19		H		H	H	A
20		H		H	H	A
21		H		H	H	A
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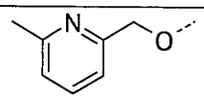
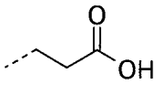
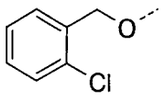
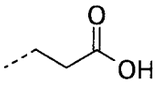
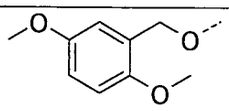
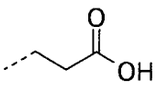
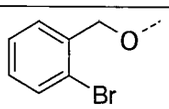
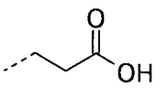
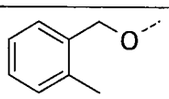
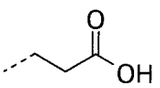
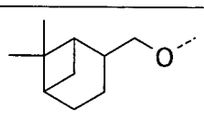
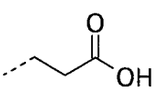
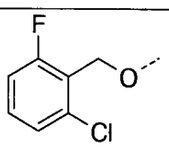
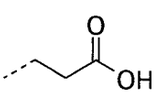
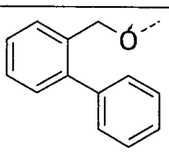
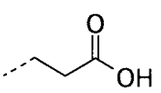
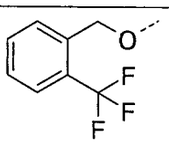
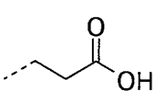
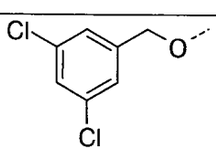
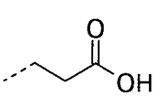
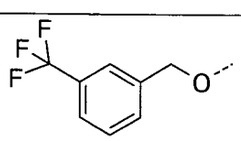
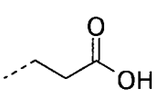
Comp no.	R1-A	R2	R3	R4	R5	Met.
26		H		H	H	A
27		H		H	H	A
28		H		H	H	A
29		H		H	H	A
30		H		H	H	A
31		H		H	H	A
32		H		H	H	A
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34a		H		H	H	B
34b		H		H	H	B

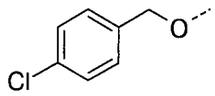
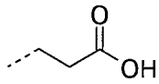
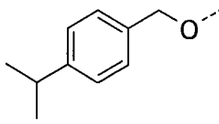
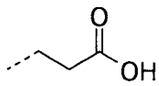
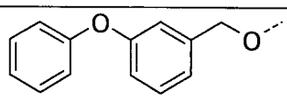
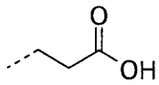
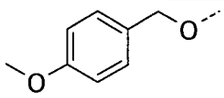
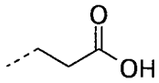
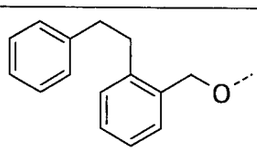
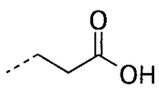
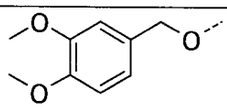
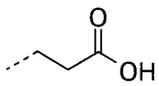
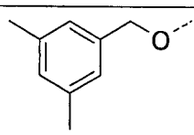
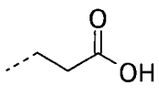
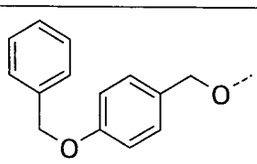
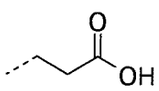
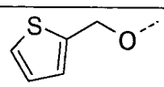
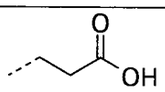
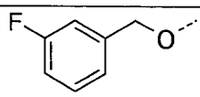
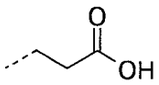
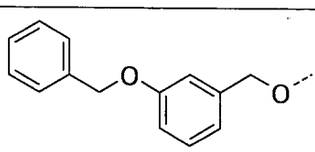
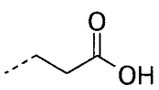
Comp no.	R1-A	R2	R3	R4	R5	Met.
35		H		H	H	B
36		H		H	H	B
37		H		H	H	B
38		H		H	H	B
39		H		H	H	B
40		H		H	H	B
41		H		H	H	B
41a		H		H	H	B
41b		H		H	H	B
42		H		H	H	B
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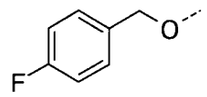
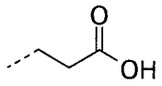
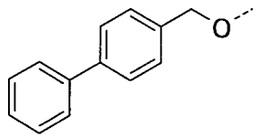
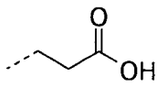
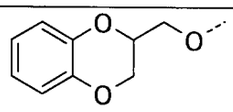
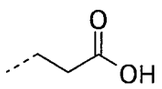
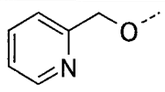
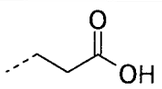
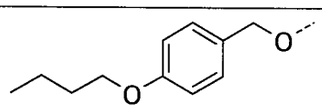
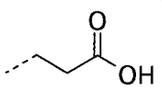
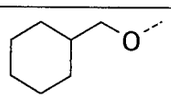
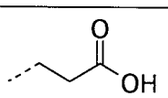
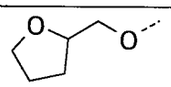
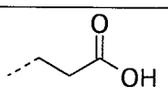
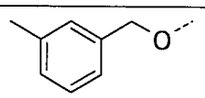
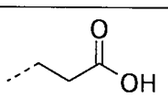
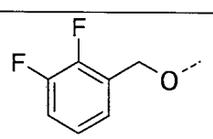
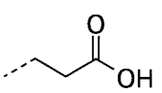
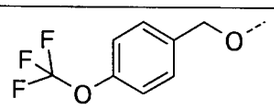
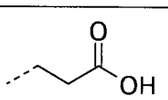
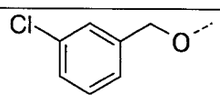
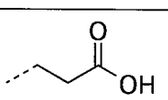
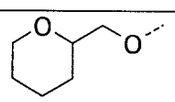
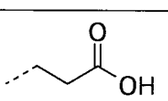
Comp no.	R1-A	R2	R3	R4	R5	Met.
47		H		H	H	B
48		H		H	H	B
49		H		H	H	B
50		H		H	H	B
51		H		H	H	B
52		H		H	H	B
53		H		H	H	B
54		H		H	H	B
55		H		H	H	B
56		H		H	H	B

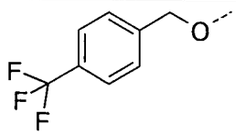
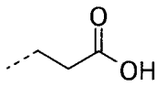
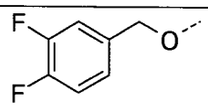
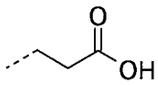
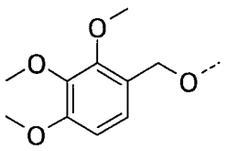
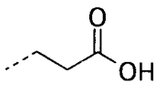
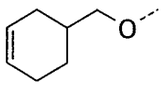
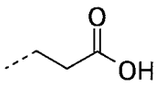
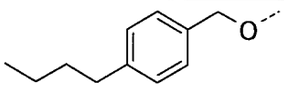
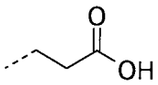
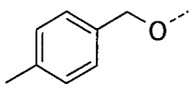
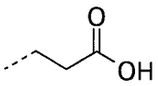
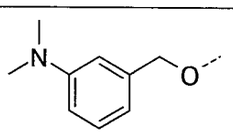
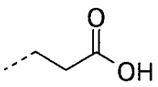
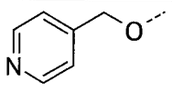
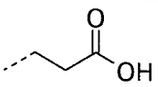
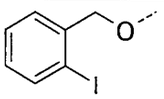
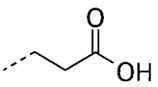
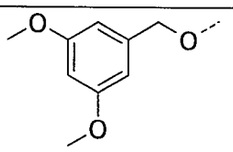
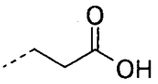
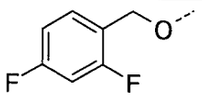
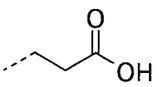
Comp no.	R1-A	R2	R3	R4	R5	Met.
57		H		H	H	B
58		H		H	H	B
59		H		Me	H	B
60		H		Me	H	B
61		H		Me	H	B
62		H		Me	H	B
63		H		H	H	B
64		H		H	H	B
65		H		H	H	B
66		3-OMe		H	H	B

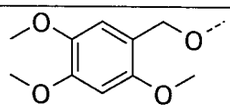
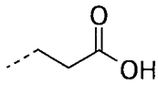
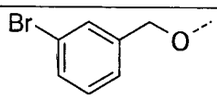
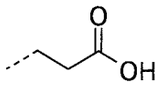
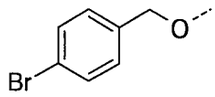
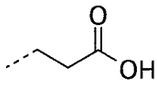
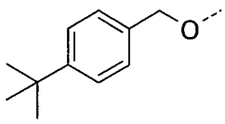
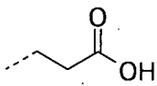
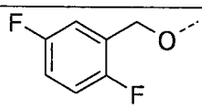
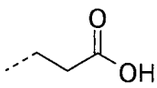
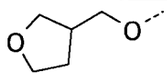
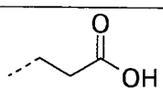
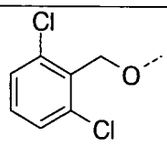
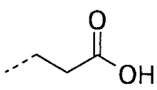
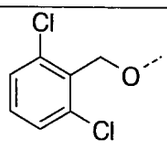
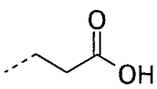
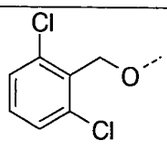
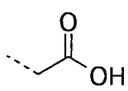
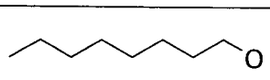
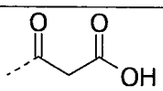
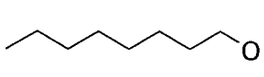
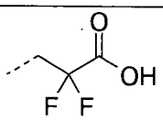
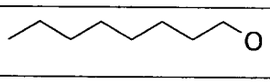
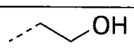
Comp no.	R1-A	R2	R3	R4	R5	Met.
67		3-OMe		H	H	B
68		3-OMe		H	H	B
69		2-Me		H	H	C
70		2-Me		H	H	C
71		2-Me		H	H	C
72		2-Me		H	H	C
73		2-Me		H	H	C
74		2-Me		H	H	C
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77		2-Me		H	H	C
78		2-Me		H	H	C

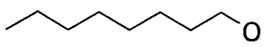
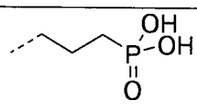
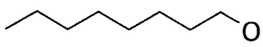
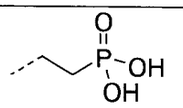
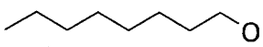
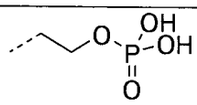
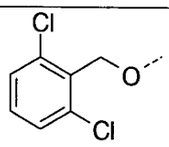
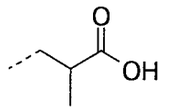
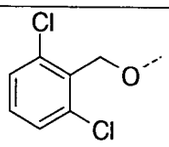
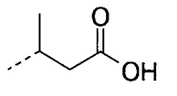
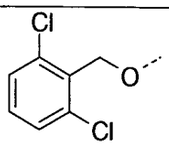
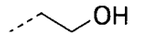
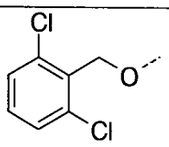
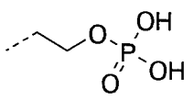
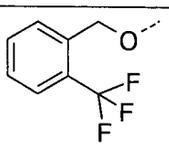
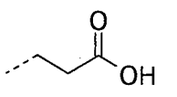
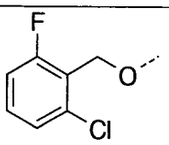
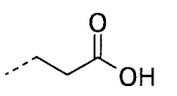
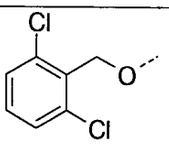
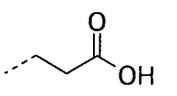
Comp no.	R1-A	R2	R3	R4	R5	Met.
79		2-Me		H	H	C
80		2-Me		H	H	C
81		2-Me		H	H	C
82		2-Me		H	H	C
83		2-Me		H	H	C
84		2-Me		H	H	C
85		2-Me		H	H	C
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89		2-Me		H	H	C

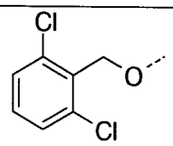
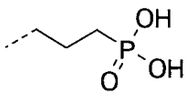
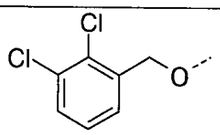
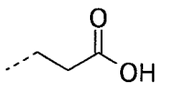
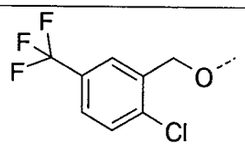
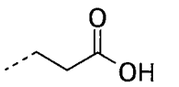
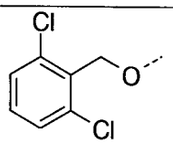
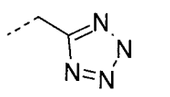
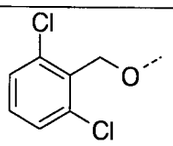
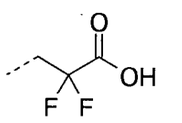
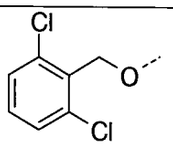
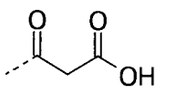
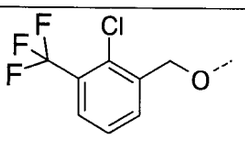
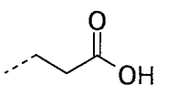
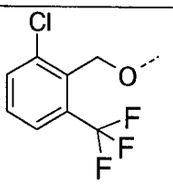
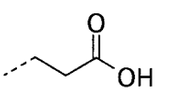
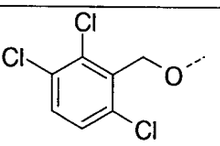
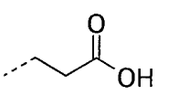
Comp no.	R1-A	R2	R3	R4	R5	Met.
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91		2-Me		H	H	C
92		2-Me		H	H	C
93		2-Me		H	H	C
94		2-Me		H	H	C
95		2-Me		H	H	C
96		2-Me		H	H	C
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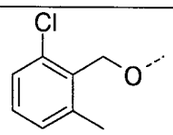
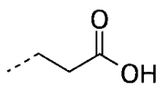
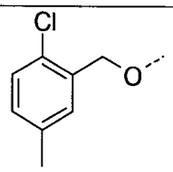
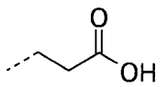
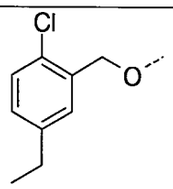
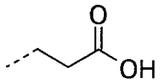
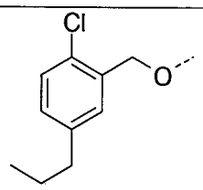
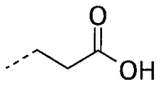
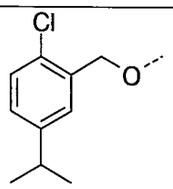
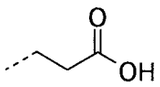
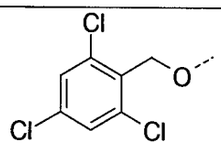
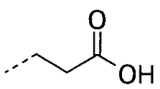
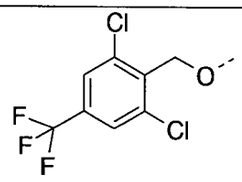
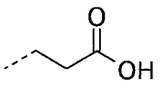
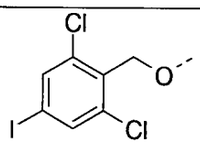
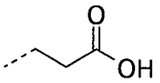
Comp no.	R1-A	R2	R3	R4	R5	Met.
101		2-Me		H	H	C
102		2-Me		H	H	C
103		2-Me		H	H	C
104		2-Me		H	H	C
105		2-Me		H	H	C
106		2-Me		H	H	C
107		2-Me		H	H	C
108		2-Me		H	H	C
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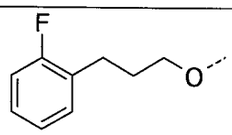
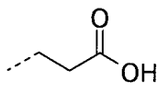
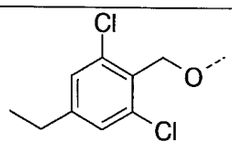
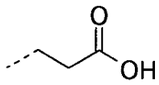
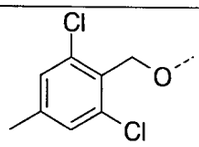
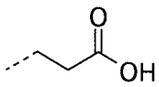
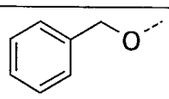
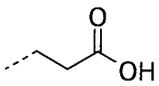
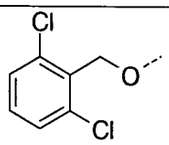
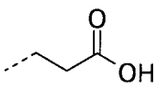
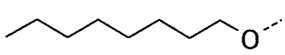
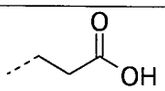
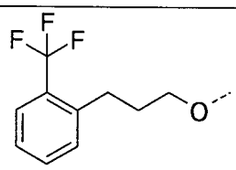
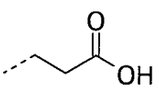
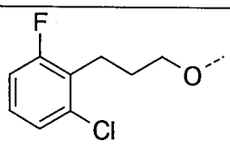
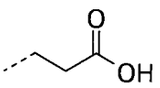
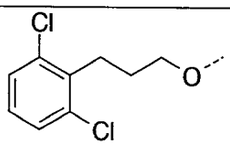
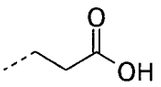
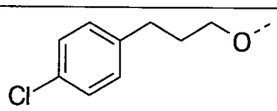
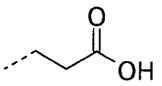
Comp no.	R1-A	R2	R3	R4	R5	Met.
113		2-Me		H	H	C
114		2-Me		H	H	C
115		2-Me		H	H	C
116		2-Me		H	H	C
117		2-Me		H	H	C
118		2-Me		H	H	C
119		2-Me		H	H	C
120		2-Me		H	H	C
121		2-Me		H	H	C
122		2-Me		H	H	C
123		2-Me		H	H	C

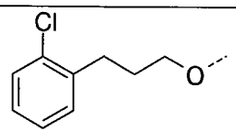
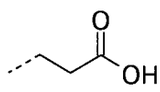
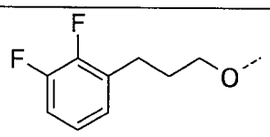
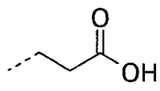
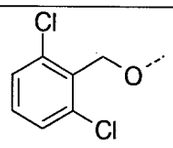
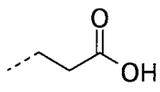
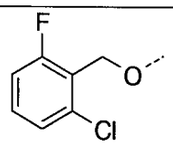
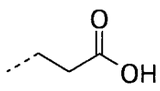
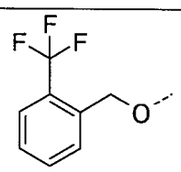
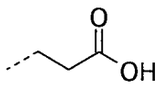
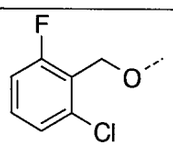
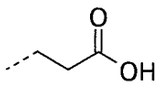
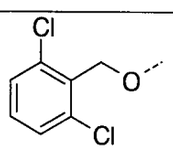
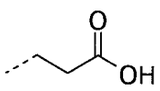
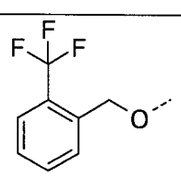
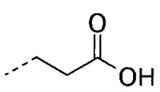
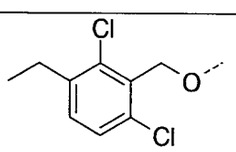
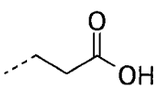
Comp no.	R1-A	R2	R3	R4	R5	Met.
124		2-Me		H	H	C
125		2-Me		H	H	C
126		2-Me		H	H	C
127		2-Me		H	H	C
128		2-Me		H	H	C
129		2-Me		H	H	C
130		2-Me		H	H	D
131		3-CF3		H	H	D
132		H		H	H	E
133		H		H	H	F
134		H		H	H	G
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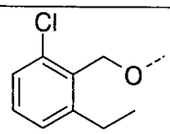
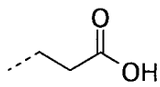
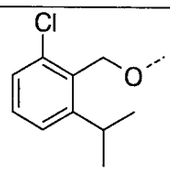
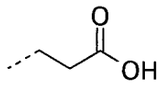
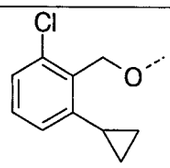
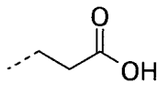
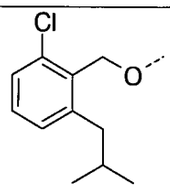
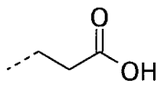
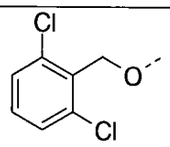
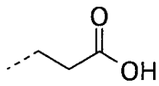
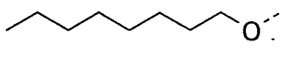
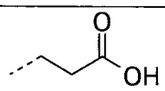
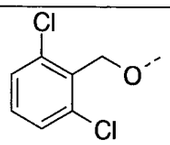
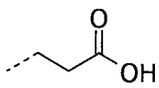
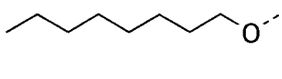
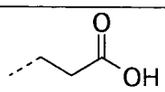
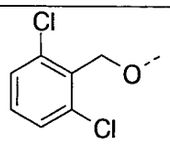
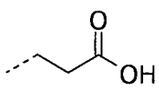
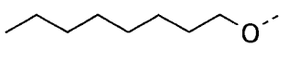
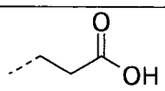
Comp no.	R1-A	R2	R3	R4	R5	Met.
136		H		H	H	I
137		H		H	H	I
138		H		H	H	J
139		H		H	H	B
140		H		H	H	B
141		H		H	H	H
142		H		H	H	B
143		3-Me		H	H	B
144		3-Me		H	H	B
145		3-Me		H	H	B

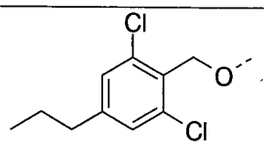
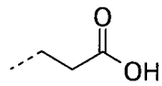
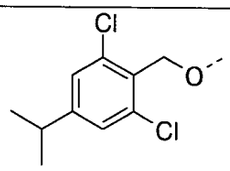
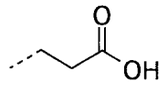
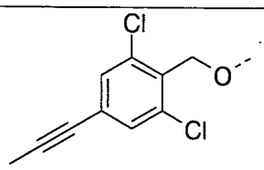
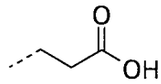
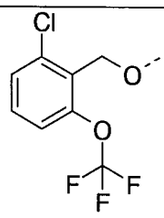
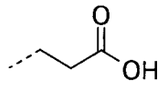
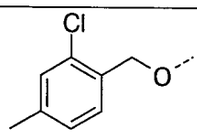
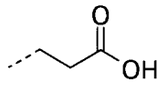
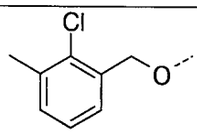
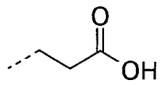
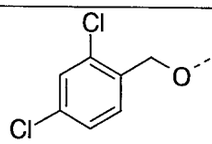
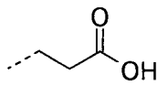
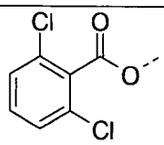
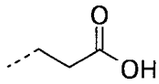
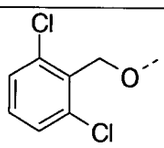
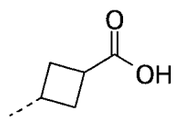
Comp no.	R1-A	R2	R3	R4	R5	Met.
146		H		H	H	I
147		H		H	H	B
148		H		H	H	B
149		H		H	H	K
150		H		H	H	G
151		H		H	H	F
152		H		H	H	B
153		H		H	H	B
154		H		H	H	B

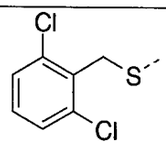
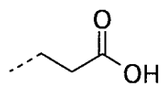
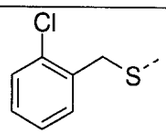
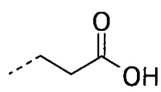
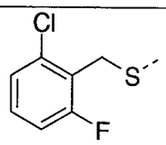
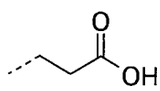
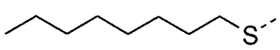
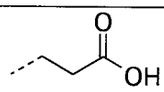
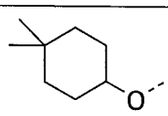
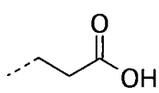
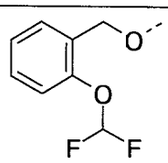
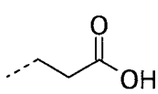
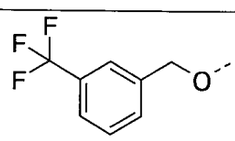
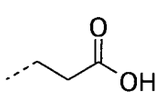
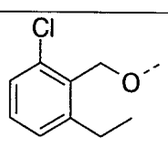
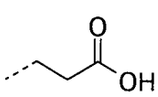
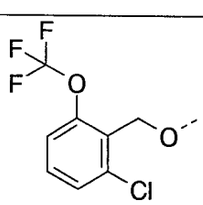
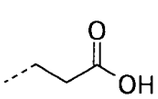
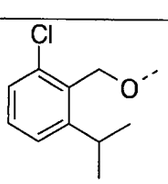
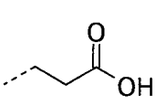
Comp no.	R1-A	R2	R3	R4	R5	Met.
155		H		H	H	B
156		H		H	H	B
157		H		H	H	B
158		H		H	H	B
159		H		H	H	B
160		H		H	H	B
161		H		H	H	B
162		H		H	H	B

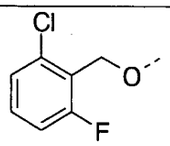
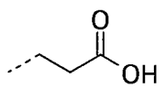
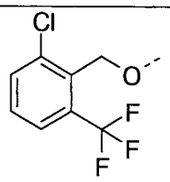
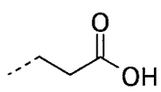
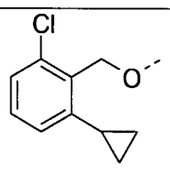
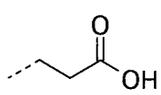
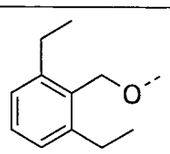
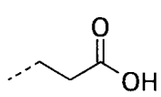
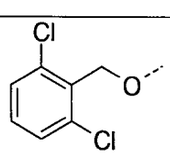
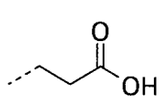
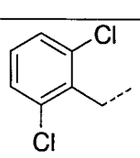
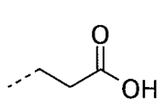
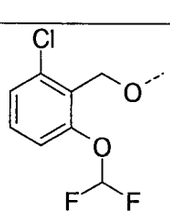
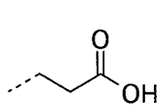
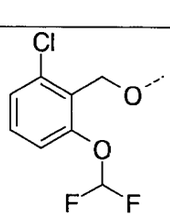
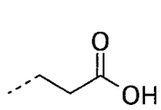
Comp no.	R1-A	R2	R3	R4	R5	Met.
163		H		H	H	B
164		H		H	H	B
165		H		H	H	B
166		H		H	5-oxo	B
167		H		H	5-oxo	B
168		H		H	5-oxo	B
169		H		H	H	B
170		H		H	H	B
171		H		H	H	B
172		H		H	H	B

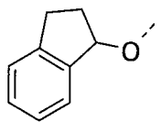
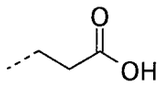
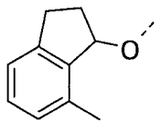
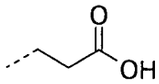
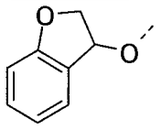
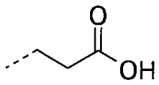
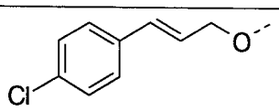
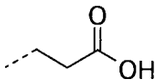
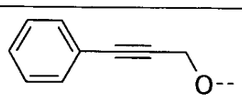
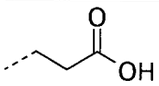
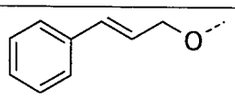
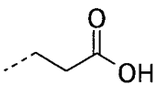
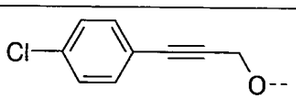
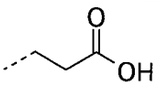
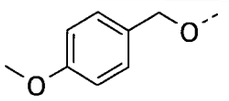
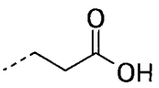
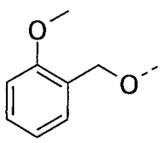
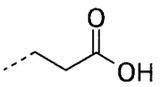
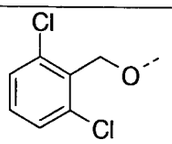
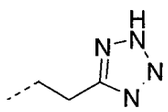
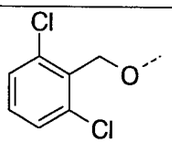
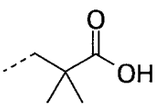
Comp no.	R1-A	R2	R3	R4	R5	Met.
173		H		H	H	B
174		H		H	H	B
175		3-Cl		H	H	B
176		3-Cl		H	H	B
177		3-Cl		H	H	B
178		2-F		H	H	B
179		2-F		H	H	B
180		2-F		H	H	B
181		H		H	H	B

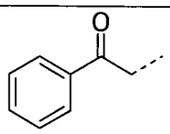
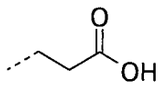
Comp no.	R1-A	R2	R3	R4	R5	Met.
182		H		H	H	B
183		H		H	H	B
184		H		H	H	B
185		H		H	H	B
186		H		H	5,5-Me2	B
187		H		H	5,5-Me2	B
188		2-CF3		H	H	B
189		2-CF3		H	H	B
190		H		H	2,2-Me2	B
191		H		H	2,2-Me2	B

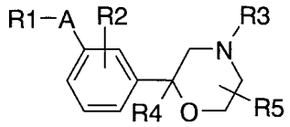
Comp no.	R1-A	R2	R3	R4	R5	Met.
192		H		H	H	B
193		H		H	H	B
194		H		H	H	B
195		H		H	H	B
196		H		H	H	B
197		H		H	H	B
198		H		H	H	B
199		H		H	H	B
200		H		H	H	B

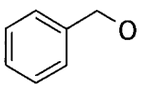
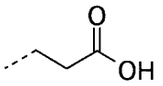
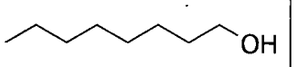
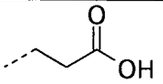
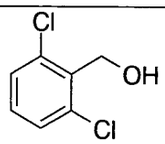
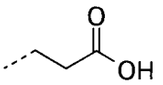
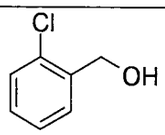
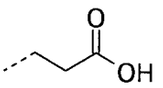
Comp no.	R1-A	R2	R3	R4	R5	Met.
201		H		H	H	B
202		H		H	H	B
203		H		H	H	B
204		H		H	H	B
205		H		H	H	B
206		H		H	H	B
207		2-CF3		H	H	B
208		2-CF3		H	H	B
209		2-CF3		H	H	B
210		2-CF3		H	H	B

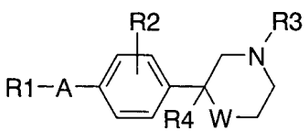
Comp no.	R1-A	R2	R3	R4	R5	Met.
211		2-CF3		H	H	B
212		2-CF3		H	H	B
213		2-CF3		H	H	B
214		H		H	H	B
215		2-Cl		H	H	B
216		H		H	H	B
217		H		H	H	B
218		2-CF3		H	H	B

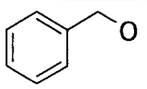
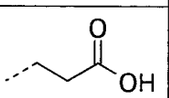
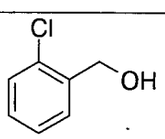
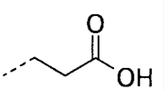
Comp no.	R1-A	R2	R3	R4	R5	Met.
219		H		H	H	E
220		H		H	H	E
221		H		H	H	E
222		H		H	H	E
223		H		H	H	E
224		H		H	H	E
225		H		H	H	E
226		H		H	H	E
227		H		H	H	E
228		H		H	H	L
229		H		H	H	M

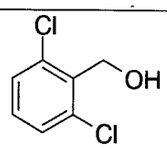
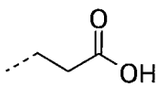
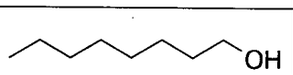
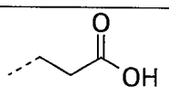
Comp no.	R1-A	R2	R3	R4	R5	Met.
239		H		H	H	B



Comp no.	R1-A	R2	R3	R4	R5	Met.
230		H		H	H	B
231		H		H	H	B
232		H		H	H	B
233		H		H	H	B



Comp no.	R1-A	R2	R3	R4	W	Met.
234		H		H	S	B
235		H		H	S	B

Comp no.	R1-A	R2	R3	R4	W	Met.
236		H		H	S	B
237		H		H	S	B

§5. FORMULACIÓN FARMACÉUTICA

Un ejemplo apropiado de una composición farmacéutica de acuerdo con la presente invención se presenta a continuación.

Se produjo un comprimido por compresión directa logrando la siguiente composición:

compuesto	función	cantidad
compuesto 34b	principio activo farmacéutico	0,4 - 6 %
Ac-di-Sol® (= croscarmelosa de sodio)	desintegrante	3 %
PRUV® (= fumarato estearílico de sodio)	lubricante	2 %
Aerosil® (=sílice)	deslizante	2 %
MCC (=celulosa microcristalina)	relleno	30 %
lactosa monohidrato DCL 15	relleno	resto

Potencias de los comprimidos: 2, 10 y 30 mg de compuesto 34b / unidad. Peso del comprimido: 500 mg.

§6. DATOS Y ANÁLISIS FARMACOLÓGICOS

Actividad funcional in vitro (agonismo) sobre los receptores de S1P5 humanos

Se adquirió el ensayo CHO-human-S1P5-Aeqorin de Euroscreen, Bruselas (Euroscreen, Technical dossier, Human Lysophospholid S1P5 (Edg8) receptor, DNA clone and CHO AequoScreenTM recombinant cell-line, catalog no: ES-593-A, September 2006). Las células S1P5-Aequorin humanas expresan apo-Aequorina orientada a la mitocondria. Las células tienen que cargarse con coelanterazina, con el fin de reconstituir la Aequorina activa. Después de la unión de los agonistas al receptor de S1P5 humano, la concentración de calcio intracelular aumenta y la unión del calcio al complejo apo-Aequorina/coelenterazina conduce a una reacción de oxidación de coelenterazina, lo cual produce la producción de apo-Aequorin, coelenteramida, CO2 y luz (□max 469nm). Esta

respuesta luminiscente depende de la concentración de agonista. La luminiscencia se mide usando el dispositivo MicroBeta Jet (Perkin Elmer). Los efectos como agonistas de los compuestos se expresan como pEC50. Los compuestos se evaluaron en un rango de concentración medio log de 10 puntos, y se realizaron 3 experimentos diferentes en mediciones de un solo punto.

Actividad funcional in vitro (agonismo) sobre receptores de S1P3 humanos

Se estableció el ensayo de CHO-human-S1P3- Aeqorin (CHO/Gα16/AEQ/h-S1P3) en Solvay Pharmaceuticals. El ADN del plásmido que codifica el receptor de S1P3 (número de acceso al GenBank NM_005226 se adquirió de UMR cDNA resource Centre (Rolla, MO). La construcción pcDNA3.1/hS1P3 que transporta apo-Aeqorin y proteína Gα16 orientadas a la mitocondria se transfectó en la línea celular.

Las células de S1P3-Aequorin humanas expresan apo-Aequorin orientada a la mitocondria. Las células tienen que cargarse con coelanterazina, con el fin de reconstituir la Aequorin activa. Después de la unión de los agonistas al receptor S1P2 humano la concentración de calcio intracelular aumenta y la unión del calcio al complejo apo-Aequorin/coelenterazina conduce a una reacción de oxidación de coelenterazina, lo cual produce la producción de apo-Aequorin, coelenteramida, CO2 y luz (□max 469nm). Esta respuesta luminiscente depende de la concentración de agonista. La luminiscencia se mide usando el aparato MicroBeta Jet (Perkin Elmer). Los efectos como agonistas de los compuestos se expresan como pEC50. Los compuestos se evaluaron en un rango de concentración medio log de 10 puntos, y se realizaron 3 experimentos diferentes en mediciones de puntos individuales.

Actividad funcional in vitro (agonismo) sobre los receptores S1P1 humanos

Se realizó el estudio CHO-K1-Human S1P1-c-AMP en Euroscreenfast, Bruselas (Euroscreen, Human S1P1 coupling Gi/0, (Edg1) receptor, catalog no: FAST-0197C, December 2009).

Las células CHO-K1 recombinantes que expresan S1P1 humanos, cultivadas hasta la Fase medio-log en medios de cultivo sin antibióticos, se desprendieron, centrifugaron y suspendieron nuevamente. Para el análisis de agonistas se mezclan las células con compuesto y Forskolin y se incuban a temperatura ambiente. Las células son lisatos y se calcula la concentración de cAMP, de acuerdo con la especificación del fabricante, Con el kit HTRF de CIS-BIO International (cat no62AM2PEB).

Los efectos como agonistas de los compuestos se expresan como porcentaje de la actividad del compuesto de referencia a su concentración EC100, EC50 se calcula y los resultados se informan como pEC50. Los compuestos se evaluaron en un rango de concentración medio log de 10 puntos duplicados en 1 experimento.

Datos farmacológicos (agonismo del receptor) para los compuestos seleccionados:

Compuesto	S1P5 pEC50	S1P1 pEC50	S1P3 pEC50
3	5,0	nd	4,8
16	6,0	nd	5,4
24	6,2	nd	<4,5
34a	6,2	nd	<4,5
34b	7,5	<5,5	<4,5
41	6,6	<5,5	5,6
53	5,7	nd	<5,0
66	6,2	nd	<5,0
76	5,6	nd	<5,0
84	5,4	nd	<5,0
92	5,3	nd	<5,0
100	5,4	nd	<5,0
117	5,4	nd	<5,0
127	6,2	nd	<5,0
130	7,1	<5,5	<4,5
131	6,0	nd	<5,0
137	7,0	nd	6,3
144	6,2	nd	<5,0
150	6,2	nd	<5,0
153	7,0	<5,5	<5,0
164	6,5	nd	5,7
174	5,8	nd	5,3
179	6,9	<5,5	<5,0
187	6,1	nd	5,5
189	6,8	5,8	5,8
196	6,0	nd	nd
204	6,4	nd	nd
220	6,8	nd	6,6
228	6,8	<5,5	<5,0
231	6,6	nd	<5,0

nd = no se determinó.

Modelo Terapéutico in vivo; laberinto T

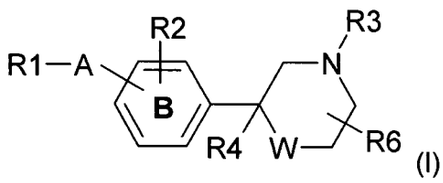
Los déficits de memoria relacionados con el proceso de envejecimiento ocurren en humanos y roedores. La alternación espontánea es la tendencia innata de los roedores a las elecciones libres alternativas en un laberinto T por sobre una serie de ciclos sucesivos. Este procedimiento secuencial se basa en la memoria funcional y es sensible a varias manipulaciones farmacológicas que afectan el problema de la memoria (Aging and the physiology of spatial memory. Barnes C.A. Neurobiol. Aging 1988:563-8; Dember WN, Fowler H. Spontaneous alternation behavior. Psychol. Bull. 1958, 55(6):412–427; Gerlai R. A new continuous alternation task in T-maze detects hippocampal dysfunction in mice. A strain comparison and lesion study. Behav Brain Res 1998 95(1):91-101).

Para este estudio, se utilizaron ratones macho C57BL/6J de 2 meses o 12 meses de edad en la tarea de alternación espontánea en el laberinto T. En síntesis, se sometió a los ratones a 1 sesión que contenía 15 estudios, que consistían en 1 estudio de "elección forzada" trial, seguido de 14 estudios de "elección libre". Se consideró que el animal entró a una de las ramas del laberinto cuando se colocaban las cuatro patas en esta rama. Una sesión se termina y el animal se retira del laberinto en cuanto se han realizado 14 ensayos de elección libre o si han transcurrido 15 min, cualquiera que ocurra primero. El porcentaje de alternación por sobre los 14 estudios de elección libre se determinó para cada ratón y se utilizó como índice de rendimiento de la memoria funcional. El compuesto 34b se administró por vía oral durante 21 días antes del ensayo de del laberinto T y el día del ensayo del laberinto T en el t = -30 min. Se demostró que el compuesto 34b a una dosis de 10 mg/kg/día revirtió la decadencia cognitiva relacionada con el proceso de envejecimiento en los ratones C57BL6J de 12 meses de edad con un 100% de efectividad. De este modo, los ratones de 12 meses de edad sometidos a tratamiento fueron idénticos en cuanto a su rendimiento que los ratones de 2 meses de vida tratados con vehículo.

Conclusión: los compuestos de la presente invención tienen un efecto positivo sobre la decadencia cognitiva relacionada con el proceso de envejecimiento.

REIVINDICACIONES

1. Un derivado de (tio)morfolina que tiene la fórmula (I)



(I)

en donde

R1 se selecciona de

ciano,

alquinilo (2-4C),

alquilo (1-4C),

cicloalquilo (3-6C),

cicloalquenilo (4-6C),

bicicloalquilo (6-8C),, grupo bicíclico (8-10C), cada uno sustituido en forma opcional con alquilo (1-4C),

fenilo, bifenilo, naftilo, cada uno sustituido en forma opcional con uno o más sustituyentes se selecciona en forma independiente de halógeno, alquilo (C1-4C) sustituido en forma opcional con uno o más átomos de fluoro, alquinilo (2-4C), alcoxi (C1-4C) sustituido en forma opcional con uno o más átomos de fluoro, amino, dialquilamino (C1-4C) , -SO2-alquilo (1-4C), -CO-alquilo (1-4C), -CO-O-alquilo (1-4C), -NH-CO-alquilo (C1-4C) y cicloalquilo (3-6C),

fenilo sustituido con fenoxi, bencilo, benciloxi, feniletilo o heterociclo monocíclico, cada uno sustituido en forma opcional con alquilo (1-4C),

heterociclo monocíclico sustituido en forma opcional con halógeno, alquilo (C1-4C) o con fenilo sustituido en forma opcional con alquilo (1-4C),

and

heterociclo bicíclico sustituido en forma opcional con alquilo (C1-4C);

A se selecciona de -CO-O-, -O-CO-, -NH-CO-, -CO-NH, -C=C-, -CCH3-O- y el grupo de enlace –Y-(CH2)n-X- en donde

Y está unido a R1 y se selecciona de un enlace, -O-, -S-, -SO-, -SO2-, -CH2-O-, -CO-, -O-CO-, -CO-O-, -CO-NH-, -NH-CO-, -C=C- y -C≡C- ;

n es un número entero desde 1 hasta 10; y

X está unido al grupo fenileno / piridilo y se selecciona de un enlace, -O-, -S-, -SO-, -SO2-, -NH, -CO-, -C=C- y -C≡C-;

la estructura del anillo B contiene en forma opcional un átomo de nitrógeno;

R2 es H, alquilo (C1-4C) sustituido en forma opcional con uno o más átomos de fluoro, alcoxi (C1-4C) sustituido en forma opcional con uno o más átomos de fluoro, o halógeno; y

R3 es alquileno (1-4C)-R5 en donde el grupo alquileno puede estar sustituido con (CH2)2 para formar un resto ciclopropilo o uno o dos átomos de halógeno, o R3 es cicloalquileno (3-6C)-R5 o -CO-CH2-R5, en donde R5 es -OH, -PO3H2, -OPO3H2, -COOH, -COOalquilo (C1-4C) o tetrazol-5-ilo;

R4 es H o alquilo (C1-4C);

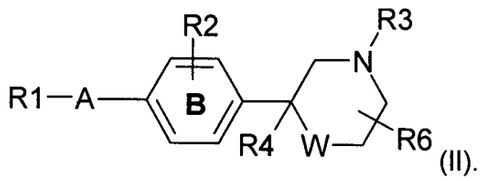
R6 es uno o más sustituyentes se selecciona en forma independiente de H, alquilo (C1-4C) o oxo;

W es -O-, -S-, -SO- o -SO2-;

o una sal, un solvato o un hidrato aceptables desde el punto de vista farmacéutico de los anteriores; con la salvedad de que el derivado que tiene la fórmula (I) no sea 2-(4-etilfenil)-4-morfolinoetanol, 4-[4-(2-hidroxietil)-2-morfolinil]bencenacetonitrilo.

2. El compuesto de la reivindicación 1, en donde la estructura del anillo B es fenileno.

3. El compuesto de la reivindicación 1 o 2, que tiene la estructura (II)



(II).

4. El compuesto de cualquiera de las reivindicaciones 1 hasta 3, en donde R3 se selecciona de -(CH2)2-OH, -CH2-COOH, -(CH2)2-COOH, -(CH2)3-COOH, -CH2-CHCH3-COOH, -CH2-C(CH3)2-COOH, -CHCH3-CH2-COOH, -CH2-CF2-COOH, -CO-CH2-COOH, 1,3-ciclobutileno-COOH, -(CH2)2-PO3H2, -(CH2)3-PO3H2, -(CH2)2-OPO3H2, -(CH2)3-OPO3H2, -CH2-tetrazol-5-ilo, -(CH2)2-tetrazol-5-ilo y -(CH2)3-tetrazol-5-ilo;

y W es -O- o -S-.

5. El compuesto de cualquiera de las reivindicaciones 1 hasta 4, en donde R2 es H, metilo, metoxi, trifluorometilo, difluorometilo, trifluorometoxi, difluorometoxi, Cl o F;

y R4 es H o metilo.

6. El compuesto de cualquiera de las reivindicaciones 1 hasta 5, en donde A se selecciona de -CO-O-, -NH-CO-, -CO-NH, -C=C-, -CCH3-O- y el grupo de enlace –Y-(CH2)n-X- en donde

Y está unido a R1 y se selecciona de un enlace, -O-, -SO2-, -CH2-O-, -CO-, -CO-O-, -NH-CO-, -C=C- y -C≡C-; n es un número entero desde 1 hasta 7; y X está unido al grupo fenileno / piridilo y se selecciona de un enlace, -O-, -S- y –NH.

7. El compuesto de cualquiera de las reivindicaciones 1 hasta 6, en donde R1 se selecciona de ciano, etinilo, alquilo (1-4C), ciclopentilo, ciclohexilo, ciclohexenilo, 6,6-dimetil-biciclo[3,1,1]hept-2-ilo, indanilo sustituido en forma opcional con metilo, bifenilo, naftilo,

fenilo sustituido en forma opcional con uno, dos o tres sustituyentes se selecciona en forma independiente de cloro, fluoro, bromo, alquilo (1-4C), alquinilo (2-4C), alcoxi (C1-4C) , dimetilamino, trifluorometilo, trifluorometoxi y cicloalquilo (3-6C),

fenilo mono sustituido con fenoxi, bencilo, benciloxi, feniletilo, pirazolilo o triazolilo, pirazolilo, tiazolilo, oxadiazolilo, tienilo, tetrahidrofuranoilo, piridinilo, tetrahidro-piranilo, cada uno sustituido en forma opcional con cloro, alquilo (C1-4C) o fenilo sustituido con alquilo (1-4C), e

indolilo, imidazopiridinilo, dihidrobenzofuranilo y benzdioxanilo, cada uno sustituido en forma opcional con (1-4C)alquilo.

8. El compuesto de la reivindicación 7, en donde R1 se selecciona de alquilo (1-4C), ciclopentilo, ciclohexilo, piridinilo y fenilo, en donde los últimos dos grupos están sustituidos en forma opcional con uno o dos substituents se selecciona en forma independiente de cloro, fluoro, bromo, alquilo (1-4C), alcoxi (C1-4C) y trifluorometilo.

9. El compuesto de la reivindicación 8, en donde R1 se selecciona de alquilo (C1-4C) y diclorofenilo.

10. El compuesto de la reivindicación 1, que tiene la estructura (II), en donde R1 es 2,6-diclorofenilo; A es el grupo de enlace -Y-(CH2)n-X-, en donde Y está unido a R1 y es un enlace, n es 1 y X está unido al grupo fenileno y es -O-; la estructura del anillo B es fenileno; R2 es H; R3 es -(CH2)2-COOH y R4 es H.

11. El compuesto de la reivindicación 1, que tiene la estructura (II), en donde R1 es alquilo (C1-4C); A es el grupo de enlace -Y-(CH2)n-X-, en donde Y está unido a R1 y es un enlace, n es un número entero seleccionado de 1 hasta 6 y X está unido al grupo fenileno y es -O- o un enlace; la estructura del anillo B es fenileno; R2 es H; R3 se selecciona de -(CH2)2-COOH, -(CH2)3-COOH, -CH2-CHCH3-COOH, -CH2-C(CH3)2-COOH, -CHCH3-CH2-COOH, -(CH2)2-PO3H2, -(CH2)3-PO3H2 y -(CH2)2-OPO3H2; y R4 es H.

12. El compuesto de la reivindicación 11, en donde R1 y -(CH2)n- juntos son un grupo octilo lineal, X es -O- y R3 es -(CH2)2-PO3H2.

13. El compuesto de la reivindicación 1, seleccionado de ácido (3-{2-[4-(benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(6-Metil-imidazo[1,2-a]piridin-2-ilmetoxi)-fenil]-morfolin-4-il}-propiónico
ácido 3-(2-{4-[3-(2-Propil-tiazol-5-iloxi)-propoxi]-fenil}-morfolin-4-il)-propiónico,
ácido 3-{2-[4-(2-Benciloxi-etoxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2-Fenoxi-etoxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-[2-(4-Hex-5-iniloxi-fenil)-morfolin-4-il]-propiónico,
ácido 3-{2-[4-(4-Acetoxi-butoxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-(2-{4-[3-(4-Fluoro-fenoxi)-propoxi]-fenil}-morfolin-4-il)-propiónico,
ácido 3-(2-{4-[2-(Naftalen-2-iloxi)-etoxi]-fenil}-morfolin-4-il)-propiónico,
ácido 3-[2-(4-Fenilcarbamoilmetoxi-fenil)-morfolin-4-il]-propiónico,
ácido 3-{2-[4-(4-Pirazol-1-il-benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(1-Metil-1H-pirazol-3-ilmetoxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(4-Cloro-benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(6-Ciano-hexiloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-[2-(4-Fenetiloxi-fenil)-morfolin-4-il]-propiónico,
ácido 3-{2-[4-(3-Fenil-propoxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(3-Benciloxi-propoxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(7-Metoxi-heptiloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-(2-{4-[3-(4-ter-butil-fenil)-[1,2,4]oxadiazol-5-ilmetoxi]-fenil}-morfolin-4-il)-propiónico,
ácido 3-{2-[4-(5-Oxo-hexiloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(4-Fenil-butoxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(3-Metoxi-benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2-Cloro-benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-[2-(4-Ciclohexilmetoxi-fenil)-morfolin-4-il]-propiónico,
ácido 3-{2-[4-(2-Bencenosulfonil-etoxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(3-Fenoxi-propoxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(4-[1,2,4]Triazol-1-il-benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2,3-Dihidro-benzofuran-2-ilmetoxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2-Bifenil-4-il-2-oxo-etoxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(4-Fenoxi-butoxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2-Oxo-2-fenil-etoxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(3-Cloro-benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-(2-{4-[2-(1H-Indol-3-il)-etoxi]-fenil}-morfolin-4-il)-propiónico,
ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido (+)-3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido (-)-3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-(2-(4-Octil-fenil)-morfolin-4-il)-propiónico,
ácido 4-[2-(4-Octil-fenil)-morfolin-4-il]-butírico,
ácido 3-[2-(4-Hexiloxi-fenil)-morfolin-4-il]-propiónico,
ácido 4-[2-(4-Hexiloxi-fenil)-morfolin-4-il]-butírico,
ácido 3-[2-(4-Heptiloxi-fenil)-morfolin-4-il]-propiónico,
ácido 4-[2-(4-Heptiloxi-fenil)-morfolin-4-il]-butírico,
ácido 3-(2-(4-Octiloxi-fenil)-morfolin-4-il)-propiónico,
ácido (+)-3-[2-(4-Octiloxi-fenil)-morfolin-4-il]-propiónico,
ácido (-)-3-[2-(4-Octiloxi-fenil)-morfolin-4-il]-propiónico,
ácido 4-[2-(4-Octiloxi-fenil)-morfolin-4-il]-butírico,
ácido 2,2-Dimetil-3-(2-(4-octiloxi-fenil)-morfolin-4-il)-propiónico,
ácido 3-[2-(4-octiloxi-fenil)-morfolin-4-il]-butírico,
ácido 2-Metil-3-[2-(4-octiloxi-fenil)-morfolin-4-il]-propiónico,
ácido 3-{2-[4-(2-Cloro-6-fluorobenciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2-Trifluorometil-benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2,6-Difluoro-benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(3-Trifluorometil-benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2,6-Dimetil-benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(3,5-Dicloro-piridin-4-ilmetoxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2,4-Dicloro-piridin-3-ilmetoxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2,6-Dicloro-fenilcarbamoil)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2,6-Dicloro-fenoximetil)-fenil]-morfolin-4-il}-propiónico,
ácido 3-(2-{4-[2-(2,6-Dicloro-fenil)-vinil]-fenil}-morfolin-4-il)-propiónico,
ácido 3-[2-(4-Fenetil-fenil)-morfolin-4-il]-propiónico,
ácido 3-{2-[4-(2,6-Dicloro-bencilamino)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2,6-Dicloro-benzoilamino)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-2-metil-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2-Cloro-6-fluoro-benciloxi)-fenil]-2-metil-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2-Trifluorometil-benciloxi)-fenil]-2-metil-morfolin-4-il}-propiónico,
ácido 3-[2-Metil-2-(4-octiloxi-fenil)-morfolin-4-il]-propiónico,
ácido 4-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-butírico,
ácido 3-(2-{4-[1-(2,6-Dicloro-fenil)-etoxi]-fenil}-morfolin-4-il)-propiónico,
ácido 3-(2-{4-[2-(2,6-Dicloro-fenil)-etil]-fenil}-morfolin-4-il)-propiónico,

ácido 3-{2-[3-Metoxi-4-(2-trifluorometil-benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2-Cloro-6-fluoro-benciloxi)-3-metoxi-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-3-metoxi-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(3-Metoxi-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(5-Bromo-2-metoxi-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2,4-Dicloro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2,3-Dimetoxi-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,
ácido 3-[2-(4-Ciclopentilmetoxi-2-metil-fenil)-morfolin-4-il]-propiónico,
ácido 3-{2-[4-(2,5-Dicloro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[2-Metil-4-(piridin-3-ilmetoxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[2-Metil-4-(naftalen-2-ilmetoxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(Benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,
3-{2-[4-(2-Metoxi-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico ácido,
ácido 3-{2-[2-Metil-4-(6-metil-piridin-2-ilmetoxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2-Cloro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2,5-Dimetoxi-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2-Bromo-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[2-Metil-4-(2-metil-benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(6,6-Dimetil-biciclo[3,1,1]hept-2-ilmetoxi)-2-metil-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2-Cloro-6-fluoro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(Bifenil-2-ilmetoxi)-2-metil-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[2-Metil-4-(2-trifluorometil-benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(3,5-Dicloro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[2-Metil-4-(3-trifluorometil-benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(4-Cloro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(4-Isopropil-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[2-Metil-4-(3-fenoxi-benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(4-Metoxi-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[2-Metil-4-(2-fenetil-benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(3,4-Dimetoxi-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(3,5-Dimetil-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(4-Benciloxi-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[2-Metil-4-(tiofen-2-ilmetoxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(3-Fluoro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(3-Benciloxi-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(4-Fluoro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(Bifenil-4-ilmetoxi)-2-metil-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2,3-Dihidro-benzo[1,4]dioxin-2-ilmetoxi)-2-metil-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[2-Metil-4-(piridin-2-ilmetoxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(4-Butoxi-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,
ácido 3-[2-(4-Ciclohexilmetoxi-2-metil-fenil)-morfolin-4-il]-propiónico,
ácido 3-{2-[2-Metil-4-(tetrahidro-furan-2-ilmetoxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[2-Metil-4-(3-metil-benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2,3-Difluoro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[2-Metil-4-(4-trifluorometoxi-benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(3-Cloro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[2-Metil-4-(tetrahidro-piran-2-ilmetoxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[2-Metil-4-(4-trifluorometil-benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(3,4-Difluoro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[2-Metil-4-(2,3,4-trimetoxi-benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(Ciclohex-3-enilmetoxi)-2-metil-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(4-Butil-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico
ácido 3-{2-[2-Metil-4-(4-metil-benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(3-Dimetilamino-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[2-Metil-4-(piridin-4-ilmetoxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2-Yodo-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(3,5-Dimetoxi-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2,4-Difluoro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[2-Metil-4-(2,4,5-trimetoxi-benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(3-Bromo-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(4-Bromo-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(4-ter-butil-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2,5-Difluoro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[2-Metil-4-(tetrahidro-furan-3-ilmetoxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-3-trifluorometil-fenil]-morfolin-4-il}-propiónico,
ácido {2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-acético,
ácido 3-[2-(4-Octiloxi-fenil)-morfolin-4-il]-3-oxo-propiónico,
ácido 2,2-Difluoro-3-[2-(4-octiloxi-fenil)-morfolin-4-il]-propiónico,
2-[2-(4-Octiloxi-fenil)-morfolin-4-il]-etanol,

2-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-etanol,
ácido {3-[2-(4-Octiloxi-fenil)-morfolin-4-il]-propil}-fosfónico,
ácido {2-[2-(4-Octiloxi-fenil)-morfolin-4-il]-etil}-fosfónico,
mono-{2-[2-(4-octiloxi-fenil)-morfolin-4-il]-etil} éster del ácido fosfórico,
ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-2-metil-propiónico,
ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-butírico,
mono-(2-{2-[4-(2,6-dicloro-benciloxi)-fenil]-morfolin-4-il}-etil) éster del ácido fosfórico,
ácido 3-{2-[3-Metil-4-(2-trifluorometil-benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2-Cloro-6-fluoro-benciloxi)-3-metil-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-3-metil-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2,3-Dicloro-benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2-Cloro-5-trifluorometil-benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2-Cloro-3-trifluorometil-benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2-Cloro-6-trifluorometil-benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2,3,6-Tricloro-benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2-Cloro-6-metil-benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2-Cloro-5-metil-benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2-Cloro-5-etil-benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2-Cloro-5-propil-benciloxi)-fenil]-morfolin-4-il}-propiónico,.
ácido 3-{2-[4-(2-Cloro-5-isopropil-benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2,4,6-Tricloro-benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2,6-Dicloro-4-trifluorometil-benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2,6-Dicloro-4-yodo-benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-(2-{4-[3-(2-Fluoro-fenil)-propoxi]-fenil}-morfolin-4-il)-propiónico,
ácido 3-{2-[4-(2,6-Dicloro-4-etil-benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2,6-Dicloro-4-metil-benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-[2-(4-Benciloxi-fenil)-5-oxo-morfolin-4-il]-propiónico,
ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-5-oxo-morfolin-4-il}-propiónico,
ácido 3-[2-(4-Octiloxi-fenil)-5-oxo-morfolin-4-il]-propiónico,
ácido 3-(2-{4-[3-(2-Trifluorometil-fenil)-propoxi]-fenil}-morfolin-4-il)-propiónico,
ácido 3-(2-{4-[3-(2-Cloro-6-fluoro-fenil)-propoxi]-fenil}-morfolin-4-il)-propiónico,
ácido 3-(2-{4-[3-(2,6-Dicloro-fenil)-propoxi]-fenil}-morfolin-4-il)-propiónico,
ácido 3-(2-{4-[3-(4-Cloro-fenil)-propoxi]-fenil}-morfolin-4-il)-propiónico,
ácido 3-(2-{4-[3-(2-Cloro-fenil)-propoxi]-fenil}-morfolin-4-il)-propiónico,
ácido 3-(2-{4-[3-(2,3-Difluoro-fenil)-propoxi]-fenil}-morfolin-4-il)-propiónico,
ácido 3-{2-[3-Cloro-4-(2,6-dicloro-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[3-Cloro-4-(2-cloro-6-fluoro-benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[3-Cloro-4-(2-trifluorometil-benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2-Cloro-6-fluoro-benciloxi)-2-fluoro-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-2-fluoro-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[2-Fluoro-4-(2-trifluorometil-benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2,6-Dicloro-3-etil-benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2-Cloro-6-etil-benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2-Cloro-6-isopropil-benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2-Cloro-6-ciclopropil-benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2-Cloro-6-isobutil-benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-5,5-dimetil-morfolin-4-il}-propiónico,
ácido 3-[5,5-Dimetil-2-(4-octiloxi-fenil)-morfolin-4-il]-propiónico,
ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-2-trifluorometil-fenil]-morfolin-4-il}-propiónico,
ácido 3-[2-(4-Octiloxi-2-trifluorometil-fenil)-morfolin-4-il]-propiónico,
ácido 3-{6-[4-(2,6-Dicloro-benciloxi)-fenil]-2,2-dimetil-morfolin-4-il}-propiónico,
ácido 3-[2,2-Dimetil-6-(4-octiloxi-fenil)-morfolin-4-il]-propiónico,
ácido 3-{2-[4-(2,6-Dicloro-4-propil-benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2,6-Dicloro-4-isopropil-benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2,6-Dicloro-4-prop-1-inil-benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2-Cloro-6-trifluorometoxi-benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2-Cloro-4-metil-benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2-Cloro-3-metil-benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2,4-Dicloro-benciloxi)-fenil]-morfolin-4-il}-propiónico,
4-[4-(2-carboxi-etil)-morfolin-2-il]-fenil éster del ácido 2,6-Dicloro-benzoico,
ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-ciclobutanocarboxílico,
ácido 3-{2-[4-(2,6-Dicloro-bencilsulfanil)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2-Cloro-bencilsulfanil)-fenil]-morfolin-4-il}-propiónico,
ácido 3 -{2-[4-(2-Cloro-6-fluoro-bencilsulfanil)-fenil]-morfolin-4-il}-propiónico,
ácido 3-[2-(4-Octilsulfanil-fenil)-morfolin-4-il]-propiónico,
ácido 3-{2-[4-(4,4-Dimetil-ciclohexiloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2-Difluorometoxi-benciloxi)-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(3-Trifluorometil-benciloxi)-2-trifluorometil-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2-Cloro-6-etil-benciloxi)-2-trifluorometil-fenil]-morfolin-4-il}-propiónico,
ácido 3-{2-[4-(2-Cloro-6-trifluorometoxi-benciloxi)-2-trifluorometil-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2-Cloro-6-isopropil-benciloxi)-2-trifluorometil-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2-Cloro-6-fluoro-benciloxi)-2-trifluorometil-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2-Cloro-6-trifluorometil-benciloxi)-2-trifluorometil-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2-Cloro-6-ciclopropil-benciloxi)-2-trifluorometil-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2,6-Dietil-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[2-Cloro-4-(2,6-dicloro-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2,6-Dicloro-bencil)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2-Cloro-6-difluorometoxi-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2-Cloro-6-difluorometoxi-benciloxi)-2-trifluorometil-fenil]-morfolin-4-il}-propiónico,

ácido 3-[2-(3-Benciloxi-fenil)-morfolin-4-il]-propiónico,

ácido 3-[2-(3-Octiloxi-fenil)-morfolin-4-il]-propiónico,

ácido 3-{2-[3-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[3-(2-Cloro-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-[2-(4-Benciloxi-fenil)-tiomorfolin-4-il]-propiónico,

ácido 3-{2-[4-(2-Cloro-benciloxi)-fenil]-tiomorfolin-4-il}-propiónico,

ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-tiomorfolin-4-il}-propiónico,

ácido 3-[2-(4-Octiloxi-fenil)-tiomorfolin-4-il]-propiónico,

ácido 3-{2-[5-(2,6-Dicloro-benciloxi)-piridin-2-il]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(Indan-1-iloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(7-Metil-indan-1-iloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2,3-Dihidro-benzofuran-3-iloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-(2-{4-[3-(4-Cloro-fenil)-alliloxi]-fenil}-morfolin-4-il)-propiónico,

ácido 3-{2-[4-(3-Fenil-prop-2-iniloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-(2-{4-[3-fenil-alliloxi]-fenil}-morfolin-4-il)-propiónico,

ácido 3-(2-{4-[3-(4-Cloro-fenil)-prop-2-iniloxi]-fenil}-morfolin-4-il)-propiónico,

ácido 3-{2-[4-(4-Metoxi-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2-Metoxi-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-3-oxo-propiónico,

ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-2,2-difluoro-propiónico,

ácido (3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-propil)-fosfónico,

2-[4-(2,6-Dicloro-benciloxi)-fenil]-4-(1(2)H-tetrazol-5-ilmetil)-morfolina,

ácido 3-{2-[4-(2-Oxo-2-fenil-etil)-fenil]-morfolin-4-il}-propiónico

2-[4-(2,6-Dicloro-benciloxi)-fenil]-4-[2-(2H-tetrazol-5-il)-etil]-morfolina y

ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-2,2-dimetil-propiónico

o una sal, un solvato o un hidrato aceptables desde el punto de vista farmacéutico de los anteriores.

14. El compuesto de la reivindicación 1, que es ácido (-)-3-{2-[4-(2,6-dicloro-benciloxi)-fenil]-morfolin-4-il}-propiónico.

15. El compuesto de cualquiera de las reivindicaciones 1 hasta 14 para usar en tratamiento.

16. Una composición farmacéutica que comprende el compuesto de cualquiera de las reivindicaciones 1 hasta 14 y por lo menos un auxiliar aceptable desde el punto de vista farmacéutico.

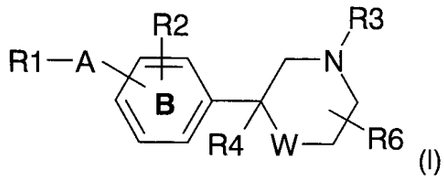
17. El uso del compuesto de cualquiera de las reivindicaciones 1 hasta 14 para la fabricación de un medicamento para el tratamiento, alivio o prevención de enfermedades y dolencias en las cuales cualquier receptor de S1P está involucrado o en el cual la modulación del sistema de señalización de S1P endógeno a través de cualquier receptor de S1P está involucrado.

18. El uso de la reivindicación 17, en donde la enfermedad es un trastorno del SNC, tales como un trastorno neurodegenerativo, en particular seleccionado de un trastorno cognitivo, Enfermedad de Alzheimer, demencia (vascular), Enfermedad de Nieman-Pick, y déficits cognitivos en pacientes con esquizofrenia, comportamiento obsesivo compulsivo, depresión mayor, autismo, esclerosis múltiple y dolor, y específicamente esta enfermedad es un trastorno cognitivo, tales como decadencia cognitiva relacionada con el proceso de envejecimiento.

19. El uso de un agonista S1P5 para la fabricación de un medicamento para el tratamiento, alivio o prevención de un trastorno neurodegenerativo seleccionado de un trastorno cognitivo, Enfermedad de Alzheimer, demencia (vascular), Enfermedad de Nieman-Pick, y déficits cognitivos en pacientes con esquizofrenia, comportamiento obsesivo compulsivo, depresión mayor, autismo, esclerosis múltiple y dolor, y específicamente el trastorno es un trastorno cognitivo, tales como decadencia cognitiva relacionada con el proceso de envejecimiento.

RESUMEN

La presente invención se refiere a derivados de (tio)morfolina que tienen la fórmula (I)



(I)

en donde

R1 se selecciona de

ciano,

alquinilo (2-4C),

alquilo (1-4C),

cicloalquilo (3-6C),

cicloalquenilo (4-6C),

bicicloalquilo (6-8C),, grupo bicíclico (8-10C), cada uno sustituido en forma opcional con alquilo (1-4C),

fenilo, bifenilo, naftilo, cada uno sustituido en forma opcional con uno o más sustituyentes se selecciona en forma independiente de halógeno, alquilo (C1-4C) sustituido en forma opcional con uno o más átomos de fluoro, alquinilo (2-4C), alcoxi (C1-4C) sustituido en forma opcional con uno o más átomos de fluoro, amino, dialquilamino (C1-4C) , -SO2-alquilo (1-4C), -CO-alquilo (1-4C), -CO-O-alquilo (1-4C), -NH-CO-alquilo (C1-4C) y cicloalquilo (3-6C),

fenilo sustituido con fenoxi, bencilo, benciloxi, feniletilo o heterociclo monocíclico, cada uno sustituido en forma opcional con alquilo (1-4C),

heterociclo monocíclico sustituido en forma opcional con halógeno, alquilo (C1-4C) o con fenilo sustituido en forma opcional con alquilo (1-4C),

y

heterociclo bicíclico sustituido en forma opcional con alquilo (C1-4C);

A se selecciona de -CO-O-, -O-CO-, -NH-CO-, -CO-NH, -C=C-, -CCH3-O- y el grupo de enlace –Y-(CH2)n-X- en donde

Y está unido a R1 y se selecciona de un enlace, -O-, -S-, -SO-, -SO2-, -CH2-O-, -CO-, -O-CO-, -CO-O-, -CO-NH-, -NH-CO-, -C=C- y -C≡C- ;

n es un número entero desde 1 hasta 10; y

X está unido al grupo fenileno / piridilo y se selecciona de un enlace, -O-, -S-, -SO-, -SO2-, -NH, -CO-, -C=C- y -C≡C-;

la estructura del anillo B contiene en forma opcional un átomo de nitrógeno;

R2 es H, alquilo (C1-4C) sustituido en forma opcional con uno o más átomos de fluoro, alcoxi (C1-4C) sustituido en forma opcional con uno o más átomos de fluoro, o halógeno; y

R3 es alquileno (1-4C)-R5 en donde el grupo alquileno puede estar sustituido con (CH2)2 para formar un resto ciclopropilo o uno o dos átomos de halógeno, o R3 es cicloalquileno (3-6C)-R5 o -CO-CH2-R5, en donde R5 es -OH, -PO3H2, -OPO3H2, -COOH, -COOalquilo (C1-4C) o tetrazol-5-ilo;

R4 es H o alquilo (C1-4C);

R6 es uno o más sustituyentes se selecciona en forma independiente de H, alquilo (C1-4C) o oxo;

W es -O-, -S-, -SO- o -SO2-;

o una sal, un solvato o un hidrato aceptables desde el punto de vista farmacéutico de los anteriores; con la salvedad de que el derivado que tiene la fórmula (I) no sea 2-(4-etilfenil)-4-morfolinoetanol o

4-[4-(2-hidroxietil)-2-morfolinil]bencenacetonitrilo

o una sal, un solvato o un hidrato aceptables desde el punto de vista farmacéutico de los anteriores.

Los compuestos de la invención tienen afinidad por los receptores de S1P y pueden usarse en el tratamiento, alivio o prevención de enfermedades y dolencias mediadas por el receptor S1P.

EFECTO DEL COMPUESTO 34B SOBRE LA CANTIDAD DE ALTERACION ESPONTÁNEA EN RATONES C57BL6J

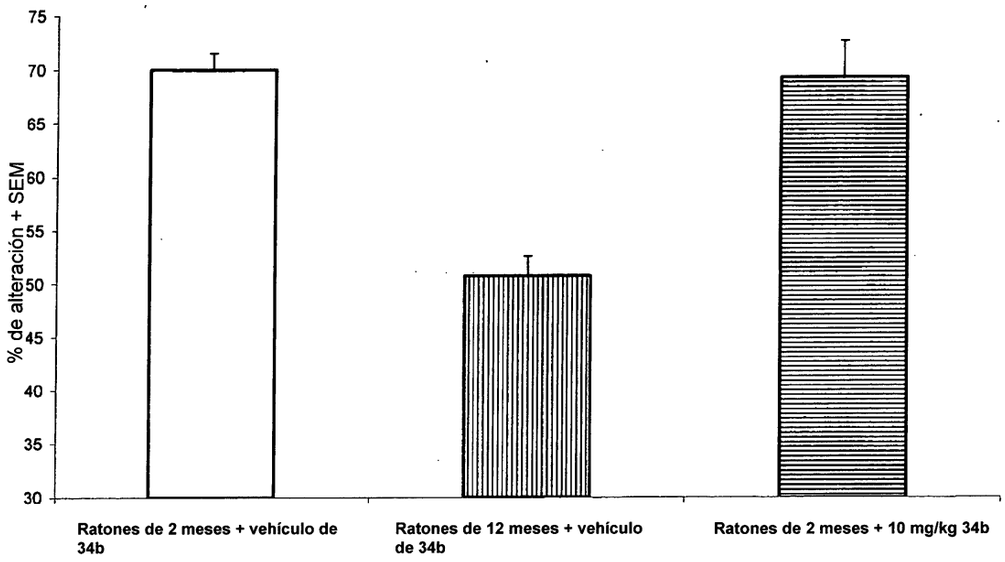


FIGURA 1

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TRADUCCION DE LOS ANEXOS DEL IPRP CAPITULO II

NUEVA PÁGINA 3 Y JUEGO DE REIVINDICACIONES

MODIFICACIÓN: Inclusión del compuesto 3-metil-2-[4-fenilmetoxi)fenil]-4-morfolinoetanol, clorhidrato dentro de las excepciones de los compuestos cubiertos por la fórmula (I)

y

heterociclo bicíclico sustituido en forma opcional con alquilo (C1-4C);

A se selecciona de -CO-O-, -O-CO-, -NH-CO-, -CO-NH, -C=C-, -CCH3-O- y el grupo de enlace –Y-(CH2)n-X- en donde

Y está unido a R1 y se selecciona de un enlace, -O-, -S-, -SO-, -SO2-, -CH2-O-, -CO-, -O-CO-, -CO-O-, -CO-NH-, -NH-CO-, -C=C- y -C≡C- ;

n es un número entero desde 1 hasta 10; y

X está unido al grupo fenileno / piridilo y se selecciona de un enlace, -O-, -S-, -SO-, -SO2-, -NH, -CO-, -C=C- y -C≡C-;

la estructura del anillo B contiene en forma opcional un átomo de nitrógeno;

R2 es H, alquilo (C1-4C) sustituido en forma opcional con uno o más átomos de fluoro, alcoxi (C1-4C) sustituido en forma opcional con uno o más átomos de fluoro, o halógeno; y

R3 es alquileno (1-4C)-R5 en donde el grupo alquileno puede estar sustituido con (CH2)2 para formar un resto ciclopropilo o uno o dos átomos de halógeno, o R3 es cicloalquileno (3-6C)-R5 o -CO-CH2-R5, en donde R5 es -OH, -PO3H2, -OPO3H2, -COOH, -COOalquilo (C1-4C) o tetrazol-5-ilo;

R4 es H o alquilo (C1-4C);

R6 es uno o más sustituyentes se selecciona en forma independiente de H, alquilo (C1-4C) o oxo;

W es -O-, -S-, -SO- o -SO2-;

o una sal, un solvato o un hidrato aceptables desde el punto de vista farmacéutico de los anteriores; con la salvedad de que el derivado que tiene la fórmula (I) no sea 2-(4-etilfenil)-4-morfolinoetanol, 4-[4-(2-hidroxietil)-2-morfolinil]bencenacetonitrilo o o 3-metil-2-[4-fenilmetoxi)fenil]-4-morfolinoetanol, clorhidrato.

muestran afinidad por los receptores de S1P. En particular, los compuestos de la invención muestran afinidad selectiva por el receptor de S1P5 por sobre el(los) receptor(es) S1P1 y/o S1P3.

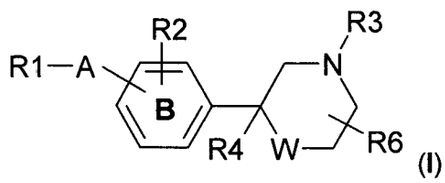
El uso del compuesto 2-(4-etilfenil)-4-morfolinoetanol como reactivo en la producción de ésteres de 2-(2-arilmorfolino)etilo de naproxeno se describe en la base de datos Database CA [Online] Chemical Abstracts Service, Columbus, OHIO, USA; 2008, Hu, Ai-Xi et al, XP002558960 recuperado de la base de datos STN con no. de acceso 2008:1527686; & Huaxue Xuebao, 66(22), 2553-2557 Coden: HHHPA4; ISSN: 0567-7351, 2008. No se presentaron reportes de actividad farmacológica del compuesto.

De manera similar, en Farmatsiya (Sofia), Vol,45, no,1, 1998, pages 3-11, XP009126794 Yordanova, K. et al., describe el uso de 4-[4-(2-hidroxietil)-2-morfolinil]-bencenacetonitrilo como reactivo en la producción de derivados de fenilmorfolina como

REIVINDICACIONES MODIFICADAS BAJO EL

ARTICULO 34 DEL PCT

1. Un derivado de (tio)morfolina que tiene la fórmula (I)



(I)

en donde

R1 se selecciona de

ciano,

alquinilo (2-4C),

alquilo (1-4C),

cicloalquilo (3-6C),

cicloalquenilo (4-6C),

bicicloalquilo (6-8C),, grupo bicíclico (8-10C), cada uno sustituido en forma opcional con alquilo (1-4C),

fenilo, bifenilo, naftilo, cada uno sustituido en forma opcional con uno o más sustituyentes se selecciona en forma independiente de halógeno, alquilo (C1-4C) sustituido en forma opcional con uno o más átomos de fluoro, alquinilo (2-4C), alcoxi (C1-4C) sustituido en forma opcional con uno o más átomos de fluoro, amino, dialquilamino (C1-4C) , -SO_2-alquilo (1-4C), -CO-alquilo (1-4C), -CO-O-alquilo (1-4C), -NH-CO-alquilo (C1-4C) y cicloalquilo (3-6C),

fenilo sustituido con fenoxi, bencilo, benciloxi, feniletilo o heterociclo monocíclico, cada uno sustituido en forma opcional con alquilo (1-4C),

heterociclo monocíclico sustituido en forma opcional con halógeno, alquilo (C1-4C) o con fenilo sustituido en forma opcional con alquilo (1-4C),

and

heterociclo bicíclico sustituido en forma opcional con alquilo (C1-4C);

A se selecciona de -CO-O-, -O-CO-, -NH-CO-, -CO-NH, -C=C-, -CCH_3-O- y el grupo de enlace –Y-$(CH_2)_n$-X- en donde

Y está unido a R1 y se selecciona de un enlace, -O-, -S-, -SO-, -SO_2-, -CH_2-O-, -CO-, -O-CO-, -CO-O-, -CO-NH-, -NH-CO-, -C=C- y -C≡C- ;

n es un número entero desde 1 hasta 10; y

X está unido al grupo fenileno / piridilo y se selecciona de un enlace, -O-, -S-, -SO-, -SO_2-, -NH, -CO-, -C=C- y -C≡C-;

la estructura del anillo **B** contiene en forma opcional un átomo de nitrógeno;

R2 es H, alquilo (C1-4C) sustituido en forma opcional con uno o más átomos de fluoro, alcoxi (C1-4C) sustituido en forma opcional con uno o más átomos de fluoro, o halógeno; y

R3 es alquileno (1-4C)-R5 en donde el grupo alquileno puede estar sustituido con $(CH_2)_2$ para formar un resto ciclopropilo o uno o dos átomos de halógeno, o R3 es cicloalquileno (3-6C)-R5 o -CO-CH_2-R5, en donde R5 es -OH, -PO_3H_2, -OPO_3H_2, -COOH, -COOalquilo (C1-4C) o tetrazol-5-ilo;

R4 es H o alquilo (C1-4C);

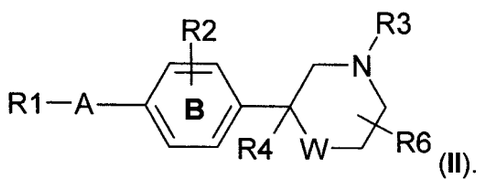
R6 es uno o más sustituyentes se selecciona en forma independiente de H, alquilo (C1-4C) o oxo;

W es -O-, -S-, -SO- o -SO_2-;

o una sal, un solvato o un hidrato aceptables desde el punto de vista farmacéutico de los anteriores; con la salvedad de que el derivado que tiene la fórmula (**I**) no sea 2-(4-etilfenil)-4-morfolinoetanol, 4-[4-(2-hidroxietil)-2-morfolinil]bencenacetonitrilo o 3-metil-2-[4-fenilmetoxi)fenil]-4-morfolinoetanol, clorhidrato .

2. El compuesto de la reivindicación 1, en donde la estructura del anillo **B** es fenileno.

3. El compuesto de la reivindicación 1 o 2, que tiene la estructura (**II**)



(**II**).

4. El compuesto de cualquiera de las reivindicaciones 1 hasta 3, en donde R3 se selecciona de -$(CH_2)_2$-OH, -CH_2-COOH, -$(CH_2)_2$-COOH, -$(CH_2)_3$-COOH, -CH_2-$CHCH_3$-COOH, -CH_2-$C(CH_3)_2$-COOH, -$CHCH_3$-CH_2-COOH, -CH_2-CF_2-COOH, -CO-

CH_2-COOH, 1,3-ciclobutileno-COOH, -$(CH_2)_2$-PO_3H_2, -$(CH_2)_3$-PO_3H_2, -$(CH_2)_2$-OPO_3H_2, -$(CH_2)_3$-OPO_3H_2, -CH_2-tetrazol-5-ilo, -$(CH_2)_2$-tetrazol-5-ilo y -$(CH_2)_3$-tetrazol-5-ilo;

y W es -O- o -S-.

5. El compuesto de cualquiera de las reivindicaciones 1 hasta 4, en donde R2 es H, metilo, metoxi, trifluorometilo, difluorometilo, trifluorometoxi, difluorometoxi, Cl o F;

y R4 es H o metilo.

6. El compuesto de cualquiera de las reivindicaciones 1 hasta 5, en donde A se selecciona de -CO-O-, -NH-CO-, -CO-NH, -C=C-, -CCH_3-O- y el grupo de enlace –Y-$(CH_2)_n$-X- en donde

Y está unido a R1 y se selecciona de un enlace, -O-, -SO_2-, -CH_2-O-, -CO-, -CO-O-, -NH-CO-, -C=C- y -C≡C-; n es un número entero desde 1 hasta 7; y X está unido al grupo fenileno / piridilo y se selecciona de un enlace, -O-, -S- y –NH.

7. El compuesto de cualquiera de las reivindicaciones 1 hasta 6, en donde R1 se selecciona de ciano, etinilo, alquilo (1-4C), ciclopentilo, ciclohexilo, ciclohexenilo, 6,6-dimetil-biciclo[3,1,1]hept-2-ilo, indanilo sustituido en forma opcional con metilo, bifenilo, naftilo,

fenilo sustituido en forma opcional con uno, dos o tres sustituyentes se selecciona en forma independiente de cloro, fluoro, bromo, alquilo (1-4C), alquinilo (2-4C), alcoxi (C1-4C) , dimetilamino, trifluorometilo, trifluorometoxi y cicloalquilo (3-6C),

fenilo mono sustituido con fenoxi, bencilo, benciloxi, feniletilo, pirazolilo o triazolilo, pirazolilo, tiazolilo, oxadiazolilo, tienilo, tetrahidrofuranoilo, piridinilo, tetrahidro-piranilo, cada uno sustituido en forma opcional con cloro, alquilo (C1-4C) o fenilo sustituido con alquilo (1-4C), e

indolilo, imidazopiridinilo, dihidrobenzofuranilo y benzdioxanilo, cada uno sustituido en forma opcional con (1-4C)alquilo.

8. El compuesto de la reivindicación 7, en donde R1 se selecciona de alquilo (1-4C), ciclopentilo, ciclohexilo, piridinilo y fenilo, en donde los últimos dos grupos están sustituidos en forma opcional con uno o dos substituents se selecciona en forma independiente de cloro, fluoro, bromo, alquilo (1-4C), alcoxi (C1-4C) y trifluorometilo.

9. El compuesto de la reivindicación 8, en donde R1 se selecciona de alquilo (C1-4C) y diclorofenilo.

10. El compuesto de la reivindicación 1, que tiene la estructura (**II**), en donde R1 es 2,6-diclorofenilo; A es el grupo de enlace -Y-$(CH_2)_n$-X-, en donde Y está unido a R1 y es un enlace, n es 1 y X está unido al grupo fenileno y es -O-; la estructura del anillo **B** es fenileno; R2 es H; R3 es -$(CH_2)_2$-COOH y R4 es H.

11. El compuesto de la reivindicación 1, que tiene la estructura (**II**), en donde R1 es alquilo (C1-4C); A es el grupo de enlace -Y-$(CH_2)_n$-X-, en donde Y está unido a R1 y es un enlace, n es un número entero seleccionado de 1 hasta 6 y X está unido al grupo fenileno y es -O- o un enlace; la estructura del anillo **B** es fenileno; R2 es H; R3 se selecciona de -$(CH_2)_2$-COOH, -$(CH_2)_3$-COOH, -CH_2-$CHCH_3$-COOH, -CH_2-$C(CH_3)_2$-COOH, -$CHCH_3$-CH_2-COOH, -$(CH_2)_2$-PO_3H_2, -$(CH_2)_3$-PO_3H_2 y -$(CH_2)_2$-OPO_3H_2; y R4 es H.

12. El compuesto de la reivindicación 11, en donde R1 y -$(CH_2)_n$- juntos son un grupo octilo lineal, X es -O- y R3 es -$(CH_2)_2$-PO_3H_2.

13. El compuesto de la reivindicación 1, seleccionado de

ácido (3-{2-[4-(benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(6-Metil-imidazo[1,2-a]piridin-2-ilmetoxi)-fenil]-morfolin-4-il}-propiónico

ácido 3-(2-{4-[3-(2-Propil-tiazol-5-iloxi)-propoxi]-fenil}-morfolin-4-il)-propiónico,

ácido 3-{2-[4-(2-Benciloxi-etoxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2-Fenoxi-etoxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-[2-(4-Hex-5-iniloxi-fenil)-morfolin-4-il]-propiónico,

ácido 3-{2-[4-(4-Acetoxi-butoxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-(2-{4-[3-(4-Fluoro-fenoxi)-propoxi]-fenil}-morfolin-4-il)-propiónico,

ácido 3-(2-{4-[2-(Naftalen-2-iloxi)-etoxi]-fenil}-morfolin-4-il)-propiónico,

ácido 3-[2-(4-Fenilcarbamoilmetoxi-fenil)-morfolin-4-il]-propiónico,

ácido 3-{2-[4-(4-Pirazol-1-il-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(1-Metil-1H-pirazol-3-ilmetoxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(4-Cloro-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(6-Ciano-hexiloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-[2-(4-Fenetiloxi-fenil)-morfolin-4-il]-propiónico,

ácido 3-{2-[4-(3-Fenil-propoxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(3-Benciloxi-propoxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(7-Metoxi-heptiloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-(2-{4-[3-(4-ter-butil-fenil)-[1,2,4]oxadiazol-5-ilmetoxi]-fenil}-morfolin-4-il)-propiónico,

ácido 3-{2-[4-(5-Oxo-hexiloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(4-Fenil-butoxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(3-Metoxi-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2-Cloro-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-[2-(4-Ciclohexilmetoxi-fenil)-morfolin-4-il]-propiónico,

ácido 3-{2-[4-(2-Bencenosulfonil-etoxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(3-Fenoxi-propoxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(4-[1,2,4]Triazol-1-il-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2,3-Dihidro-benzofuran-2-ilmetoxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2-Bifenil-4-il-2-oxo-etoxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(4-Fenoxi-butoxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2-Oxo-2-fenil-etoxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(3-Cloro-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-(2-{4-[2-(1H-Indol-3-il)-etoxi]-fenil}-morfolin-4-il)-propiónico,

ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido (+)-3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido (-)-3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-(2-(4-Octil-fenil)-morfolin-4-il)-propiónico,

ácido 4-[2-(4-Octil-fenil)-morfolin-4-il]-butírico,

ácido 3-[2-(4-Hexiloxi-fenil)-morfolin-4-il]-propiónico,

ácido 4-[2-(4-Hexiloxi-fenil)-morfolin-4-il]-butírico,

ácido 3-[2-(4-Heptiloxi-fenil)-morfolin-4-il]-propiónico,

ácido 4-[2-(4-Heptiloxi-fenil)-morfolin-4-il]-butírico,

ácido 3-(2-(4-Octiloxi-fenil)-morfolin-4-il)-propiónico,

ácido (+)-3-[2-(4-Octiloxi-fenil)-morfolin-4-il]-propiónico,

ácido (-)-3-[2-(4-Octiloxi-fenil)-morfolin-4-il]-propiónico,

ácido 4-[2-(4-Octiloxi-fenil)-morfolin-4-il]-butírico,

ácido 2,2-Dimetil-3-(2-(4-octiloxi-fenil)-morfolin-4-il)-propiónico,

ácido 3-[2-(4-octiloxi-fenil)-morfolin-4-il]-butírico,

ácido 2-Metil-3-[2-(4-octiloxi-fenil)-morfolin-4-il]-propiónico,

ácido 3-{2-[4-(2-Cloro-6-fluorobenciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2-Trifluorometil-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2,6-Difluoro-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(3-Trifluorometil-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2,6-Dimetil-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(3,5-Dicloro-piridin-4-ilmetoxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2,4-Dicloro-piridin-3-ilmetoxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2,6-Dicloro-fenilcarbamoil)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2,6-Dicloro-fenoximetil)-fenil]-morfolin-4-il}-propiónico,

ácido 3-(2-{4-[2-(2,6-Dicloro-fenil)-vinil]-fenil}-morfolin-4-il)-propiónico,

ácido 3-[2-(4-Fenetil-fenil)-morfolin-4-il]-propiónico,

ácido 3-{2-[4-(2,6-Dicloro-bencilamino)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2,6-Dicloro-benzoilamino)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-2-metil-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2-Cloro-6-fluoro-benciloxi)-fenil]-2-metil-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2-Trifluorometil-benciloxi)-fenil]-2-metil-morfolin-4-il}-propiónico,

ácido 3-[2-Metil-2-(4-octiloxi-fenil)-morfolin-4-il]-propiónico,

ácido 4-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-butírico,

ácido 3-(2-{4-[1-(2,6-Dicloro-fenil)-etoxi]-fenil}-morfolin-4-il)-propiónico,

ácido 3-(2-{4-[2-(2,6-Dicloro-fenil)-etil]-fenil}-morfolin-4-il)-propiónico,

ácido 3-{2-[3-Metoxi-4-(2-trifluorometil-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2-Cloro-6-fluoro-benciloxi)-3-metoxi-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-3-metoxi-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(3-Metoxi-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(5-Bromo-2-metoxi-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2,4-Dicloro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2,3-Dimetoxi-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,

ácido 3-[2-(4-Ciclopentilmetoxi-2-metil-fenil)-morfolin-4-il]-propiónico,

ácido 3-{2-[4-(2,5-Dicloro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[2-Metil-4-(piridin-3-ilmetoxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[2-Metil-4-(naftalen-2-ilmetoxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(Benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,

3-{2-[4-(2-Metoxi-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico ácido,

ácido 3-{2-[2-Metil-4-(6-metil-piridin-2-ilmetoxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2-Cloro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2,5-Dimetoxi-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2-Bromo-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[2-Metil-4-(2-metil-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(6,6-Dimetil-biciclo[3,1,1]hept-2-ilmetoxi)-2-metil-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2-Cloro-6-fluoro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(Bifenil-2-ilmetoxi)-2-metil-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[2-Metil-4-(2-trifluorometil-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(3,5-Dicloro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[2-Metil-4-(3-trifluorometil-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(4-Cloro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(4-Isopropil-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[2-Metil-4-(3-fenoxi-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(4-Metoxi-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[2-Metil-4-(2-fenetil-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(3,4-Dimetoxi-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(3,5-Dimetil-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(4-Benciloxi-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[2-Metil-4-(tiofen-2-ilmetoxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(3-Fluoro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(3-Benciloxi-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(4-Fluoro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(Bifenil-4-ilmetoxi)-2-metil-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2,3-Dihidro-benzo[1,4]dioxin-2-ilmetoxi)-2-metil-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[2-Metil-4-(piridin-2-ilmetoxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(4-Butoxi-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,

ácido 3-[2-(4-Ciclohexilmetoxi-2-metil-fenil)-morfolin-4-il]-propiónico,

ácido 3-{2-[2-Metil-4-(tetrahidro-furan-2-ilmetoxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[2-Metil-4-(3-metil-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2,3-Difluoro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[2-Metil-4-(4-trifluorometoxi-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(3-Cloro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[2-Metil-4-(tetrahidro-piran-2-ilmetoxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[2-Metil-4-(4-trifluorometil-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(3,4-Difluoro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[2-Metil-4-(2,3,4-trimetoxi-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(Ciclohex-3-enilmetoxi)-2-metil-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(4-Butil-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico

ácido 3-{2-[2-Metil-4-(4-metil-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(3-Dimetilamino-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[2-Metil-4-(piridin-4-ilmetoxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2-Yodo-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(3,5-Dimetoxi-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2,4-Difluoro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[2-Metil-4-(2,4,5-trimetoxi-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(3-Bromo-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(4-Bromo-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(4-ter-butil-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2,5-Difluoro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[2-Metil-4-(tetrahidro-furan-3-ilmetoxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-2-metil-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-3-trifluorometil-fenil]-morfolin-4-il}-propiónico,

ácido {2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-acético,

ácido 3-[2-(4-Octiloxi-fenil)-morfolin-4-il]-3-oxo-propiónico,

ácido 2,2-Difluoro-3-[2-(4-octiloxi-fenil)-morfolin-4-il]-propiónico,

2-[2-(4-Octiloxi-fenil)-morfolin-4-il]-etanol,

2-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-etanol,

ácido {3-[2-(4-Octiloxi-fenil)-morfolin-4-il]-propil}-fosfónico,

ácido {2-[2-(4-Octiloxi-fenil)-morfolin-4-il]-etil}-fosfónico,

mono-{2-[2-(4-octiloxi-fenil)-morfolin-4-il]-etil} éster del ácido fosfórico,

ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-2-metil-propiónico,

ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-butírico,

mono-(2-{2-[4-(2,6-dicloro-benciloxi)-fenil]-morfolin-4-il}-etil) éster del ácido fosfórico,

ácido 3-{2-[3-Metil-4-(2-trifluorometil-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2-Cloro-6-fluoro-benciloxi)-3-metil-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-3-metil-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2,3-Dicloro-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2-Cloro-5-trifluorometil-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2-Cloro-3-trifluorometil-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2-Cloro-6-trifluorometil-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2,3,6-Tricloro-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2-Cloro-6-metil-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2-Cloro-5-metil-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2-Cloro-5-etil-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2-Cloro-5-propil-benciloxi)-fenil]-morfolin-4-il}-propiónico,.

ácido 3-{2-[4-(2-Cloro-5-isopropil-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2,4,6-Tricloro-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2,6-Dicloro-4-trifluorometil-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2,6-Dicloro-4-yodo-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-(2-{4-[3-(2-Fluoro-fenil)-propoxi]-fenil}-morfolin-4-il)-propiónico,

ácido 3-{2-[4-(2,6-Dicloro-4-etil-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2,6-Dicloro-4-metil-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-[2-(4-Benciloxi-fenil)-5-oxo-morfolin-4-il]-propiónico,

ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-5-oxo-morfolin-4-il}-propiónico,

ácido 3-[2-(4-Octiloxi-fenil)-5-oxo-morfolin-4-il]-propiónico·

ácido 3-(2-{4-[3-(2-Trifluorometil-fenil)-propoxi]-fenil}-morfolin-4-il)-propiónico,

ácido 3-(2-{4-[3-(2-Cloro-6-fluoro-fenil)-propoxi]-fenil}-morfolin-4-il)-propiónico,

ácido 3-(2-{4-[3-(2,6-Dicloro-fenil)-propoxi]-fenil}-morfolin-4-il)-propiónico,

ácido 3-(2-{4-[3-(4-Cloro-fenil)-propoxi]-fenil}-morfolin-4-il)-propiónico,

ácido 3-(2-{4-[3-(2-Cloro-fenil)-propoxi]-fenil}-morfolin-4-il)-propiónico,

ácido 3-(2-{4-[3-(2,3-Difluoro-fenil)-propoxi]-fenil}-morfolin-4-il)-propiónico,

ácido 3-{2-[3-Cloro-4-(2,6-dicloro-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[3-Cloro-4-(2-cloro-6-fluoro-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[3-Cloro-4-(2-trifluorometil-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2-Cloro-6-fluoro-benciloxi)-2-fluoro-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-2-fluoro-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[2-Fluoro-4-(2-trifluorometil-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2,6-Dicloro-3-etil-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2-Cloro-6-etil-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2-Cloro-6-isopropil-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2-Cloro-6-ciclopropil-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2-Cloro-6-isobutil-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-5,5-dimetil-morfolin-4-il}-propiónico,

ácido 3-[5,5-Dimetil-2-(4-octiloxi-fenil)-morfolin-4-il]-propiónico,

ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-2-trifluorometil-fenil]-morfolin-4-il}-propiónico,

ácido 3-[2-(4-Octiloxi-2-trifluorometil-fenil)-morfolin-4-il]-propiónico,

ácido 3-{6-[4-(2,6-Dicloro-benciloxi)-fenil]-2,2-dimetil-morfolin-4-il}-propiónico,

ácido 3-[2,2-Dimetil-6-(4-octiloxi-fenil)-morfolin-4-il]-propiónico,

ácido 3-{2-[4-(2,6-Dicloro-4-propil-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2,6-Dicloro-4-isopropil-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2,6-Dicloro-4-prop-1-inil-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2-Cloro-6-trifluorometoxi-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2-Cloro-4-metil-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2-Cloro-3-metil-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2,4-Dicloro-benciloxi)-fenil]-morfolin-4-il}-propiónico,

4-[4-(2-carboxi-etil)-morfolin-2-il]-fenil éster del ácido 2,6-Dicloro-benzoico,

ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-ciclobutanocarboxílico,

ácido 3-{2-[4-(2,6-Dicloro-bencilsulfanil)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2-Cloro-bencilsulfanil)-fenil]-morfolin-4-il}-propiónico,

ácido 3 -{2-[4-(2-Cloro-6-fluoro-bencilsulfanil)-fenil]-morfolin-4-il}-propiónico,

ácido 3-[2-(4-Octilsulfanil-fenil)-morfolin-4-il]-propiónico,

ácido 3-{2-[4-(4,4-Dimetil-ciclohexiloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2-Difluorometoxi-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(3-Trifluorometil-benciloxi)-2-trifluorometil-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2-Cloro-6-etil-benciloxi)-2-trifluorometil-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2-Cloro-6-trifluorometoxi-benciloxi)-2-trifluorometil-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2-Cloro-6-isopropil-benciloxi)-2-trifluorometil-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2-Cloro-6-fluoro-benciloxi)-2-trifluorometil-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2-Cloro-6-trifluorometil-benciloxi)-2-trifluorometil-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2-Cloro-6-ciclopropil-benciloxi)-2-trifluorometil-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2,6-Dietil-benciloxi)-fenil]-morfolin-4-il}-propiónico·

ácido 3-{2-[2-Cloro-4-(2,6-dicloro-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2,6-Dicloro-bencil)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2-Cloro-6-difluorometoxi-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2-Cloro-6-difluorometoxi-benciloxi)-2-trifluorometil-fenil]-morfolin-4-il}-propiónico,

ácido 3-[2-(3-Benciloxi-fenil)-morfolin-4-il]-propiónico,

ácido 3-[2-(3-Octiloxi-fenil)-morfolin-4-il]-propiónico,

ácido 3-{2-[3-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[3-(2-Cloro-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-[2-(4-Benciloxi-fenil)-tiomorfolin-4-il]-propiónico,

ácido 3-{2-[4-(2-Cloro-benciloxi)-fenil]-tiomorfolin-4-il}-propiónico,

ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-tiomorfolin-4-il}-propiónico,

ácido 3-[2-(4-Octiloxi-fenil)-tiomorfolin-4-il]-propiónico,

ácido 3-{2-[5-(2,6-Dicloro-benciloxi)-piridin-2-il]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(Indan-1-iloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(7-Metil-indan-1-iloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2,3-Dihidro-benzofuran-3-iloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-(2-{4-[3-(4-Cloro-fenil)-alliloxi]-fenil}-morfolin-4-il)-propiónico,

ácido 3-{2-[4-(3-Fenil-prop-2-iniloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-(2-{4-[3-fenil-alliloxi]-fenil}-morfolin-4-il)-propiónico,

ácido 3-(2-{4-[3-(4-Cloro-fenil)-prop-2-iniloxi]-fenil}-morfolin-4-il)-propiónico,

ácido 3-{2-[4-(4-Metoxi-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2-Metoxi-benciloxi)-fenil]-morfolin-4-il}-propiónico,

ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-3-oxo-propiónico,

ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-2,2-difluoro-propiónico,

ácido (3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-propil)-fosfónico,

2-[4-(2,6-Dicloro-benciloxi)-fenil]-4-(1(2)H-tetrazol-5-ilmetil)-morfolina,

ácido 3-{2-[4-(2-Oxo-2-fenil-etil)-fenil]-morfolin-4-il}-propiónico

2-[4-(2,6-Dicloro-benciloxi)-fenil]-4-[2-(2H-tetrazol-5-il)-etil]-morfolina y

ácido 3-{2-[4-(2,6-Dicloro-benciloxi)-fenil]-morfolin-4-il}-2,2-dimetil-propiónico

o una sal, un solvato o un hidrato aceptables desde el punto de vista farmacéutico de los anteriores.

14. El compuesto de la reivindicación 1, que es ácido (-)-3-{2-[4-(2,6-dicloro-benciloxi)-fenil]-morfolin-4-il}-propiónico.

15. El compuesto de cualquiera de las reivindicaciones 1 hasta 14 para usar en tratamiento.

16. Una composición farmacéutica que comprende el compuesto de cualquiera de las reivindicaciones 1 hasta 14 y por lo menos un auxiliar aceptable desde el punto de vista farmacéutico.

17. El uso del compuesto de cualquiera de las reivindicaciones 1 hasta 14 para la fabricación de un medicamento para el tratamiento, alivio o prevención de enfermedades y dolencias en las cuales cualquier receptor de S1P está involucrado o en

el cual la modulación del sistema de señalización de S1P endógeno a través de cualquier receptor de S1P está involucrado.

18. El uso de la reivindicación 17, en donde la enfermedad es un trastorno del SNC, tales como un trastorno neurodegenerativo, en particular seleccionado de un trastorno cognitivo, Enfermedad de Alzheimer, demencia (vascular), Enfermedad de Nieman-Pick, y déficits cognitivos en pacientes con esquizofrenia, comportamiento obsesivo compulsivo, depresión mayor, autismo, esclerosis múltiple y dolor, y específicamente esta enfermedad es un trastorno cognitivo, tales como decadencia cognitiva relacionada con el proceso de envejecimiento.

19. El uso de un agonista S1P5 para la fabricación de un medicamento para el tratamiento, alivio o prevención de un trastorno neurodegenerativo seleccionado de un trastorno cognitivo, Enfermedad de Alzheimer, demencia (vascular), Enfermedad de Nieman-Pick, y déficits cognitivos en pacientes con esquizofrenia, comportamiento obsesivo compulsivo, depresión mayor, autismo, esclerosis múltiple y dolor, y específicamente el trastorno es un trastorno cognitivo, tales como decadencia cognitiva relacionada con el proceso de envejecimiento.

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Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
TARJETA ARCHIVO PROPIETARIOS

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(71)Solicitante(s) **ABBOTT HEALTHCARE PRODUCTS B.V.**

(72) Inventor(es) **WOUTER I. IWEMA BAKKER, HEIN K.A.C. COOLEN, HARMEN MONS, AXEL STOIT, ERIC BONKEN, ELIZABETH VAN DER KAM, JURJEN FRANKENA**

(74) Apoderado: **DRA. MARGARITA CASTELLANOS ABONDANO**

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(54) Titulo: **DERIVADOS DE (TIO)MORFOLINA COMO MODULADORES DE S1P**

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SUPERINTENDENCIA

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DIVISION DE NUEVAS CREACIONES
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HEIN K.A.C. COOLEN
HARMEN MONS
Y OTROS

(74) Apoderado: **MARGARITA CASTELLANOS ABONDANO**

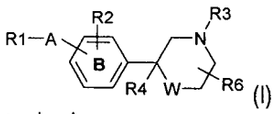
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Reivindicación(es):

1. Un derivado de (tio)morfolina que tiene la fórmula (I)

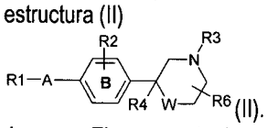


(I)

en donde
R1 se selecciona de
ciano,
alquinilo (2-4C),
alquilo (1-4C),
cicloalquilo (3-6C),
cicloalquenilo (4-6C),
bicicloalquilo (6-8C),, grupo bicíclico (8-10C), cada uno sustituido en forma opcional con alquilo (1-4C),
fenilo, bifenilo, naftilo, cada uno sustituido en forma opcional con uno o más sustituyentes se selecciona en forma independiente de halógeno, alquilo (C1-4C) sustituido en forma opcional con uno o más átomos de fluoro, alquinilo (2-4C), alcoxi (C1-4C) sustituido en forma opcional con uno o más átomos de fluoro, amino, dialquilamino (C1-4C) , -SO2-alquilo (1-4C), -CO-alquilo (1-4C), -CO-O-alquilo (1-4C), -NH-CO-alquilo (C1-4C) y cicloalquilo (3-6C),
fenilo sustituido con fenoxi, bencilo, benciloxi, feniletilo o heterociclo monocíclico, cada uno sustituido en forma opcional con alquilo (1-4C),
heterociclo monociclico sustituido en forma opcional con halógeno, alquilo (C1-4C) o con fenilo sustituido en forma opcional con alquilo (1-4C),
and
heterociclo bicíclico sustituido en forma opcional con alquilo (C1-4C);
A se selecciona de -CO-O-, -O-CO-, -NH-CO-, -CO-NH, -C=C-, -CCH3-O- y el grupo de enlace –Y-(CH2)n-X- en donde Y está unido a R1 y se selecciona de un enlace, -O-, -S-, -SO-, -SO2-, -CH2-O-, -CO-, -O-CO-, -CO-O-, -CO-NH-, -NH-CO-, -C=C- y -C≡C- ;
n es un número entero desde 1 hasta 10; y
X está unido al grupo fenileno / piridilo y se selecciona de un enlace, -O-, -S-, -SO-, -SO2-, -NH, -CO-, -C=C- y -C≡C-;
la estructura del anillo B contiene en forma opcional un átomo de nitrógeno;
R2 es H, alquilo (C1-4C) sustituido en forma opcional con uno o más átomos de fluoro, alcoxi (C1-4C) sustituido en forma opcional con uno o más átomos de fluoro, o halógeno; y
R3 es alquileno (1-4C)-R5 en donde el grupo alquileno puede estar sustituido con (CH2)2 para formar un resto ciclopropilo o uno o dos átomos de halógeno, o R3 es cicloalquileno (3-6C)-R5 o -CO-CH2-R5, en donde R5 es -OH, -PO3H2, -OPO3H2, -COOH, -COOalquilo (C1-4C) o tetrazol-5-ilo;
R4 es H o alquilo (C1-4C);
R6 es uno o más sustituyentes se selecciona en forma independiente de H, alquilo (C1-4C) o oxo;
W es -O-, -S-, -SO- o -SO2-;
o una sal, un solvato o un hidrato aceptables desde el punto de vista farmacéutico de los anteriores; con la salvedad de que el derivado que tiene la fórmula (I) no sea 2-(4-etilfenil)-4-morfolinoetanol, 4-[4-(2-hidroxietil)-2-morfolinil]bencenacetonitrilo o 3-metil-2-[4-fenilmetoxi)fenil]-4-morfolinoetanol, clorhidrato .

2. El compuesto de la reivindicación 1, en donde la estructura del anillo B es fenileno.

3. El compuesto de la reivindicación 1 o 2, que tiene la estructura (II)



(II).

4. El compuesto de cualquiera de las reivindicaciones 1 hasta 3, en donde R3 se selecciona de -(CH2)2-OH, -CH2-COOH, -(CH2)2-COOH, -(CH2)3-COOH, -CH2-CHCH3-COOH, -CH2-C(CH3)2-COOH, -CHCH3-CH2-COOH, -CH2-CF2-COOH, -CO-CH2-COOH, 1,3-ciclobutileno-COOH, -(CH2)2-PO3H2, -(CH2)3-PO3H2, -(CH2)2-OPO3H2, -(CH2)3-OPO3H2, -CH2-tetrazol-5-ilo, -(CH2)2-tetrazol-5-ilo y -(CH2)3-tetrazol-5-ilo;
y W es -O- o -S-.

5. El compuesto de cualquiera de las reivindicaciones 1 hasta 4, en donde R2 es H, metilo, metoxi, trifluorometilo, difluorometilo, trifluorometoxi, difluorometoxi, Cl o F;
y R4 es H o metilo.

6. El compuesto de cualquiera de las reivindicaciones 1 hasta 5, en donde A se selecciona de -CO-O-, -NH-CO-, -CO-NH, -C=C-, -CCH3-O- y el grupo de enlace –Y-(CH2)n-X- en donde
Y está unido a R1 y se selecciona de un enlace, -O-, -SO2-, -CH2-O-, -CO-, -CO-O-, -NH-CO-, -C=C- y -C≡C-; n es un número entero desde 1 hasta 7; y X está unido al grupo fenileno / piridilo y se selecciona de un enlace, -O-, -S- y –NH.

...

CASTELLANOS & CO LTDA
ABOGADOS
Calle 94 A No. 7 A-09
Bogotá, D.C. – COLOMBIA

ANEXO # 1
INVENTORES

1. **WOUTER I. IWEMA BAKKER**
   ABBOTT HEALTHCARE PRODUCTS B.V.
   C.J. van Houtenlaan 36
   NL-1381 CP Weesp
   HOLANDA

2. **HEIN K.A.C. COOLEN**
   ABBOTT HEALTHCARE PRODUCTS B.V.
   C.J. van Houtenlaan 36
   NL-1381 CP Weesp
   HOLANDA

3. **HARMEN MONS**
   ABBOTT HEALTHCARE PRODUCTS B.V.
   C.J. van Houtenlaan 36
   NL-1381 CP Weesp
   HOLANDA

4. **AXEL STOIT**
   ABBOTT HEALTHCARE PRODUCTS B.V.
   C.J. van Houtenlaan 36
   NL-1381 CP Weesp
   HOLANDA

5. **ERIC BONKEN**
   ABBOTT HEALTHCARE PRODUCTS B.V.
   C.J. van Houtenlaan 36
   NL-1381 CP Weesp
   HOLANDA

6. **ELIZABETH VAN DER KAM**
   ABBOTT HEALTHCARE PRODUCTS B.V.
   C.J. van Houtenlaan 36
   NL-1381 CP Weesp
   HOLANDA

7. **JURJEN FRANKENA**
   ABBOTT HEALTHCARE PRODUCTS B.V.
   C.J. van Houtenlaan 36
   NL-1381 CP Weesp
   HOLANDA

Referentienummer : 20110008.01\S\S

P2424

I, mr. Antonius Lodewijk Maria Schulte, civil-law notary, practising in Amsterdam, have identified the signature of Mr. **Marinus Verhage**, born in Yerseke on the 29th day of June 1953, holder of a Dutch passport with number NW4L9LKB9, issued in Huizen on the 3rd day of February 2010 whom I know to be the person(s) who signed this document as representative(s) of the Corporation / Company named

ABBOTT HEALTHCARE PRODUCTS B.V.

I certify:

a) that **ABBOTT HEALTHCARE PRODUCTS B.V.** is a corporation / Company legally constituted and in existence in accordance with the laws of the Kingdom of the Netherlands.

b) That de domicile of said Corporation/Company is **Van Houtenlaan 36, NL-1381 CP WEESP, Netherlands.**

c) That the purpose or purposes for which the Power of Attorney has been signed comprised within the object set forth in the charter of the mentioned Corporation/Company.

d) That Mr. Marinus Verhage is authorized to sign the Power of Attorney. The aforementioned was duly proven through the following documents and I duly certify having seen them: Extract of the Chamber of Commerce Gooi-, Eem- en Flevoland dated 23rd March 2011, Almere, The Netherlands.

Signed in Amsterdam on 6th day of April 2011

mr. A.L.M. Schulte
NOTARIS te AMSTERDAM

mr. A.L.M. Schulte
civil-law notary in Amsterdam

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NOTARIO VEINTISIETE

APOSTILLE

Convention de La Haye du 5 octobre 1961

1. Country: THE NETHERLANDS
   This public document
2. Has been signed by: mr. A.L.M. Schulte
3. Acting in the capacity of: civil law notary in Amsterdam
4. Bears the seal/stamp of:
   mr. A.L.M. Schulte
   Certified
5. At Amsterdam
6. On 6 april 2011
7. By the clerk of the Court of Amsterdam
8. No:
9. Seal/Stamp: — 12755 10. Signature
   dhr. J. Hoogeveen

AMSTERDAM RECHTBANK

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GUSTAVO SAMPER RODRIGUEZ
NOTARIO VEINTISEIS

EN BLANCO
NOTARIA VEINTISEIS

COLOMBIA

ODER

El (los)
ABBOTT HEALTHCARE PRODUCTS B.V.

Domiciliados en **C.J. van Houtenlaan 36, NL-1381 CP Weesp, Países bajos**

Nombran por el presente a **XIMENA CASTELLANOS A. y/o MARGARITA CASTELLANOS A.** abogadas con oficinas en la Calle 94A No. 7A-09, Bogotá- Colombia para tramitar la solicitud de patente titulada **DERIVADOS DE (TIO)MORFOLINA COMO MODULADORES DE S1P**
y para obtener la protección de mi (nuestra) propiedad Industrial e intelectual y con este fin autorizamos a dichos apoderados para que nos representen ante cualesquiera autoridades o personas de los órdenes administrativo, contencioso –administrativo y judicial en todo lo relacionado con los siguientes actos y gestiones:

Obtención de patentes de invención, modelos y dibujos industriales; su renovación, prórroga, inscripción de traspaso y cambio de nombre o domicilio, cancelación voluntaria y el registro de licencias de uso de esos derechos;

Acciones de oposición, observación, cancelación, nulidad, medidas cautelares y en general los juicios civiles, penales, administrativos o contencioso - administrativos que promovamos o se nos promuevan.
Pudiendo en todos los actos y gestiones arriba mencionados sustituir éste mandato entre los apoderados, transigir, desistir, recibir, cancelar, renunciar, aceptar notificaciones y nombrar apoderados judiciales y extra-judiciales.

Finalmente, este poder ratifica la validez de todos los actos y solicitudes que, a nombre de la poderdante hubieren realizado los apoderados en relación con las facultades anteriormente enumeradas, antes de la suscripción del presente poder

Dado y firmado hoy 1 de Abril de 2011
en Weesp, Holanda.

por Dr. Marjaus Verhage (director of Propriedad Industrial).
(El notario debe suscribir el documento en la pagina siguiente)
(Se requiere legalización consular o mediante apostilla)

SPW0912 CO

POWER OF ATTORNEY

I (we) the undersigned
ABBOTT HEALTHCARE PRODUCTS B.V.

Of **C.J van Houtenlaan 36, NL-1381 CP Weesp, Netherlands**

hereby grant(s) Power of Attorney to **XIMENA CASTELLANOS A. and /or MARGARITA CASTELLANOS** a. attorneys residing at Calle 94A No. 7A-09, Bogotá- Colombia, to prosecute patent application entitled **(THIO)MORPHOLINE DERIVATIVES AS S1P MODULATORS**
and to obtain the protection of my (our) Intellectual Property, for which purpose we authorize the said attorneys to represent us before any authorities, or persons, specially those, administrative, contentious and judicial, in all matters concerning the following:

Obtainment of patents, models and designs; its renewal, extension, recordal of assignments, change of name or domicile, voluntary cancellation, and the registration of licenses of use of the above rights;

Actions of opposition, cancellation, nullity, infringement, granting of licenses; and in general the civil, criminal and administrative suits related to those rights; actions and suits instituted by us or against us;

In all the above matters they may substitute this power of attorney within the appointed attorneys, compromise, cancel, receive, withdraw, renounce, accept notifications and appoint attorneys in fact in or out of court.

Finally, this power of attorney ratifies the validity of all acts and applications made by the representatives in the name of the signatory of this power of attorney, with regard to the faculties above given, before the execution of the present power of attorney.

Given and signed this April 1, 2011
in Weesp, The Netherlands

by Dr. Marinus Verhage (director of IP)

(Notary shall execute on the other side)
(Consular legalization or apostille is required)

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CASTELLANOS & Co.
INTELLECTUAL PROPERTY LAW FIRM

CALLE 94 A No. 7 A – 09 / P.O. BOX 6349
PHONE (57 1) 756 07 70 / FAX (57 1) 755 01 58
BOGOTÁ D.C. COLOMBIA
info@castellanosyco.com

File number: 32039508 Page 00001

English translation of an extract from the trade register of the Chambers of Commerce. This registration is administrated by the Chamber of Commerce for Gooi-, Eem- en Flevoland

---

Legal person:

Legal form	:Besloten Vennootschap (Private Limited Liability Company; 'Structure' company according to articles)
Name	:Abbott Healthcare Products B.V.
Statutory seat	:Weesp
Incorporation deed	:31-10-1930
Deed of latest amendment of articles	:16-02-2010
Authorized capital	:EUR 136.134.000,00
Issued capital	:EUR 116.848.350,00
Paid up capital	:EUR 116.848.350,00

Undertaking:

Tradename(s)	:Abbott Healthcare Products B.V. Solvay Duphar Solvay Pharmaceuticals
Address	:C J van Houtenlaan 36, 1381CP Weesp
Mailing address	:Postbus 164, 1380AD Weesp
Telephone number(s)	:0294477000
Fax number	:0318529374
Date of establishment	:31-10-1930
The legal person conducts the undertaking since	:15-11-1972
Description of business	See Dutch extract
Employees	:1156

Single shareholder:

Name	:Abbott Healthcare B.V.
Address	:C J van Houtenlaan 36, 1381CP Weesp
Registration trade register under file number	:32061264
Single shareholder since	:24-12-1980

Director(s):

Name :Stam, Pieter Teunis

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Date and place of birth :30-04-1960, Sliedrecht
Date of entry into office :09-09-2010
Title :Algemeen directeur
Powers :Solely/independently authorised

Supervisory director(s):

Name :Roobeek, Johanna Maria
Date and place of birth :13-10-1958, Amsterdam
Date of entry into office :01-11-2009

Name :Weitekämper, Frank
Date and place of birth :20-05-1963, Bielefeld, Federal Republic of Germany
Date of entry into office :16-08-2010

Name :Warner, Glenn Soule
Date and place of birth :10-11-1962, Columbus, United States of America
Date of entry into office :16-08-2010

Authorized signatory(signatories):

Name :van der Geest, Gerardus Jacobus Maria
Date and place of birth :10-06-1951, Warmond
Function and entry into office :Holder of power of attorney for signature, 01-02-1988
Powers :See Dutch extract
Commencement (present) power of attorney :01-11-1991

Name :Naus, Marijke Laetitia
Date and place of birth :16-02-1960, Breda
Function and entry into office :Holder of power of attorney for signature, 01-05-1990
Powers :See Dutch extract
Commencement (present) power of attorney :02-01-2004

Name :Dragt, Johan Andries
Date and place of birth :22-05-1953, Amsterdam
Function and entry into

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office	:Holder of power of attorney for signature, ... 01-09-1991 .....
Powers	:See Dutch extract .....
Commencement (present) power of attorney	:01-09-2007 .....
Name	:Timmerman, Philippus .....
Date and place of birth	:05-07-1954, Rotterdam .....
Function and entry into office	:Holder of power of attorney for signature, ... 01-09-1991 .....
Powers	:See Dutch extract .....
Commencement (present) power of attorney	:01-11-2009 .....
Name	:Prent, Marja Jeane .....
Date and place of birth	:23-11-1949, Weesp .....
Function and entry into office	:Holder of power of attorney for signature, ... 19-11-1991 .....
Powers	:See Dutch extract .....
Name	:van de Rol, Adriana Maria .....
Date and place of birth	:19-02-1957, Weesperkarspel .....
Function and entry into office	:Holder of power of attorney for signature, ... 19-11-1991 .....
Powers	:See Dutch extract .....
Commencement (present) power of attorney	:01-12-2005 .....
Name	:Schwarzwälder-van der Mooren, Judith .....
Date and place of birth	:15-01-1963, Heerlen .....
Function and entry into office	:Holder of power of attorney for signature, ... 01-01-1993 .....
Powers	:See Dutch extract .....
Name	:Bruinzeel, Marien Christiaan .....
Date and place of birth	:15-03-1952, Beverwijk .....
Function and entry into office	:Holder of power of attorney for signature, ... 01-06-1994 .....

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NOTARIO VEINTISEIS

Powers	:See Dutch extract
Commencement (present) power of attorney	:01-05-2003
Name	:Feenstra-Bielders, Gemma Gerardina Louis Maria
Date and place of birth	:17-12-1954, Sittard
Function and entry into office	:Holder of power of attorney for signature, 01-06-1994
Powers	:See Dutch extract
Commencement (present) power of attorney	:01-10-1997
Name	:Jansen, Sonja Elisabeth
Date and place of birth	:31-10-1964, Katwijk
Function and entry into office	:Holder of power of attorney for signature, 01-06-1995
Powers	:See Dutch extract
Name	:Debets, Felix Maria Hubert
Date and place of birth	:25-03-1955, Heerlen
Function and entry into office	:Holder of power of attorney for signature, 01-07-1995
Powers	:See Dutch extract
Commencement (present) power of attorney	:10-01-2008
Name	:ten Cate, Wouter
Date and place of birth	:23-02-1956, Nijmegen
Function and entry into office	:Holder of power of attorney for signature, 01-12-1997
Powers	:See Dutch extract
Name	:Overbeeke, Martinus Cornelis
Date and place of birth	:15-11-1950, Schiedam
Function and entry into office	:Holder of power of attorney for signature, 01-10-1997
Powers	:See Dutch extract

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File number: 32039508 Page 00005

Name	:Jansen-Blom, Lambertje Cornelia Willempje .....
Date and place of birth	:25-05-1971, Utrecht .....
Function and entry into office	:Holder of power of attorney for signature, ... 17-08-1998 .....
Powers	:See Dutch extract .....
Name	:Niemann, Leonarda Constantia .....
Date and place of birth	:15-09-1960, Amsterdam .....
Function and entry into office	:Holder of power of attorney for signature, ... 01-07-1999 .....
Powers	:See Dutch extract .....
Commencement (present) power of attorney	:01-09-2007 .....
Name	:Hellendoorn, Frederik Cornelis .....
Date and place of birth	:19-06-1960, Geleen .....
Function and entry into office	:Holder of power of attorney for signature, ... 01-10-1999 .....
Powers	:See Dutch extract .....
Commencement (present) power of attorney	:06-11-2005 .....
Name	:van Rossum, Abraham .....
Date and place of birth	:19-11-1947, Leerdam .....
Function and entry into office	:Holder of power of attorney for signature, ... 15-11-1999 .....
Powers	:See Dutch extract .....
Commencement (present) power of attorney	:01-04-2007 .....
Name	:van Gent, Eduard Theodorus .....
Date and place of birth	:24-02-1959, Leiden .....
Function and entry into office	:Holder of power of attorney for signature, ... 17-04-2001 .....
Powers	:See Dutch extract .....
Name	:Boonstra-Tuijtjens, Herma Johanna Clasina .....
Date and place of birth	:03-11-1952, Weesp .....

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Function and entry into office	:Holder of power of attorney for signature, 17-04-2001
Powers	:See Dutch extract
Name	:Geuns, Eduard Robert Martinus
Date and place of birth	:06-06-1961, Venlo
Function and entry into office	:Holder of power of attorney for signature, 01-02-2002
Powers	:See Dutch extract
Name	:van der Strate, Herbert John
Date and place of birth	:01-07-1965, Hellendoorn
Function and entry into office	:Holder of power of attorney for signature, 01-01-2002
Powers	:See Dutch extract
Commencement (present) power of attorney	:02-07-2007
Name	:Bult-Muntinga, Geziena Tjaatje
Date and place of birth	:20-12-1963, Groningen
Function and entry into office	:Holder of power of attorney for signature, 02-09-2002
Powers	:See Dutch extract
Name	:Booij, Anne-Marieke
Date and place of birth	:25-02-1969, Amstelveen
Function and entry into office	:Holder of power of attorney for signature, 19-11-2002
Powers	:See Dutch extract
Commencement (present) power of attorney	:01-01-2006
Name	:Post-Wolfert, Cornelia Elizabeth
Date and place of birth	:21-09-1972, Alkmaar
Function and entry into office	:Holder of power of attorney for signature, 19-11-2002
Powers	:See Dutch extract

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Commencement (present) power of attorney	:01-01-2006
Name	:Buser, Winfred Arnold
Date and place of birth	:24-09-1960, Haarlem
Function and entry into office	:Holder of power of attorney for signature, 01-05-2003
Powers	:See Dutch extract
Commencement (present) power of attorney	:02-01-2004
Name	:Junyent Martin, Francisco
Date and place of birth	:08-06-1952, Barcelona, Spain
Function and entry into office	:Holder of power of attorney for signature, 01-10-2003
Powers	:See Dutch extract
Name	:Lam, Marc Willem Johannes
Date and place of birth	:14-05-1966, Hilversum
Function and entry into office	:Holder of power of attorney for signature, 01-10-2003
Powers	:See Dutch extract
Name	:van Moorst, Robert
Date and place of birth	:04-08-1963, Bussum
Function and entry into office	:Holder of power of attorney for signature, 11-05-2004
Powers	:See Dutch extract
Name	:Ligtenberg, Eric Adrianus Antonius Maria
Date and place of birth	:02-10-1954, Dongen
Function and entry into office	:Holder of power of attorney for signature, 11-05-2004
Powers	:See Dutch extract
Name	:van Bentem, Marcel Anthonius Maria
Date and place of birth	:09-11-1972, Heemstede
Function and entry into	

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office	:Holder of power of attorney for signature, ... 01-10-2004 .....
Powers	:See Dutch extract .....
Name	:Bossert, Elisabeth Margaretha .....
Date and place of birth	:11-06-1959, Bussum .....
Function and entry into office	:Holder of power of attorney for signature, ... 01-01-2005 .....
Powers	:See Dutch extract .....
Commencement (present) power of attorney	:27-11-2007 .....
Name	:Bleijenberg-Okhuijzen, Antoinetta Maria .....
Date and place of birth	:27-05-1950, Rotterdam .....
Function and entry into office	:Holder of power of attorney for signature, ... 15-06-2005 .....
Powers	:See Dutch extract .....
Name	:Heuberger, Shari Elizabeth .....
Date and place of birth	:04-02-1960, Almelo .....
Function and entry into office	:Holder of power of attorney for signature, ... 15-06-2005 .....
Powers	:See Dutch extract .....
Name	:Broecks, Bert Christiaan .....
Date and place of birth	:02-06-1966, Hilversum .....
Function and entry into office	:Holder of power of attorney for signature, ... 01-07-2007 .....
Powers	:See Dutch extract .....
Name	:Straub, Paulus Hermanus Maria .....
Date and place of birth	:31-05-1963, Bussum .....
Function and entry into office	:Holder of power of attorney for signature, ... 01-09-2007 .....
Powers	:See Dutch extract .....
Commencement (present) power of attorney	:01-03-2010 .....

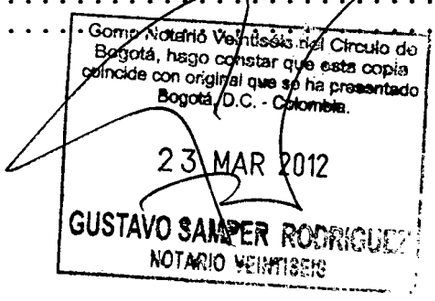
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Name	:Duchene, Philippe Louis Marie Jean Ghislain ...
Date and place of birth	:18-04-1961, Saint Marc, Belgium .....
Function and entry into office	:Holder of power of attorney for signature, ... 01-09-2007 .....
Powers	:See Dutch extract .....
Name	:van der Heijden, Johannes Antonius Maria .....
Date and place of birth	:30-05-1953, Breda .....
Function and entry into office	:Holder of power of attorney for signature, ... 01-01-2008 .....
Title	:procuratiehouder .....
Powers	:See Dutch extract .....
Name	:Kreike, Catharina Maria Cornelia .....
Date and place of birth	:01-01-1972, Haarlemmermeer .....
Function and entry into office	:Holder of power of attorney for signature, ... 01-02-2008 .....
Powers	:See Dutch extract .....
Name	:de Jong, Ronald .....
Date and place of birth	:17-08-1952, Amsterdam .....
Function and entry into office	:Holder of power of attorney for signature, ... 01-05-2008 .....
Powers	:See Dutch extract .....
Name	:Stam, Pieter Teunis .....
Date and place of birth	:30-04-1960, Sliedrecht .....
Function and entry into office	:Holder of power of attorney for signature, ... 16-07-2008 .....
Title	:Procuratiehouder .....
Powers	:See Dutch extract .....
Name	:Monster, Arie Johannes .....
Date and place of birth	:16-10-1957, Oud-Beijerland .....
Function and entry into office	:Holder of power of attorney for signature, ... 01-09-2008 .....
Powers	:See Dutch extract .....

23-03-2011 Page 00010 follows.



Name :Schager, Edwin
Date and place of birth :24-12-1967, Weesp
Function and entry into office :Holder of power of attorney for signature, 01-12-2007
Powers :See Dutch extract

Name :Sail, Philip Louis Olivier Ghislain
Date and place of birth :04-08-1962, Nivelles, Belgium
Function and entry into office :Holder of power of attorney for signature, 01-05-2009
Powers :See Dutch extract

Name :Langereis, Johannes
Date and place of birth :13-03-1951, Ursem
Function and entry into office :Holder of power of attorney for signature, 01-07-2009
Powers :See Dutch extract

Name :de Groot, Wouthera Antoinette
Date and place of birth :17-01-1975, Putten
Function and entry into office :Holder of power of attorney for signature, 01-04-2010
Powers :See Dutch extract

Name :Voogel, Johannes
Date and place of birth :18-09-1968, Amsterdam
Function and entry into office :Holder of power of attorney for signature, 01-04-2010
Powers :See Dutch extract

Name :Verhage, Marinus
Date and place of birth :29-06-1953, Yerseke
Function and entry into office :Holder of power of attorney for signature, 01-04-1999
Powers :See Dutch extract
Commencement (present)

23-03-2011

Page 00011 follows.

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NO

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power of attorney	:01-09-2000
Name	:Dalmulder-de Beus, Elysabeth
Date and place of birth	:14-09-1949, Weesp
Function and entry into office	:Holder of power of attorney for signature, 28-09-1999
Powers	:See Dutch extract
Name	:Witjes, Johan Theodorus Stephanus
Date and place of birth	:30-10-1960, Gendt
Date of entry into office	:01-12-2000
Title	:Procuratiehouder
Powers	:See Dutch extract
Name	:van Heemstra, Herman Theodoor
Date and place of birth	:21-02-1955, Madrid, Spain
Function and entry into office	:Holder of power of attorney for signature, 01-09-2005
Powers	:See Dutch extract
Name	:Boom, Erna Monique
Date and place of birth	:03-09-1963, Weesp
Date of entry into office	:03-07-2006
Powers	:See Dutch extract
Name	:de Bruin-van der Flier, Monique Everarda Arnolda
Date and place of birth	:22-06-1964, Amersfoort
Date of entry into office	:01-09-2006
Powers	:See Dutch extract
Name	:van Dijk, Willem Aart
Date and place of birth	:12-06-1966, Veenendaal
Date of entry into office	:01-09-2008
Title	:Procuratiehouder
Powers	:See Dutch extract
Name	:Kok, Sjirk
Date and place of birth	:28-05-1952, Leerdam
Date of entry into office	:13-07-2009
Title	:Gevolmachtigde

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kamer van koophandel

Powers	:See Dutch extract
Commencement (present) power of attorney	:20-07-2010
Name	:Tuurenhout-Batelaan, Désirée Nicoline
Date and place of birth	:03-01-1969, 's-Gravenhage
Date of entry into office	:01-07-2010
Title	:Procuratiehouder
Powers	:See Dutch extract

Issued by the chamber of commerce

Almere, 23-03-2011
Extract has been produced at 09.37

For extract

mC Kroon Maliepaard

mw. M.C. Kroon-Maliepaard
Adm. medewerkster bedrijfsvoering

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TRADUCCION OFICIAL No. 053-12, DE UN DOCUMENTO ESCRITO EN INGLES, SELLADO CON EL SELLO DEL SUSCRITO TRADUCTOR OFICIAL, HOY MARZO 16 DEL 2012, EN LA CIUDAD DE BOGOTÁ D.C., REPUBLICA DE COLOMBIA.

Documento de poder escrito en ingles y español

BOEKEL DE NEREE

Referencia numero: 20110008.01/S/S

Yo Antonius Lodewijk Maria Schulte, , notario de ley civil en Amsterdam, he identificado la firma de marinus Verhage, nacido en Yerseke en Junio 29 de 1953, titular del pasaporte Holandes con numero NW4L9LKB9, expedido en Huizen en Febrero 3 de 2010 a quien conozco como la persona que firma este documento como representante de la Compañía llamada

ABBOTT HEALTHCARE PRODUCTS B.V.

Certifico

a) Que ABBOTT HEALTHCARE PRODUCTS B.V es una compañía legalmente constituida y existente de acuerdo con las leyes del Reino de Holanda.
b) Que el domicilio de dicha compañía es van Houtenlann 36, NL-1381 CP WEESP, HOLANDA
c) Que el propósito o propósitos de dicho poder se ha firmado comprendido dentro del objeto establecido en los estatutos de dicha compañía.

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NOTARIO VEINTISEIS

Sergio Eleuterio Latorre Mendoza
Traductor e Interprete Oficial
Resol. No. 2859 Minjusticia 1[illegible]

d) Que Marinus verhage esta autorizado a firmar el poder. Lo anterior fue debidamente probado a través de los siguientes documentos y los acredite debidamente: extracto de cámara y Comercio Gooi, Eem en Flevolan de fecha Marzo 23 de 2011, Almere, Holanda.

Firmado en Amsterdam este dia 6 de Abril de 2011.

A.L.M SCHULTE

Notario de ley civil en Emsterdam

Adjunto al documento se encuentra lo siguiente

APOSTILLE

(CONVENCION DE LA HAYE DE 5 OCTOBRE 1961)

1. PAIS: PAISES BAJOS
   ESTE DOCUMENTO PUBLICO
2. HA SIDO FIRMADO POR: SR. A.L.M SCHULTE
3. ACTUANDO EN CAPACIDAD DE: NOTARIO DE LEY CIVIL EN AMSTERDAM
4. LLEVA EL SELLO/ESTAMPILLA SR. A.L.M SCHULTE

CERTIFICADO

5. EN: AMSTERDAM
6. EL DIA: 6 DE ABRIL DEL 2011
7. POR: EL REGISTRADOR DE LA CORTE EN ÁMSTERDAM
8. No. 12755
9. SELLO/ESTAMPILLA
10. FIRMA
    J HOOGEVEEN

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NOTARIO VEINTISEIS

Sergio Eleuterio Gutiérrez Mendoza
Traductor e Interprete Oficial
Resol. No. 2839 Minjusticia 1[illegible]

REPÚBLICA DE COLOMBIA
MINISTERIO DE RELACIONES EXTERIORES
LEGALIZACION

País: ***REPUBLICA DE COLOMBIA***
(Country: - Pays:)

El presente documento público
(This public document - Le présent acte public)

Ha sido firmado por: ***LATORRE MENDOZA SERGIO ELEUTERIO***
(Has been signed by: - A été signé par:)

Actuando en calidad de: ***TRADUCTOR OFICIAL***
(Acting in the capacity of: - Agissant en qualité de:)

Lleva el sello/estampilla de: ***TRADUCTOR E INTERPRETE OFICIAL***
(Bears the seal/stamp of: - Est revétu du sceau de / timbre de:)

Certificado
(Certified - Attesté)

En: ***BOGOTA D.C***
(At: - Á:)

El: ***3/22/2012 9:24:39 AM***
(On: - Le:)

Por: ***APOSTILLA Y LEGALIZACIÓN***
(By: The Ministry of Foreign Affairs of Colombia - Par: Ministère des Affaires Étrangères de la Colombie)

No: ***LMDW92440369***
(Under Number: - Sous le numéro:)

Nombre del Titular: ***12755***
(Name of the holder of document: - Nom du titulaire:)

Tipo de documento: ***TRADUCCION APOSTILLA***
(Type of document: - Type du document:)

Número de hojas: ***2***
(Number of pages: - Nombre de pages:)

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Ministerio de Relaciones Exteriores de Colombia
AMPARO DE LA CRUZ TAMAYO RODRIGUEZ
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23 MAR 2012

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 12-049461- -00000-0000

Fecha: 2012-03-23 14:55:11 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 411 PRESENTACION Folios: 363

Industria y Comercio
SUPERINTENDENCIA

ADMISION A TRAMITE - NUEVAS CREACIONES

PATENTE DE INVENCION [ ] **MODELO DE UTILIDAD** [ ] **Art. 33 Decisión 486/00**

- [ ] Indicación que se solicita una patente
- [ ] Datos de identificación del solicitante o de la persona que presenta la solicitud
- [ ] Descripción de la invención
- [ ] Dibujos de ser estos pertinentes
- [ ] Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa [ ] Incompleta [ ]

PATENTE DE INVENCION PCT [X] **MODELO DE UTILIDAD PCT** [ ] **Art. 33 Decisión 486/00 Circular Única**

- [X] Indicación que se solicita una PCT
- [X] Datos de identificación del solicitante o de la persona que presenta la solicitud
- [X] Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
- [ ] Dibujos de ser estos pertinentes
- [X] Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa [X] Incompleta [ ]

DISEÑO INDUSTRIAL [ ] **(Art. 119 Decisión 486/00)**

- [ ] Indicación que se solicita diseño industrial
- [ ] Datos de identificación del solicitante o de la persona que presenta la solicitud
- [ ] Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño
- [ ] Comprobante de pago de las tasas establecidas

Completa [ ] Incompleta [ ]

ESQUEMA DE TRAZADO [ ] **(Art. 92 Decisión 486/00)**

- [ ] Indicación que se solicita un esquema de trazado
- [ ] Datos de identificación del solicitante o de la persona que presenta la solicitud
- [ ] Representación gráfica de un esquema de trazado
- [ ] Comprobante de pago de las tasas establecidas

Completa [ ] Incompleta [ ]